LIONEL SAWYER & COLLINS
Cam Ferenbach (Nevada State Bar No. 96)
1700 Bank America Plaza
300 S. Fourth Street
Las Vegas, Nevada 89101
(702) 383-8826 (phone)
(702) 383-8845 (fax)

PATTERSON, BELKNAP, WEBB & TYLER LLP
Jeffrey I.D. Lewis
Richard J. McCormick
1133 Avenue of the Americas
New York, NY 10036-6710
(212) 336-2000

Attorneys for Alza Corporation

KAYE SCHOLER LLP
Gerald Sobel
Milton Sherman
Steven Roth
425 Park Avenue
New York, New York 10022
(212) 836-8000

Attorneys for Pfizer Inc.

UNITED STATES DISTRICT COURT
DISTRICT OF NEVADA

ALZA CORPORATION AND PFIZER INC.,	**NO.**
Plaintiffs,	**COMPLAINT**
v.	CV-S-02-1703-PMP-LRL
WATSON PHARMACEUTICALS, INC.,	
Defendant.	

LIONEL SAWYER & COLLINS
ATTORNEYS AT LAW
1700 BANK OF AMERICA PLAZA
300 SOUTH FOURTH ST.
LAS VEGAS,
NEVADA 89101
(702) 383-8888

Alza Corporation ("Alza") and Pfizer Inc. ("Pfizer") (collectively, "Plaintiffs"), by their attorneys, for their Complaint against Watson Pharmaceuticals, Inc. ("Watson"), allege as follows:

1. This is an action by Alza and Pfizer against Watson for infringement of United States Letters Patent Nos. 4,612,008 ("the '008 patent"), 5,024,843 ("the '843 patent"), 5,082,668 ("the '668 patent"), 5,091,190 ("the '190 patent"), 5,545,413 ("the '413 patent") and 5,591,454 ("the '454 patent"). A copy of each of the foregoing patents is attached hereto.

THE PARTIES

2. Alza is a corporation organized and existing under the laws of the State of Delaware and has its principal place of business at 1900 Charleston Road, Mountain View, California 94039.

3. Pfizer is a corporation organized and existing under the laws of the State of Delaware and has a principal place of business at 235 East 42nd Street, New York, New York.

4. Upon information and belief, Watson is a corporation organized and existing under the laws of the State of Nevada, having its Corporate Headquarters at 311 Bonnie Circle, Corona, California 92880, and its Commercial Headquarters at 360 Mount Kemble Avenue, Morristown, New Jersey 07962.

JURISDICTION AND VENUE

5. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331, 1338(a) and 1400(b).

LIONEL SAWYER & COLLINS
ATTORNEYS AT LAW
1700 BANK OF AMERICA PLAZA
300 SOUTH FOURTH ST.
LAS VEGAS,
NEVADA 89101
(702) 383-8888

6. This Court has general jurisdiction over Watson, a company organized and existing under the laws of the state of Nevada.

7. Venue is proper in this judicial district pursuant to 28 U.S.C. §§ 1391 and 1400(b).

FACTS COMMON TO ALL CLAIMS FOR RELIEF

8. Pfizer holds an approved New Drug Application for Glucotrol XL® tablets, 5 mg and 10 mg dosage strength, which it sells under the registered name Glucotrol XL®.

9. On or about November 13, 2002, Plaintiffs received letters dated November 8, 2002 from Watson, stating that Watson had filed ANDA No. 76-467 with the FDA under § 505(j) of the Federal Food, Drug and Cosmetic Act seeking approval to manufacture, use, and sell glipizide extended-release tablets, 5 mg and 10 mg ("Watson's Proposed ANDA Products") before the expiration of the '008, '843, '668, '190, '413 and '454 patents ("Watson's ANDA certification letter"). Watson's ANDA certification letter provided only very limited information about its ANDA products and unsupported conclusory assertions of non-infringement.

10. By letters and requests to Watson's attorneys, Plaintiffs requested key portions of ANDA No. 76-467 and tablet samples necessary to ascertain whether Watson's Proposed ANDA Products would infringe the '008, '843, '668, '190, '413 and/or '454 patents. Watson refused to reasonably disclose further information regarding its Proposed ANDA Products, preventing Plaintiffs from evaluating in a timely manner whether Watson's Proposed ANDA Products would likely infringe the '008, '843, '668, '190, '413 and/or '454 patents without conducting discovery as part of a litigation.

LIONEL SAWYER & COLLINS
ATTORNEYS AT LAW
1700 BANK OF AMERICA PLAZA
300 SOUTH FOURTH ST.
LAS VEGAS,
NEVADA 89101
(702) 383-8888

FIRST CLAIM FOR RELIEF: INFRINGEMENT OF THE '008 PATENT

11. Plaintiffs reallege paragraphs 1 through 10 above as if fully set forth herein.

12. On September 16, 1986, the United States Patent and Trademark Office (the "PTO") issued the '008 patent, entitled "Osmotic Device With Dual Thermodynamic Activity," which had been assigned to Alza. Alza is currently and continuously has been the title owner of the '008 patent since it was issued. Pfizer is an exclusive licensee under the '008 patent for Pfizer's Glucotrol XL® tablets, 5 mg and 10 mg tablets.

13. Pursuant to 21 U.S.C. § 355(b)(1), the '008 patent is identified in the FDA publication entitled "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book"), as covering Pfizer's Glucotrol XL®, 5 mg and 10 mg tablets.

14. Watson's ANDA certification letter states that Watson ANDA No. 76-467 certifies, pursuant to 21 U.S.C. § 355(b)(2)(A)(iv) ("paragraph IV certification"), that the manufacture, use or sale of Watson's Proposed ANDA Products will not infringe the '008 patent.

15. Upon reasonable opportunity for further investigation or discovery, Plaintiffs are likely to have substantial evidentiary support that Watson has infringed or actively induced infringement of the '008 patent by filing ANDA No. 76-467, which includes the paragraph IV certification as to the '008 patent and which seeks approval from the FDA to engage in the commercial manufacture, use, or sale of Watson's Proposed ANDA Products prior to the expiration of the '008 patent.

LIONEL SAWYER & COLLINS
ATTORNEYS AT LAW
1700 BANK OF AMERICA PLAZA
300 SOUTH FOURTH ST.
LAS VEGAS,
NEVADA 89101
(702) 383-8888

SECOND CLAIM FOR RELIEF: INFRINGEMENT OF THE '843 PATENT

16. Plaintiffs reallege paragraphs 1 through 15 above as if fully set forth herein.

17. On June 18, 1991, the PTO issued the '843 patent, entitled "Oral Hypoglycemic Glipizide Granulation," which had been assigned to Alza. Alza is and it continuously has been the title owner of the '843 patent since the PTO issued it. Pfizer is an exclusive licensee under the '843 patent for Pfizer's Glucotrol XL®, 5 mg and 10 mg tablets.

18. Pursuant to 21 U.S.C. § 355(b)(1), the '843 patent is identified in the Orange Book as covering Pfizer's Glucotrol XL®, 5 mg and 10 mg tablets.

19. Watson's ANDA certification letter states that Watson ANDA No. 76-467 includes a paragraph IV certification as to the '843 patent, that the manufacture, use, or sale of Watson's Proposed ANDA Products will not infringe the '843 patent.

20. Upon reasonable opportunity for further investigation or discovery, Plaintiffs are likely to have substantial evidentiary support that Watson has infringed or actively induced infringement of the '843 patent by filing ANDA No. 76-467, which includes the paragraph IV certification as to the '843 patent and which seeks approval from the FDA to engage in the commercial manufacture, use, or sale of Watson's Proposed ANDA Products prior to the expiration of the '843 patent.

LIONEL SAWYER & COLLINS
ATTORNEYS AT LAW
1700 BANK OF AMERICA PLAZA
300 SOUTH FOURTH ST.
LAS VEGAS,
NEVADA 89101
(702) 383-8888

THIRD CLAIM FOR RELIEF: INFRINGEMENT OF THE '668 PATENT

21. Plaintiffs reallege paragraphs 1 through 20 above as if fully set forth herein.

22. On January 21, 1992, the PTO issued the '668 patent, entitled "Controlled-Release System With Constant Pushing Source," which had been assigned to Alza. Alza is and it continuously has been the title owner of the '668 patent since the PTO issued it. Pfizer is an exclusive licensee under the '668 patent for Pfizer's Glucotrol XL®, 5 mg and 10 mg tablets.

23. Pursuant to 21 U.S.C. § 355(b)(1), the '668 patent is identified in the Orange Book as covering Pfizer's Glucotrol XL®, 5 mg and 10 mg tablets.

24. Watson's ANDA certification letter states that Watson ANDA No. 76-467 includes a paragraph IV certification as to the '668 patent, that the manufacture, use, or sale of Watson's Proposed ANDA Products will not infringe the '668 patent.

25. Upon reasonable opportunity for further investigation or discovery, Plaintiffs are likely to have substantial evidentiary support that Watson has infringed or actively induced infringement of the '668 patent by filing ANDA No. 76-467, which includes the paragraph IV certification as to the '668 patent and which seeks approval from the FDA to engage in the commercial manufacture, use, or sale of Watson's Proposed ANDA Products prior to the expiration of the '668 patent.

LIONEL SAWYER & COLLINS
ATTORNEYS AT LAW
1700 BANK OF AMERICA PLAZA
300 SOUTH FOURTH ST.
LAS VEGAS,
NEVADA 89101
(702) 383-8888

FOURTH CLAIM FOR RELIEF: INFRINGEMENT OF THE '190 PATENT

26. Plaintiffs reallege paragraphs 1 through 25 above as if fully set forth herein.

27. On February 25, 1992, the PTO issued the '190 patent, entitled "Delivery System for Administration Blood-Glucose Lowering Drug," which had been assigned to Alza. Alza is and it continuously has been the title owner of the '190 patent since the PTO issued it. Pfizer is an exclusive licensee of the '190 patent for Pfizer's Glucotrol XL®, 5 mg and 10 mg tablets.

28. Pursuant to 21 U.S.C. § 355(b)(1), the '190 patent is identified in the Orange Book as covering Pfizer's Glucotrol XL®, 5 mg and 10 mg tablets.

29. Watson's ANDA certification letter states that Watson ANDA No. 76-467 includes a paragraph IV certification as to the '190 patent, that the manufacture, use, or sale of Watson's Proposed ANDA Products will not infringe the '190 patent.

30. Upon reasonable opportunity for further investigation or discovery, Plaintiffs are likely to have substantial evidentiary support that Watson has infringed or actively induced infringement of the '190 patent by filing ANDA No. 76-467, which includes the paragraph IV certification as to the '190 patent and which seeks approval from the FDA to engage in the commercial manufacture, use, or sale of Watson's Proposed ANDA Products prior to the expiration of the '190 patent.

LIONEL SAWYER & COLLINS
ATTORNEYS AT LAW
1700 BANK OF AMERICA PLAZA
300 SOUTH FOURTH ST.
LAS VEGAS, NEVADA 89101
(702) 383-8888

FIFTH CLAIM FOR RELIEF: INFRINGEMENT OF THE '413 PATENT

31. Plaintiffs reallege paragraphs 1 through 30 above as if fully set forth herein.

32. On August 13, 1996, the PTO issued the '413 patent, entitled "Dosage Form for Administering Oral Hypoglycemic Glipizide," which had been assigned to Alza. Alza is and it continuously has been the title owner of the '413 patent since the PTO issued it. Pfizer is an exclusive licensee under the '413 patent for Pfizer's Glucotrol XL®, 5 mg and 10 mg tablets.

33. Pursuant to 21 U.S.C. § 355(b)(1), the '413 patent is identified in the Orange Book as covering Pfizer's Glucotrol XL®, 5 mg and 10 mg tablets.

34. Watson's ANDA certification letter states that Watson ANDA No. 76-467 includes a paragraph IV certification as to the '413 patent, that the manufacture, use, or sale of Watson's Proposed ANDA Products will not infringe the '413 patent.

35. Upon reasonable opportunity for further investigation or discovery, Plaintiffs are likely to have substantial evidentiary support that Watson has infringed or actively induced infringement of the '413 patent by filing ANDA No. 76-467, which includes the paragraph IV certification as to the '413 patent and which seeks approval from the FDA to engage in the commercial manufacture, use, or sale of Watson's Proposed ANDA Products prior to the expiration of the '413 patent.

LIONEL SAWYER & COLLINS
ATTORNEYS AT LAW
1700 BANK OF AMERICA PLAZA
300 SOUTH FOURTH ST.
LAS VEGAS,
NEVADA 89101
(702) 383-8888

SIXTH CLAIM FOR RELIEF: INFRINGEMENT OF THE '454 PATENT

36. Plaintiffs reallege paragraphs 1 through 35 above as if fully set forth herein.

37. On January 7, 1997, the PTO issued the '454 patent, entitled "Method for Lowering Blood Glucose", which had been assigned to Alza. Alza is and it continuously has been the title owner of the '454 patent since the PTO issued it. Pfizer is an exclusive licensee under the '454 patent for Pfizer's Glucotrol XL®, 5 mg and 10 mg tablets.

38. Alza submitted the '454 patent for reexamination by the Patent & Trademark Office on or about April 9, 2002.

39. Pursuant to 21 U.S.C. § 355(b)(1), the '454 patent is identified in the Orange Book as covering Pfizer's Glucotrol XL®, 5 mg and 10 mg tablets.

40. Watson's ANDA certification letter states that Watson ANDA No. 76-467 includes a paragraph IV certification as to the '454 patent, that the manufacture, use, or sale of Watson's Proposed ANDA Products will not infringe the '454 patent.

41. Upon reasonable opportunity for further investigation or discovery, Plaintiffs are likely to have substantial evidentiary support that Watson has infringed or actively induced infringement of the '454 patent by filing ANDA No. 76-467, which includes the paragraph IV certification as to the '454 patent and which seeks approval from the FDA to engage in the commercial manufacture, use, or sale of Watson's Proposed ANDA Products prior to the expiration of the '454 patent.

LIONEL SAWYER & COLLINS
ATTORNEYS AT LAW
1700 BANK OF AMERICA PLAZA
300 SOUTH FOURTH ST.
LAS VEGAS,
NEVADA 89101
(702) 383-8888

WHEREFORE, Alza and Pfizer request the following relief:

A. A judgment providing that the effective date of any FDA approval for Watson to make, use, sell, offer for sale, or import the glipizide extended-release tablets, 5 mg and 10 mg, described in ANDA No. 76-467 be no earlier than the date on which each of the '008, '843, '668, '190, '413 and '454 patents expires;

B. A judgment declaring that Watson's making, using, selling, offering to sell, or importing of the glipizide extended-release tablets, 5 mg and 10 mg, described in ANDA No. 76-467, or actively inducing any of the above, would constitute infringement of each of the '008, '843, '668, '190, '413 and '454 patents.

C. A judgment permanently enjoining Watson from making, using, selling, offering to sell, or importing the glipizide extended-release tablets, 5 mg and 10 mg, described in ANDA No. 76-467, or actively inducing any of the above, until after expiration of each of the '008, '843, '668, '190, '413 and '454 patents;

D. Attorneys' fees in this action pursuant to 35 U.S.C. § 285;

E. Damages sufficient to compensate Plaintiffs for any harm that they incur should Watson market or sell or actively induce the marketing or selling of its Proposed ANDA Products prior to the expiration of each of the '008, '843, '668, '190, '413 and '454 patents;

F. Costs and expenses in this action; and

G. Such further and other relief as this Court determines to be just and

LIONEL SAWYER & COLLINS
ATTORNEYS AT LAW
1700 BANK OF AMERICA PLAZA
300 SOUTH FOURTH ST.
LAS VEGAS,
NEVADA 89101
(702) 383-8888

proper.

Dated: December 20, 2002

Cam Ferenbach
LIONEL SAWYER & COLLINS
1100 Bank of America Plaza
50 W. Liberty Street
Reno, Nevada 89501
(702) 383-8826

Attorneys for Alza Corp. and Pfizer Inc.

Of Counsel:

PATTERSON, BELKNAP, WEBB & TYLER LLP
Jeffrey I.D. Lewis
Richard J. McCormick
1133 Avenue of the Americas
New York, NY 10036-6710
(212) 336-2000

JOHNSON & JOHNSON
Patricia Lukens
Ralph R. Palo
One Johnson & Johnson Plaza
New Brunswick, New Jersey 08933

Counsel for Alza Corporation

KAYE SCHOLER LLP
Gerald Sobel
Milton Sherman
Steven Roth
425 Park Avenue
New York, New York 10022
(212) 836-8000

United States Patent [19]

Wong et al.

[11] Patent Number: 4,612,008

[45] Date of Patent: Sep. 16, 1986

[54] **OSMOTIC DEVICE WITH DUAL THERMODYNAMIC ACTIVITY**

[75] Inventors: **Patrick S. L. Wong**, Hayward; **Brian Barclay**, Sunnyvale; **Joseph C. Deters**, Mt. View; **Felix Theeuwes**, Los Altos, all of Calif.

[73] Assignee: **Alza Corporation**, Palo Alto, Calif.

[21] Appl. No.: **685,092**

[22] Filed: **Dec. 21, 1984**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 493,760, May 11, 1983, abandoned.

[51] **Int. Cl.**[4] **A61M 7/00**; A61M 31/00

[52] **U.S. Cl.** **604/892**; 604/890; 604/891; 604/285

[58] **Field of Search** 604/890, 285, 892, 891

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,186,184	1/1980	Zaffaroni	604/892
4,210,139	6/1980	Higuchi	604/892
4,298,003	11/1981	Theeuwes et al.	604/892
4,320,759	3/1982	Theeuwes	604/892
4,350,271	9/1982	Eckenhoff	604/892

Primary Examiner—John Kight
Assistant Examiner—M. L. Moore
Attorney, Agent, or Firm—Paul L. Sabatine; Edward L. Mandell; Steven F. Stone

[57] **ABSTRACT**

An osmotic system is disclosed comprising a wall formed in at least a part of a semipermeable material that surrounds a compartment. The compartment contains a first osmotic composition comprising a beneficial agent, and a second and different osmotic composition. A passageway in the wall connects the first composition with the exterior of the system.

27 Claims, 14 Drawing Figures

FIG.1

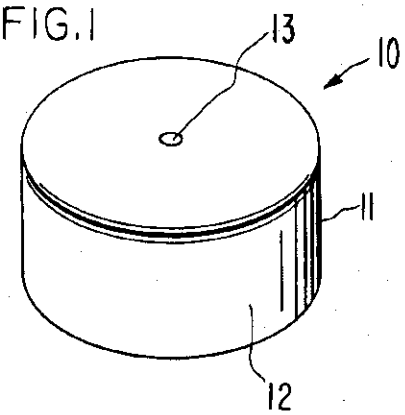


FIG.2

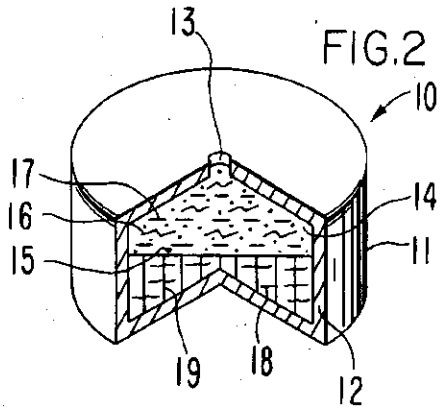


FIG.3

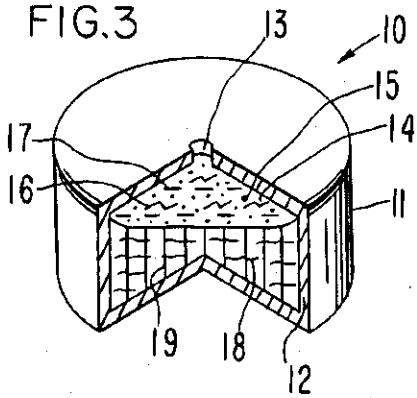


FIG.4

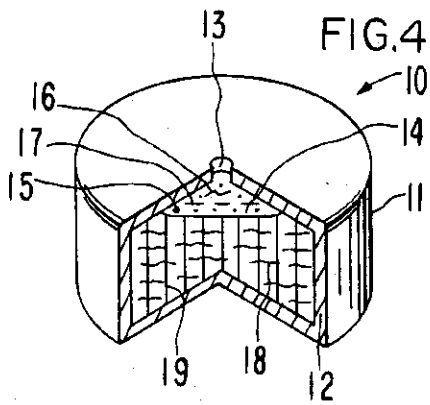


FIG.5

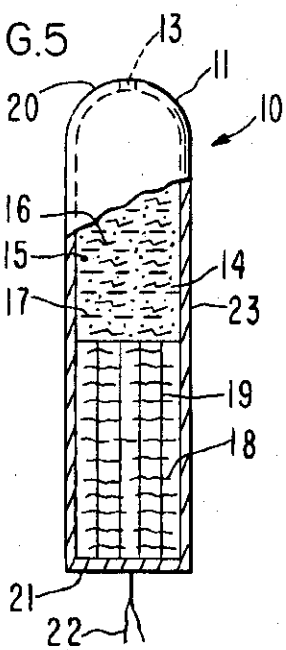


FIG.6

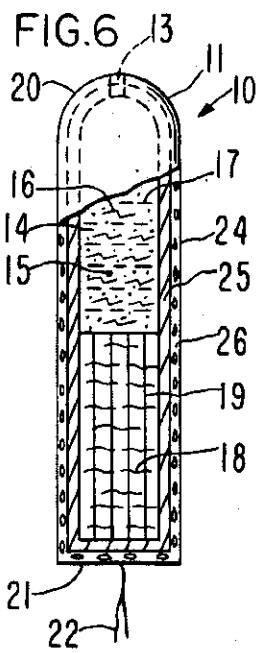


FIG.7

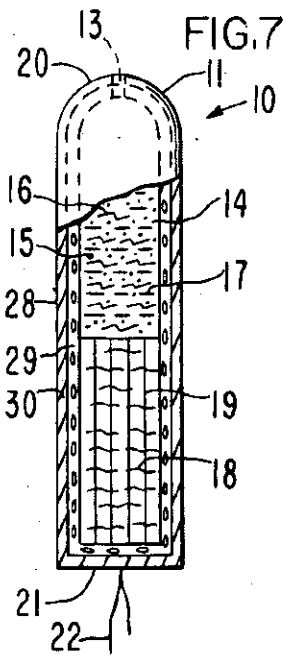
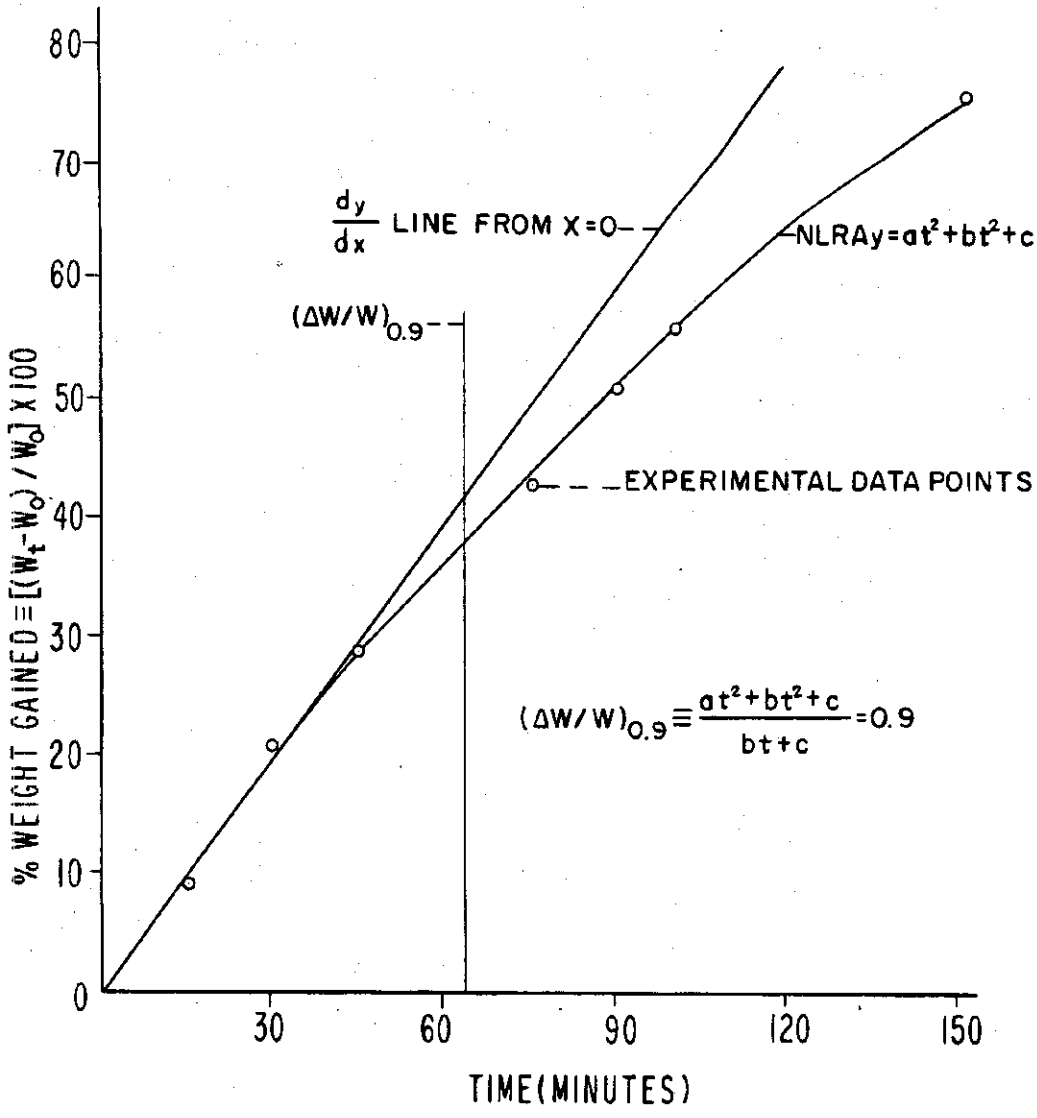


FIG. 8


80
70
60
50
40
30
20
10
0
30
60
90
120
150
% WEIGHT GAINED = [(W_t - W_o) / W_o] X 100
TIME (MINUTES)
dy/dx LINE FROM X=0
NLRAy=at²+bt²+c
(ΔW/W)0.9
EXPERIMENTAL DATA POINTS
(ΔW/W)0.9 ≡ (at²+bt²+c)/(bt+c) = 0.9

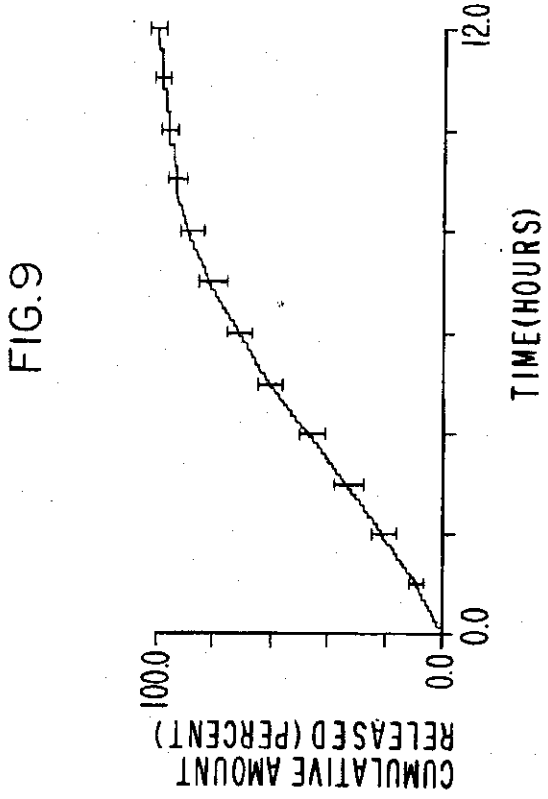

CUMULATIVE AMOUNT RELEASED (PERCENT)
100.0
0.0
0.0
12.0
TIME(HOURS)

FIG. 9

FIG. 10

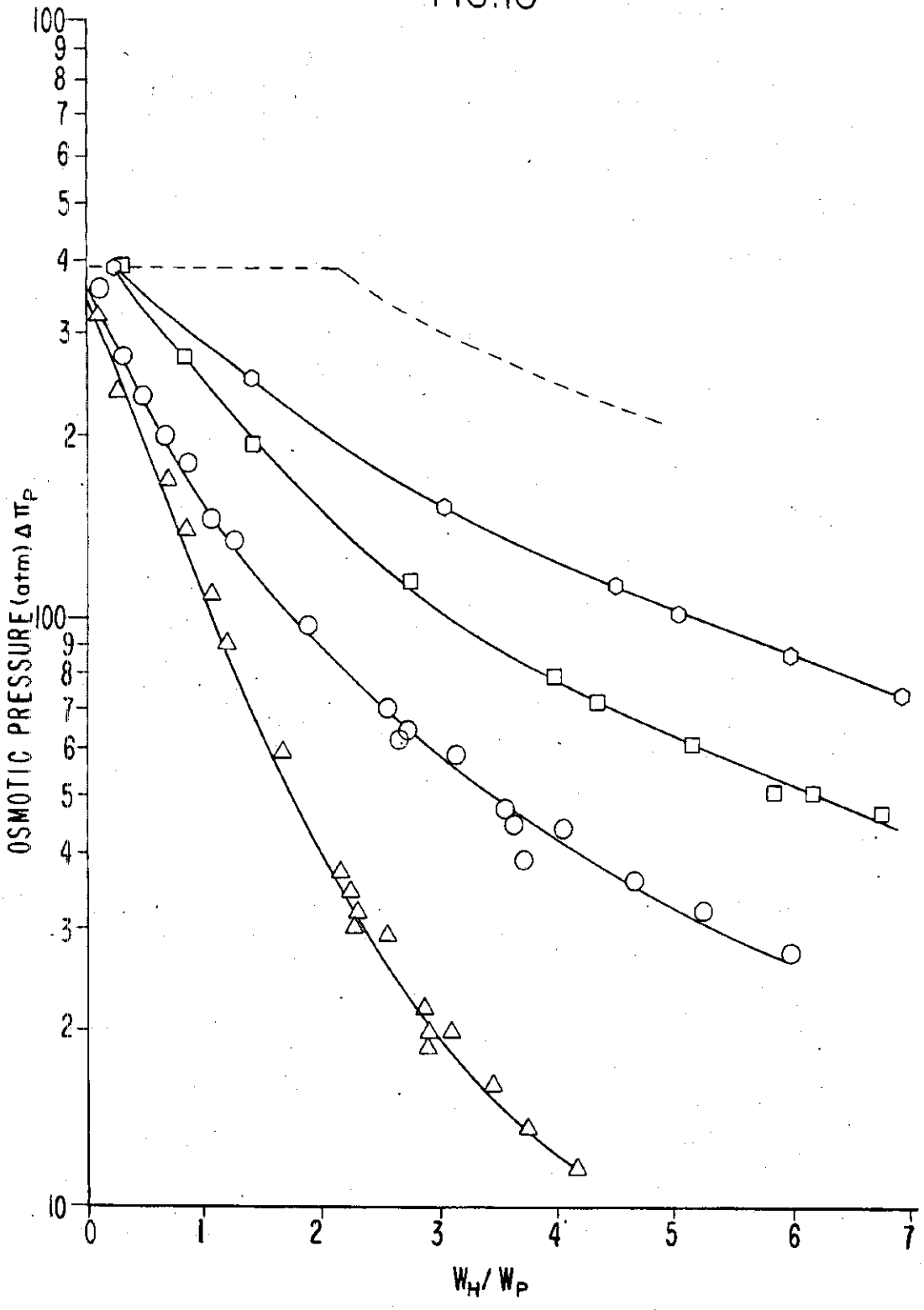

OSMOTIC PRESSURE (atm) $\Delta\pi_P$
100
9
8
7
6
5
4
3
2
100
9
8
7
6
5
4
3
2
10
0
1
2
3
4
5
6
7
W_H / W_P

FIG. 11

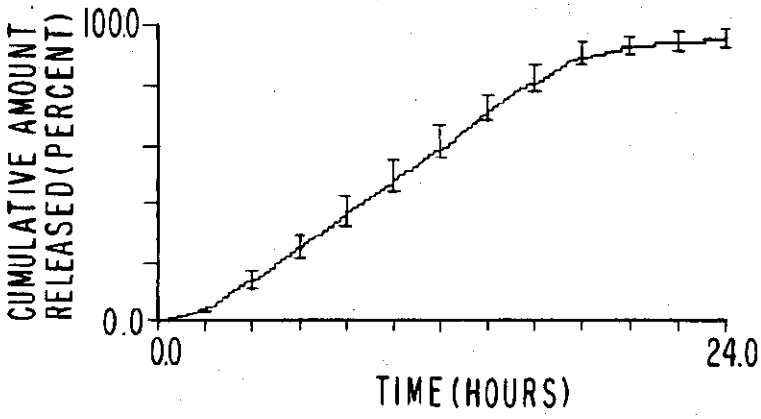


FIG. 12

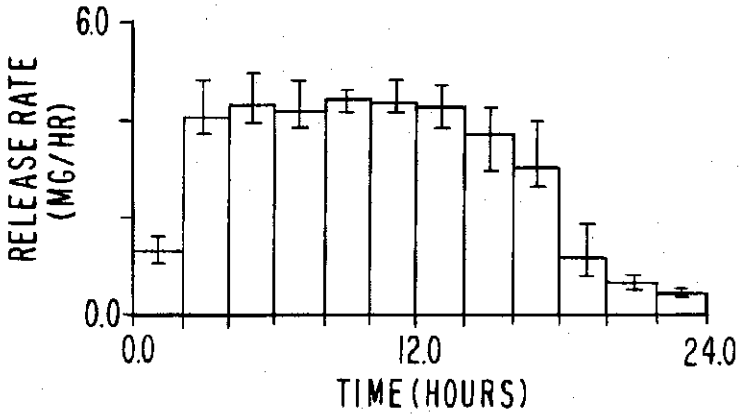
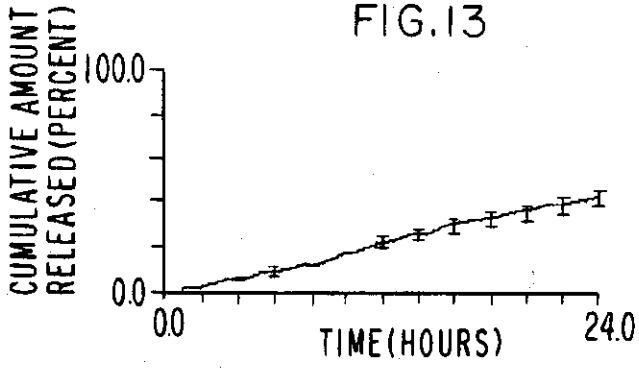


FIG. 13



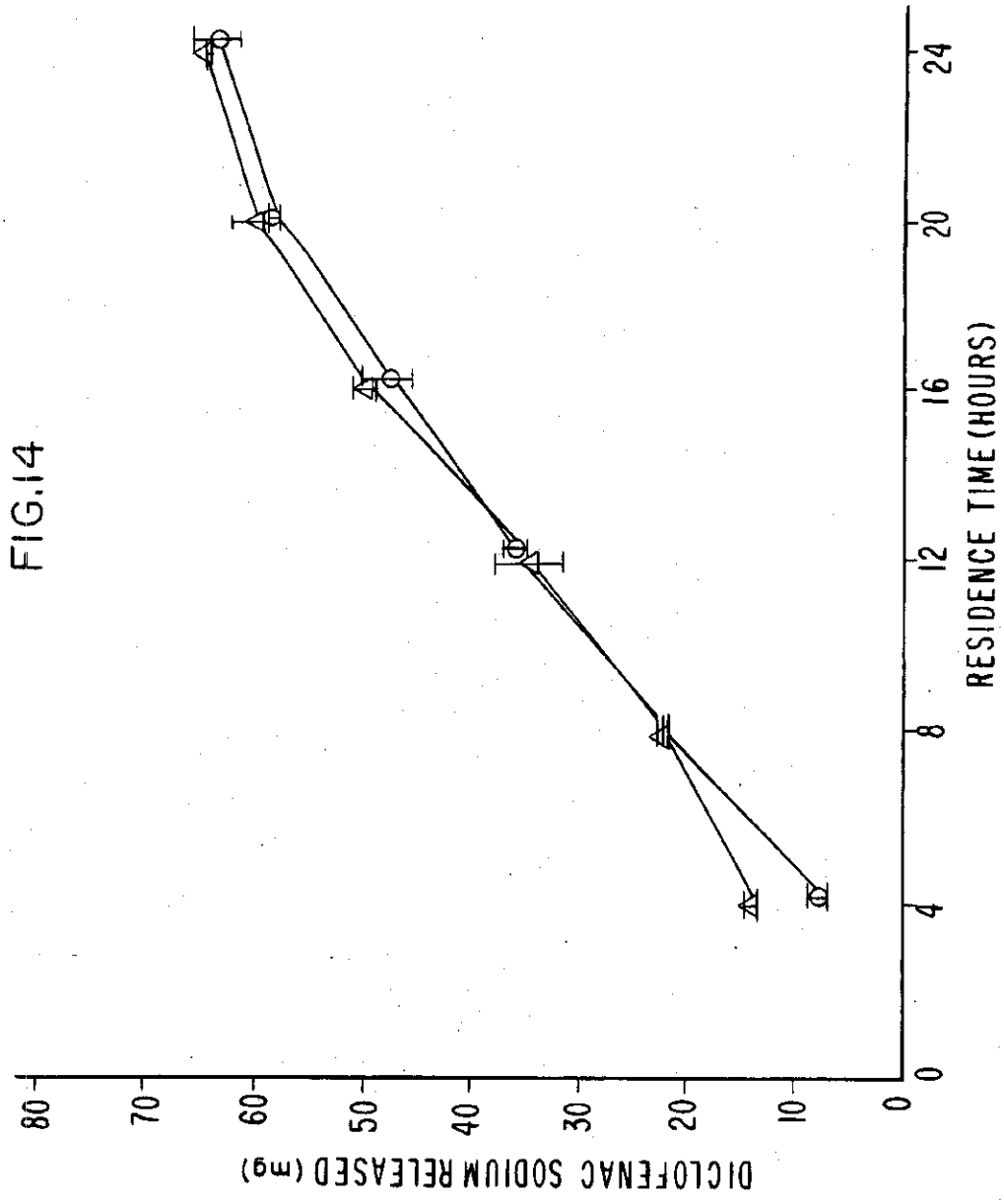

DICLOFENAC SODIUM RELEASED (mg)
80
70
60
50
40
30
20
10
0
0
4
8
12
16
20
24
RESIDENCE TIME (HOURS)

FIG.14

OSMOTIC DEVICE WITH DUAL THERMODYNAMIC ACTIVITY

CROSS-REFERENCE TO RELATED PATENT APPLICATIONS

This application is a continuation-in-part of U.S. Pat. Appln. Ser. No. 493,760 filed on May 11, 1983, now abandoned, which application is incorporated herein by reference and benefit is claimed of its filing date. This application is copending with the applicants' application ARC 1019 CIP-2 identified as U.S. Pat. Appln. 685,687 filed Dec. 24, 1984. These patent applications are assigned to the ALZA Corporation of Palo Alto, California.

FIELD OF THE INVENTION

This invention pertains to both a novel and unique delivery system. More particularly, the invention relates to an osmotic device comprising a wall formed in at least a part of a semipermeable material that surrounds a compartment comprising: (1) a first osmotic composition comprising a beneficial agent, an osmagent and an osmopolymer, said composition in contacting arrangement with (2) a second osmotic composition comprising an osmagent and an osmopolymer. A passageway through the wall connects the exterior of the osmotic device with the first osmotic composition containing the beneficial agent for delivering the first composition from the osmotic device. The osmotic device is useful for delivering beneficial agents that because of their solubilities are difficult to deliver in a known amount at a controlled rate from an osmotic dispensing system.

BACKGROUND OF THE INVENTION

Since the beginning of antiquity, both pharmacy and medicine have sought a delivery system for administering a beneficial drug. The first written reference to a delivery system is to the Eber Papyrus, written about 1552 B.C. The Eber papyrus mentions delivery systems made as dosage forms such as anal suppositories, vaginal pessaries, ointments, oral pill formulations, and other dosage preparations. About 2500 years passed without any advance in delivery system development, when the Arab physician Rhazes, 865–925 A.D., invented the coated pill. About a century later the Persian Avicenna, 980–1037 A.D., coated pills with gold or silver for increasing patient acceptability and for enhancing the effectiveness of the drug. Also around this time the first tablet was described in Arabian manuscripts written by al-Zahrawi, 936–1009 A.D. The manuscripts described a tablet formed from the follow impressions in two facing tablet molds. Pharmacy and medicine waited about 800 years for the next innovation in delivery systems, when in 1883 Mothes invented the capsule for administering drug. The next quantum leap in dosage forms came in 1972 with the invention of the osmotic delivery system by inventors Theeuwes and Higuchi as disclosed in U.S. Pat. Nos. 3,845,770 and 3,916,899. The osmotic system disclosed in those patents comprise a semipermeable wall that surrounds a compartment containing a useful agent. The wall is permeable to the passage of an external fluid, and it is substantially impermeable to the passage of useful agent. There is an osmotic passageway through the wall for delivering the useful agent from the osmotic system. These systems release a useful agent by fluid being imbibed through the semipermeable wall into the compartment at a rate determined by the permeability of the semipermeable wall and the osmotic pressure gradient across the semipermeable wall to produce an aqueous solution containing useful agent that is dispensed through the passageway from the system. These systems are extraordinarily effective for delivering a useful agent that is soluble in the fluid and exhibits an osmotic pressure gradient across the semipermeable wall against the external fluid.

A pioneer advancement in osmotic delivery systems, manufactured in the form of an osmotic device, was presented to the dispensing arts by inventor Felix Theeuwes in U.S. Pat. No. 4,111,202. In this patent, the delivery kinetics of the osmotic device are enhanced for delivering useful agents, including drugs that are insoluble to very soluble in the fluid, by manufacturing the osmotic device with a useful agent compartment and an osmagent compartment separated by an internal film. The internal film is movable from a rested to an expanded state. The osmotic device delivers agent by fluid being imbided through the semipermeable wall into the osmagent compartment producing a solution that causes the compartment to increase in volume and act as a driving force that is applied against the film. This force urges the film to expand in the device against the useful agent compartment and, correspondingly, diminish the volume of the useful agent compartment whereby useful agent is dispensed through the passageway from the osmotic device. While this device operates successfully for its intended use, and while it can deliver numerous useful agents of varying solubilities, its use can be limited because of the manufacturing steps and costs needed for fabricating and placing the movable film in the compartment of the osmotic device.

In U.S. Pat. No. 4,327,725 patentees Richard Cortese and Felix Theeuwes provided an osmotic dispensing device for delivering beneficial agents that, because of its solubilities in aqueous and biological fluids, are difficult to deliver in meaningful amounts at controlled rates over time. The osmotic devices of this patent comprise a semipermeable wall surrounding a compartment containing a beneficial agent that is insoluble to very soluble in aqueous and biological fluids and an expendable hydrogel. In operation, the hydrogel expands in the presence of external fluid that is imbided into the device and in some operations mixes with the beneficial agent, thereby forming a dispensable formulation that is dispensed through the passageway from the device. This device operates successfully for its intended use, and it delivers many difficult to deliver beneficial agents for their intended purpose. Now it has been observed, its use can be limited because the hydrogel can lack a present ability to imbide sufficient fluid for the maximum self-expansion needed for urging all beneficial agent from the device.

It will be appreciated by those versed in the dispensing art, that if an osmotic device can be provided that exhibits a high level of osmotic activity for delivering a beneficial agent by generating in situ an expanding force sufficient for delivering the maximum amount of agent at a controlled rate such as osmotic device would have a positive value and represent an advancement in the dispensing art. Likewise, it will be immediately appreciated by those versed in the dispensing art that if an osmotic device is made available possessing dual thermodynamic osmotic activity for delivering increased

amounts of a beneficial agent, said osmotic device would find practical application in the fields of pharmacy and medicine.

OBJECT OF THE INVENTION

Accordingly, in view of the above presentation, it is an immediate object of this invention to provide an osmotic system that can be manufactured by standard manufacturing techniques into osmotic devices of various sizes, shapes and forms that represent a further improvement and advancement in the dispensing art.

Another object of the invention is to provide an osmotic system manufactured in the form of an osmotic device for delivering in vivo a beneficial drug that is difficult to deliver and now can be delivered by the osmotic device in therapeutically effective amounts over time.

Another object of the invention is to provide an osmotic system possessing dual osmotic activity that operates as a unit, which system comprises a compartment containing a first osmotic composition comprising a drug, an osmagent and an osmopolymer, and a second osmotic composition comprising an osmagent and an osmopolymer, with the compositions acting in concert for delivering the drug through an osmotic passageway from the osmotic device.

Yet another object of the invention is to provide an osmotic device having means for high loading of a water insoluble or a slightly water soluble drug and means for delivering the drug in either instance at a controlled rate and continuously over time to a drug recipient.

Yet another object of the invention is to provide an osmotic device that can deliver a pH dependent beneficial agent by providing a neutral medium for delivering the beneficial agent in a finely dispersed form for increasing its surface area and for maximizing the dissolution rate of the beneficial agent.

Still yet another object of the invention is to provide an osmotic system for delivering a drug having a very low dissolution rate that is the rate limiting step for delivering the drug from the system, but now can be delivered by using an osmotic composition that functions in situ as a carrier, or a suspension agent, as a wetting agent and a solubilizing agent for increasing the dissolution rate and the solubility of the drug, thereby enhancing its delivery from the osmotic system.

Still yet another object of the invention is to provide an osmotic system comprising means for maintaining a high level of osmotic activity of a polymer used for delivering a beneficial agent from the osmotic system.

A further object of the invention is to provide an osmotic, therapeutic device that can administer a complete pharmaceutical dosage regimen comprising poorly soluble to very soluble agents, at a controlled rate and continuously for a particular time period, the use of which requires intervention only for the initiation and possibly for the termination of the regimen.

Still a further object of the invention is to provide an osmotic device that possesses the ability to deliver a broad range of drug delivery rates and simultaneously can deliver the drug according to a predetermined drug time release pattern to a biological recipient over time.

Other objects, features, aspects and advantages of the invention will be more apparent to those versed in the dispensing art from the following detailed specification taken in conjunction with the figures and the accompanying claims.

BRIEF DESCRIPTION OF THE DRAWINGS

In the drawings, which are not drawn to scale, but are set forth to illustrate various embodiments of the invention, the drawing figures are as follows:

FIG. **1** is an isometric view of an osmotic device designed for orally administering a beneficial agent to the gastrointestinal tract;

FIG. **2** is an opened view of the osmotic device of FIG. **1** illustrating the structure of the osmotic device of FIG. **1**;

FIG. **3** is an opened view of the osmotic device of FIG. **1** illustrating the osmotic device in operation and delivering a beneficial agent from the osmotic device;

FIG. **4** is an opened view of the osmotic device of FIG. **1** considered with FIG. **3** illustrating the osmotic device in operation and delivering a major amount of a beneficial agent from the osmotic device;

FIG. **5** shows an osmotic therapeutic device with its wall partially broken away, designed for delivering a beneficial agent into a body passageway, such as the ano-rectal and vaginal passageways;

FIG. **6** shows the osmotic device of FIG. **5** with a different wall structure;

FIG. **7** shows the osmotic device of FIG. **5** depicting a different wall structure than the wall structure depicted in FIG. **6**;

FIG. **8** represents the weight gain as a function of time for a polymer encapsulated in a semipermeable membrane when the encapsulated polymer is placed in water;

FIG. **9** depicts the cumulative amount of drug released from a device comprising an osmopolymer having two different molecular weights;

FIG. **10** depicts the osmotic pressure curves for a number of osmagent and a number of osmopolymer/osmagent compositions;

FIG. **11** depicts the cumulative release profile for an osmotic system using two different osmopolymers;

FIG. **12** depicts the release rate per hour for an osmotic system different from FIG. **9** containing an osmopolymer having two different molecular weights;

FIG. **13** depicts the cumulative amount released from a single composition device comprising only one layer;

FIG. **14** illustrates the in vivo and in vitro cumulative release for one drug delivered by the osmotic device;

In the drawings and the specification, like parts in related figures are identified by like parts. The terms appearing earlier in the specification and in the description of the drawings, as well as embodiments thereof, are further detailed elsewhere in the disclosure.

DETAILED DESCRIPTION OF THE DRAWINGS

Turning now to the drawings in detail, which are examples of various osmotic devices provided by the invention, and which examples are not to be construed as limiting, one example of an osmotic device is seen in FIG. **1**. In FIG. **1**, osmotic device **10** is seeen comprising a body member **11** having a wall **12** and a passageway **13** for releasing a beneficial agent from osmotic device **10**.

In FIG. **2**, osmotic device **10** of FIG. **1** is seen in opened section. In FIG. **2**, osmotic device **10** comprises a body **11**, a semipermeable wall **12** that surrounds and forms internal compartment **14**, that communicates through a passageway **13** with the exterior of osmotic device **10**. Compartment **14** contains a first osmotic

composition comprising a beneficial agent **15**, represented by dots, which agent **15** can be from insoluble to very soluble in fluid imbibed into compartment **14**, an osmagent **16**, represented by wavy lines, that is soluble in fluid imbibed into compartment **14** and exhibits an osmotic pressure gradient across semipermeable wall **12** against an external fluid, and, an osmopolymer **17**, represented by horizontal dashes, that imbibes fluid into compartment **14** and exhibits an osmotic pressure gradient across semipermeable wall **12** against an exterior fluid present in the environment of use. Wall **12** is formed of a semipermeable composition that is substantially permeable to the passage of the exterior fluid, and it is substantially impermeable to the passage of agent **15**, osmagent **16** and osmopolymer **17**. Semipermeable wall **12** is non-toxic and it maintains its physical and chemical integrity during the delivery life of device **10**.

Compartment **14** also houses a second osmotic composition that is distant from passageway **13** and in contacting relation with the first composition. The second composition is an expandable driving force that acts in cooperation with the first expandable osmotic composition for delivering the maximum amount of beneficial agent **15** from osmotic device **10**. The second osmotic composition comprises an osmagent **18**, that is soluble in fluid imbibed into compartment **14** and exhibits an osmotic pressure gradient across semipermeable wall **12** against an external fluid, blended with an osmopolymer **19** that imbibes fluid into compartment **14** and exhibits an osmotic pressure gradient across semipermeable wall **12** against external fluid. Osmopolymer **17** and osmopolymer **19** are hydrophilic water soluble or lightly cross-linked water insoluble polymers, and they possess osmotic properties such as the ability to imbibe external fluid through the semipermeable wall, exhibit an osmotic pressure gradient across the semipermeable wall against the external fluid, and swell or expand in the presence of the fluid in the compartment. Osmopolymers **17** and **19** are mixed with osmagent **16** and **18**, respectively, for imbibing the maximum volume of external fluid into compartment **14**. This fluid is available to osmopolymers **17** and **19** to optimize the volumetric rate and for total expansion of osmopolymers **17** and **19**. That is, osmopolymers **17** and **19** absorb fluid imbibed into compartment **14** by the osmotic imbibition action of osmopolymers **17** and **19** supplemented by the osmotic imbibition action of osmagents **16** and **18** for effecting the maximum expansion of osmopolymers **17** and **19** to an enlarged state.

In operation, the delivery of beneficial agent **15** from osmotic device **10** is carried out, in one presently preferred embodiment, by (1) imbibition of fluid by the first composition to form a fluid composition in situ and delivery of the fluidic composition through the passageway; and concurrently by (2) imbibition of fluid by the second composition causing the second composition to swell and cooperate with the first composition for driving the agent suspension through the passageway. According to the operation described, the osmotic device may be visualized as a cylinder, with the second composition expanding like the movement of a piston for aiding in delivering the agent composition from the osmotic device. For the purpose of the present analysis, the volume rate delivered by the osmotic device F_t is composed of two sources; the water imbibition rate by the first composition F, and the water imbibition rate by the second composition Q wherein:

$$F_t = F + Q \tag{1}$$

Since the boundary between the first composition and the second composition hydrates very little during the functioning of the osmotic device, there is insignificant water migration between the compositions. Thus, the water imbibition rate of the second composition, Q, equals the expansion of its volume:

$$\frac{dv_p}{dt} = Q \tag{2}$$

The total delivery rate from the osmotic device is then,

$$\frac{dm}{dt} = F_t \cdot C = (F + Q)C \tag{3}$$

wherein C is the concentration of beneficial agent in the delivered slurry. Conservation of the osmotic device volume, V, and the surface area, A, gives equations (4) and (5):

$$V = V_d + V_p \tag{4}$$

$$A = A_d + A_p \tag{5}$$

wherein V_d and V_p equal the volumes of the first composition and the second composition, respectively; and wherein A_d and A_p equal the surface area contact with the wall by the first composition and the second composition, respectively. In operation, both V_p and A_p increase with time, while V_d and A_d decrease with time as the device delivers beneficial agent.

The volume of the second composition that expands with time when fluid is imbibed into the compartment is given by equation (6):

$$V_p = \int \left(\frac{W_H}{W_p}\right) \tag{6}$$

wherein W_H is the weight of fluid imbibed by the second composition, W_p is the weight of the second composition initially present in the device, W_H/W_P is the ratio of fluid to initial solid of the second composition, and

$$V_p = \left(1 + \frac{W_H}{W_p}\right) \frac{W_p}{\rho} \tag{7}$$

wherein ρ is the density of the second composition corresponding to W_H/W_p. Thus, based on the geometry of a cylinder, where r is the radius of the cylinder, the area of imbibition is related to the volume of the swollen second composition as follows:

$$A_p = \pi r^2 + \frac{2}{r} \frac{W_p}{\rho} (1 + W_H/W_p) \tag{8}$$

$$A_d = A - A_p \tag{9}$$

The fluid imbibition rates into each composition are:

$$F = \left(\frac{k}{h}\right) (A_d \cdot \Delta\pi_d) \tag{10}$$

-continued

$$Q = \left(\frac{k}{h}\right)(A_p \cdot \Delta\pi_p) \quad (11)$$

wherein k equals the osmotic permeability of the wall, h equals the wall thickness, $\Delta\pi_d$ and $\Delta\pi_p$ are the osmotic gradients for the first composition and the second composition, respectively. The total delivery rate, therefore, is:

$$\frac{dm}{dt} = \frac{k}{h} C\left\{\left[A - \pi r^2 - \frac{2}{r}\,\frac{W_p}{\rho}(1 + W_H/W_p)\right]\Delta\pi_d + \left[\pi r^2 + \frac{2}{r}\,\frac{W_p}{\rho}(1 + W_H/W_p)\right]\Delta\pi_p\right\} \quad (12)$$

FIGS. 3 and 4 illustrate the osmotic device in operation as described for FIGS. 1 and 2. In FIGS. 3 and 4, for osmotic device 10, fluid is imbibed by the first composition at a rate determined by the permeability of the wall and the osmotic pressure gradient across the wall. The imbibed fluid continuously forms a solution containing beneficial agent, or a solution of a gel of osmagent and osmopolymer containing beneficial agent in suspension, which solution or suspension in either operation is released by the combined operations of device 10. These operations include the solution, or the suspension being osmotically delivered through the passageway due to the continuous formation of solution or suspension, and by the swelling and increasing volume of the second composition, represented by the increase in height of the vertical lines in FIGS. 3 and 4. This latter swelling and increase in volume applies pressure against the solution or suspension thereby aiding the first composition and simultaneously causing delivery of beneficial agent to the exterior of the device. Thus, the osmotic device provided by this invention can be viewed as a single unit construction device comprising two compositions containing two polymeric structures acting in concert for effective drug administration to a patient.

The first composition and the second composition act together to substantially insure that delivery of beneficial agent from the compartment is constant over a prolonged period of time by two methods. First, the first composition imbibes external fluid across the wall, thereby forming either a solution or a suspension the latter which would be substantially delivered at non-zero order (without the second composition present), since the driving force decays with time. Second, the second composition operates by two simultaneous operations: (1) the second composition operates to continuously concentrate beneficial agent by imbibing some fluid from the first composition to help keep the concentration of beneficial agent from falling below saturation and, (2), the second composition by imbibing external fluid across the wall and creating continuous increases in volume, thereby exerting a force against the first composition and diminishing the volume of beneficial agent, thusly directing beneficial agent to the passageway in the compartment. Additionally, as the extra solution or suspension formed in the first composition is squeezed out, the osmotic composition closely contacts the internal wall and generates a constant osmotic pressure and, therefore, a constant delivery rate in conjunction with the second composition. The swelling and expansion of the second composition, with its accompanying increase in volume, along with the simultaneous corresponding reduction in volume of the first composition assures the delivery of beneficial agent at a controlled rate over time.

Device 10 of FIGS. 1 through 4 can be made into many embodiments including the presently preferred embodiments for oral use; for releasing either a locally or systemically acting therapeutic agent in a gastrointestinal tract. Oral system 10 can have various conventional shapes and sizes such as round with a diameter of 3/16 inches to ⅝ inches. In these forms system 10 can be adapted for administering beneficial agent to numerous animals, including warm blooded animals, humans, avians, reptiles and pisces.

FIGS. 5, 6 and 7 show another embodiment provided by this invention. FIGS. 5, 6 and 7 show an osmotic device 10 designed for placement in a body passageway, such as a vagina, or the ano-rectal canal. Device 10 has an elongated, cylindrical, self-sustaining shape with a rounded lead end 20, a trailing end 21, and it is equipped with manually controlled strings 22 for easily removing device 10 from the biological passageway. Device 10 is structurally identical with the device described above in FIGS. 1 through 4, and it operates in a like manner. In FIG. 5, device 10 is depicted with a semipermeable wall 23, in FIG. 6 with a laminated wall 24 comprising an inner semipermeable lamina 25 adjacent to compartment 14 and an external microporous lamina 26 distant from compartment 14. In FIG. 7, device 10 comprises a laminated wall 28 formed of a microporous lamina 29 next to compartment 14, and a semipermeable lamina 30 facing the environment of use and in laminar arrangement with microporous lamina 29. The semipermeable lamina used for manufacturing these osmotic devices is permselective since it is permeable to the passage of fluid and substantially impermeable to the passage of agent, osmagent and osmopolymer. Device 10 delivers a beneficial agent for absorption by the vaginal mucosa, or the ano-rectal mucosa, to produce an in vivo local or systemic effect over a prolonged period of time.

The osmotic devices of FIGS. 1 through 7 can be used for delivering numerous agents including drugs at a controlled rate independent of the drug pH dependency, or where the dissolution rate of the agent can vary between low and high in fluid environments, such as gastric fluid and intestinal fluid. The osmotic devices also provide for the high loading of agents of low solubility and their delivery at meaningful, therapeutic amounts. While FIGS. 1 through 7 are illustrative of various osmotic devices that can be made according to the invention, it is to be understood these devices are not to be construed as limiting, as the devices can take a wide variety of shapes, sizes and forms adapted for delivering beneficial agents to the environment of use. For example, the devices include buccal, implant, artificial gland, cervical, intrauterine, ear, nose, dermal, subcutaneous, and like delivery devices. The devices also can be sized, shaped, structured and adapted for delivering an active agent in streams, aquariums, fields, factories, reservoirs, laboratory facilities, hot houses, transportation means, naval means, military means, hospitals, veterinary clinics, nursing homes, farms, zoos, sickrooms, chemical reactions, and other environments of use.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the practice of this invention it has now been found that osmotic delivery device **10** can be manufactured with a first osmotic composition and a second osmotic composition mutually housed in cooperative relationship in the compartment of the device. The compartment is formed by a wall semipermeable comprising a material that does not adversely affect the beneficial agent, osmagent, osmopolymer, and the like. The semipermeable wall is permeable to the passage of an external fluid such as water and biological fluids, and it is substantially impermeable to the passage of agents, osmagents, osmopolymers, and the like. The wall is formed of a material that does not adversely affect an animal, or host, or the components comprising the device, and the selectively semipermeable materials used for forming the wall are non-erodible and they are insoluble in fluids. Typical materials for forming the wall are in one embodiment cellulose esters, cellulose ethers and cellulose ester-ethers. These cellulosic polymers have a degree of substitution, D.S., on the anhydroglucose unit, from greater than 0 up to 3 inclusive. By degree of substitution is meant the average number of hydroxyl groups originally present on the anhydroglucose unit comprising the cellulose polymer that are replaced by a substituting group. Representative materials include a member selected from the group consisting of cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, moni, di and tricellulose alkanylates, mono, di and tricellulose aroylates, and the like. Exemplary polymers include cellulose acetate having a D.S. up to 1 and an acetyl content up to 21%; cellulose acetate having an acetyl content of 32 to 39.8%; cellulose acetate having a D.S. of 1 to 2 and an acetyl content of 21 to 35%; cellulose acetate having a D.S. of 2 to 3 and an acetyl content of 35 to 44.8%, and the like. More specific cellulosic polymers include cellulose propionate having a D.S. of 1.8 and a propionyl content of 39.2 to 45% and a hydroxyl content of 2.8 to 5.4%; cellulose acetate butyrate having a D.S. of 1.8, an acetyl content of 13 to 15% and a butyryl content of 34 to 39%; cellulose acetate butyrate having an acetyl content of 2 to 29%, a butyryl content of 17 to 53% and a hydroxyl content of 0.5 to 4.7%; cellulose triacylates having a D.S. of 2.9 to 3 such as cellulose trivalerate, cellulose trilaurate, cellulose tripalmitate, cellulose trisuccinate, and cellulose trioctanoate; cellulose diacylates having a D.S. of 2.2 to 2.6 such as cellulose disuccinate, cellulose dipalmitate, cellulose dioclanoate, cellulose dipentale, co-esters of cellulose such as cellulose acetate butyrate and cellulose acetate propionate, and the like.

Additional semipermeable polymers include cellulose acetaldehyde dimethyl acetate, cellulose acetate ethyl carbamate, cellulose acetate methyl carbamate, cellulose acetate dimethyl aminoacetate, semipermeable polyamides, semipermeable polyurethanes, semipermeable sulfonated polystyrenes, semipermeable crosslinked selectively polymers formed by the coprecipitation of a polyanion and a polycation as disclosed in U.S. Pat. Nos. 3,173,876; 3,276,586; 3,541,005; 3,541,006; and 3,546,142; semipermeable polymers as disclosed by Loeb and Sourirajan in U.S. Pat. No. 3,133,132; semipermeable lightly cross-linked polystyrene derivatives; semipermeable crosslinked poly(sodium styrene sulfonate); semipermeable cross-linked poly(vinylbenzyltrimethyl amonium chloride); semipermeable polymers exhibiting a fluid permeability of 10^{-5} to 10^{-1} (cc.mil/cm^2.hr.atm) expressed per atmosphere 10^{-8} of hydrostatic or osmotic pressure difference across the semipermeable wall. The polymers are known to the art in U.S. Pat. Nos. 3,845,770; 3,916,899; and 4,160,020; and in *Handbook of Common Polymers* by Scott, J. R. and Roff, W. J., 1971, published by CRC Press, Cleveland, OH.

The laminated wall comprising a semipermeable lamina and a microporous lamina are in laminar arrangement and they act in concert to form an integral laminated wall that maintains its physical and chemical integrity and does not separate into the original lamina throughout the operative agent release history of the osmotic device. The semipermeable lamina is made from the semipermeable polymeric materials presented above, the semipermeable homopolymers, the semipermeable copolymers, and the like.

Microporous lamina suitable for manufacturing the laminated osmotic device generally comprises preformed microporous polymeric materials, and polymeric materials that can form a microporous lamina in the environment of use. The microporous materials in both embodiments are laminated to a semipermeable lamina to form the laminated wall. The preformed materials suitable for forming the microporous lamina area essentially inert, they maintain their physical and chemical integrity during the period of agent release and they can be described generically as having a sponge like appearance that provides a supporting structure for a semipermeable lamina and also provides a supporting structure for microscopic sized interconnected pores or voids. The materials can be isotropic wherein the structure is homogeneous throughout a cross sectional area, or they can be anisotropic wherein the structure is nonhomogeneous throughout a cross sectional area. The pores can be continuous pores that have an opening on both faces of microporous lamina, pores interconnected through totuous paths of regular and irregular shapes, including curved, curved-linear, randomly oriented continuous pores, hindered connected pores and other porous paths discernible by microscopic examination. Generally, microporous lamina are defined by the pore size, the number of pores, the tortuosity of the microporous path and the porosity which relates to the size and the number of pores. The pore size of a microporous lamina is easily ascertained by measuring the observed pore diameter at the surface of the material under the electron microscope. Generally, materials possessing from 5% to 95% pores and having a pore size of from 10 angstroms to 100 microns can be used for making a microporous lamina. The pore size and other parameters characterizing the microporous structure also can be obtained from flow measurements, where a liquid flux, J, is produced by a pressure difference ΔP, across the lamina. The liquid flux through a lamina with pores of uniform radius extended through the lamina and perpendicular to its surface with area A given by relation (13):

$$J = \frac{N\pi r^4 \Delta P}{8\eta \Delta x} \tag{13}$$

wherein J is the volume transported per unit time and lamina area containing N number of pores of radius r, ρ is the viscosity of the liquid and ΔP is the pressure

difference across the lamina with thickness Δx. For this type of lamina, the number of pores N can be calculated from relation (14), wherein ϵ is the porosity defined as the ratio of void volume to total volume of the lamina; and A is the cross sectional area of the lamina containing N pores.

$$N = \frac{\epsilon A}{\pi r^2} \tag{14}$$

The pore radius then is calculated from relation (15):

$$r = \left[8 \eta \frac{\Delta x \tau}{\Delta P \epsilon} J' \right]^{\frac{1}{2}} \tag{15}$$

wherein J' is the volume flux through the lamina per unit area produced by the pressure difference ΔP across the lamina, ρ, ϵ and Δx have the meaning defined above and τ is the tortuosity defined as the ratio of the diffusional path length in the lamina to the lamina thickness. Relations of the above type are discussed in *Transport Phenomena In Membranes*, by Lakshminatayanaiah, N. Chapter 6, 1969, published by Academic Press, Inc., New York.

As discussed in this reference, supra, on page 336, in Table 6.13, the porosity of the lamina having pores with radius r can be expressed relative to the size of the transported molecule having a radius a, and as the ratio of molecular radius to pore radius a/r decreases, the lamina becomes porous with respect to this molecule. That is, when the ratio a/r is less than 0.3, the lamina becomes substantially microporous as expressed by the osmotic reflection coefficient σ which decreases below 0.5. Microporous lamina with a reflection coefficient σ in the range of less than 1, usually from 0 to 0.5, and preferably less than 0.1 with respect to the active agent are suitable for fabricating the system. The reflection coefficient is determined by shaping the material in the form of a lamina and carrying out water flux measurements as a function of hydrostatic pressure difference and as a function of the osmotic pressure difference caused by the active agent. The osmotic pressure difference creates a hydrostatic volume flux, and the reflection coefficient is expressed by relation (16):

$$\sigma = \frac{\text{osmotic volume flux}}{\text{hydrostatic volume flux}} \tag{16}$$

Properties of microporous materials are described in *Science*, Vol. 170, 1970, pp 1302–1305; *Nature*, Vol. 214, 1967, page 285; *Polymer Engineering and Science*, Vol. 11, 1971, pp 284–288; U.S. Pat. Nos. 3,567,809 and 3,751,536; and in *Industrial Processing With Membranes*, by Lacey, R. E., and Loeb, Sidney, 1972, pp 131–134.

Microporous materials having a preformed structure are commercially available and they can be made by art known methods. The microporous materials can be made by etching, nuclear tracking, by cooling a solution of flowable polymer below the freezing point whereby solvent evaporates from the solution in the form of crystals dispersed in the polymer and then curing the polymer followed by removing the solvent crystals, by cold or hot stretching at low or high temperatures until pores are formed, by leaching from a polymer a soluble component by an appropriate solvent, by ion exchange reaction, and by polyelectrolyte process. Process for repairing microporous materials are described in *Synthetic Polymer Membranes*, by R. E. Kesting, Chapters 4 and 5, 1971, published by McGraw Hill, Inc.; *chemical Reviews*, Ultrafiltration, Vol. 18., pp 373 to 455, 1934; *Polymer Eng. and Sci.*, Vol. 11. No. 4, pp 284–288, 1971; *J. Appl. Poly. Sci.*, Vol. 15, pp 811–829, 1971; and in U.S. Pat. Nos. 3,565,259; 3,615,024; 3,751,536; 3,801,692; 3,852,224, and 3,849,528.

Microporous materials useful for making the lamina include microporous polycarbonates comprised of linear polyesters of carbonic acid in which carbonate groups recur in the polymer chain; microporous materials prepared by the phosgenation of a dihydroxyl aromatic, such as bisphenol A; microporous poly(vinyl chloride); microporous polyamides such as polyhexamethylene adipamide; microporous modacrylic copolymers including those formed from poly(vinylchloride) 60% and acrylonitrile; styrene acrylic and its copolymers; porous polysulfones characterized by diphenylene sulfone groups in a linear chain thereof; halogenated poly(vinylidene); polychloroethers; acetal polymers; polyesters prepared by esterification of a dicarboxylic acid or anhydride with an alkylene polyol; poly(alkylenesulfides); phenolic polyesters; microporous poly(-saccharides); microporous poly(saccharides) having substituted and unsubstituted anhydroglucose units exhibiting an increased permeability to the passage of water and biological fluids than a nonporous semipermeable lamina; asymmetric porous polymers; cross-linked olefin polymers; hydrophobic or hydrophilic microporous homopolymers, copolymers or interpolymers having a reduced bulk density; and materials described in U.S. Pat. Nos. 3,597,752; 3,643,178; 3,654,066; 3,709,774; 3,718,532; 3,803,061; 3,852,224; 3,853,601; and 3,852,388; in British Patent No. 1,126,849, and in *Chem. Abst.*, 1969, Vol. 71 4274F, 22572F, 22573F.

Additional microporous materials include microporous poly(urethanes); microporous cross-linked, chain extended poly(urethanes); microporous poly(urethanes) in U.S. Pat. No. 3,524,753; microporous poly(imides); microporous poly(benzimidazoles); regenerated microporous proteins; semi-solid cross-linked microporous poly(vinylpyrrolidone); microporous materials prepared by diffusion of multivalent cations into polyelectrolyte sols as in U.S. Pat. No. 3,565,259; anisotropic microporous materials of ionically associated polyelectrolytes; porous polymers formed by the coprecipitation of a polycation and a polyanion as described in U.S. Pat. Nos. 3,276,589; 3,541,055; 3,541,066 and 3,546,142; derivatives of poly(styrene), such as microporous poly(-sodium styrenesulfonate) and microporous poly(vinyl benzyltrimethyl-ammonium chloride); the microporous materials disclosed in U.S. Pat. No. 3,615,024; and U.S. Pat. Nos. 3,646,178 and 3,852,224.

Further, the micropore forming material used for the purpose of the invention includes the embodiment wherein the microporous lamina is formed in situ by a pore former being removed by dissolving or leaching it to form the microporous lamina during the operation of the system. The pore former can be a solid or a liquid. The term liquid, for this invention, embraces semi-solids and viscous fluids. The pore formers can be inorganic or organic. The pore formers suitable for the invention include pore formers that can be extracted without any chemical change in the polymer. The pore forming solids have a size of about 0.1 to 200 micrometers and they include alkali metal salts such as sodium chloride,

sodium bromide, potassium chloride, potassium sulfate, potassium phosphate, sodium benzoate, sodium acetate, sodium citrate, potassium nitrate, and the like. The alkali earth metal salts include calcium phosphate, calcium nitrate, and the like. The transition metal salts include ferric chloride, ferrous sulfate, zinc sulfate, cupric chloride, manganese, fluoride, manganese fluorosilicate, and the like. The pore formers include organic compounds such as polysaccharides. The polysaccharides include the sugars: succrose, glucose, fructose, mannitol, mannose, galactose, aldohexose, altrose, talose, sorbitol, lactose, monosaccharides and disaccharides. Also, organic aliphatic and aromatic oils and solids, including diols and polyols, as exemplified by polyhydric alcohols, poly(alkylene glycols), polyglycols, alkylene glycols, poly(α-ω)-alkylenediols esters or alkylene glycols and the like; water soluble cellulosic polymers such as hydroxyloweralkyl cellulose, hydroxypropyl methylcellulose, methyl cellulose, methylethyl cellulose, hydroxyethyl cellulose and the like; water soluble polymers such as polyvinylpyrrolidone, sodium carboxymethylicellulose and the like. The pore-formers are nontoxic and on their removal from the lamina channels are formed through the lamina. In a preferred embodiment the non-toxic, poreforming agents are selected from the group consisting of inorganic and organic salts, carbohydrates, polyalkylene glycols, poly-(α-ω)-alkylene-diols, esters of alkylene glycols, glycols and water soluble polymers used for for forming a microporous lamina in a biological environment. Generally, for the purpose of this invention, when the polymer forming the lamina contains more than 15% by weight of a poreformer, the polymer is a precursor microporous lamina that on removing the poreformer yields a lamina which is substantially microporous.

The expression passageway as used herein comprises means and methods suitable for releasing the agent or drug from the osmotic system. The expression includes osmotic aperture, osmotic orifice, osmotic hole or osmotic bore through the semipermeable wall or the laminated wall. The osmotic passageway can be formed by mechanical drilling, laser drilling or by eroding an erodible element such as a gelatin plug in the environment of use. A detailed description of osmotic passageways, and the maximum and minimum dimensions for a passageway, are disclosed in U.S. Pat. Nos. 3,845,770 and 3,916,899. The osmotic passageway has a maximum cross-sectional area, A_s, defined by the relation (17) as follows:

$$A_{s(max)} = \frac{L}{F} \times \frac{Qp}{t} \times \frac{1}{DS} \quad (17)$$

wherein L is the length of the passageway Q_p/t is the mass delivery rate of the agent, D is the diffusion coefficient of the agent, S is the solubility of the agent in the fluid, and F is from 2 to 1000, said passageway having a minimum area A_s defined by relation (18) as follows:

$$A_{s(min)} = \left[\frac{Lv}{t} \times 8 \times \frac{\pi\eta}{\Delta P} \right]^{\frac{1}{2}} \quad (18)$$

wherein L is the length of the passageway, v/t is the agent solution volume delivery rate, π is 3.14; ρ is the viscosity of agent solution dispensed from the device and ΔP is the hydrostatic pressure difference between the inside and the outside of the compartment having a value up to 20 atmospheres.

The osmotically effective compounds that can be used for the purpose of this invention include inorganic and organic compounds that exhibit an osmotic pressure gradient across the semipermeable wall, or across a semipermeable microporous laminated wall, against an external fluid. The osmotically effective compounds, along with the osmopolymers, imbibe fluid into the osmotic device thereby making available in situ fluid for imbibition by an osmopolymer to enhance its expansion, and/or for forming a solution or suspension containing a beneficial agent for its delivery through the passageway from the osmotic device. The osmotically effective compounds are known also as osmotically effective solutes, or osmagents. The osmotically effective compounds are used by mixing them with a beneficial agent and osmopolymer for forming a solution, or suspension containing the beneficial agent that is osmotically delivered from the device. The expression limited solubility as used herein means the agent has a solubility of about less then 5% by weight in the aqueous fluid present in the environment. The osmotic solutes are used by homogeneously or heterogeneously mixing the solute with the agent or osmopolymer and then charging them into the reservoir. The solutes and osmopolymers attract fluid into the reservoir producing a solution of solute in a gel which is delivered from the system concomitantly transporting undissolved and dissolved beneficial agent to the exterior of the system. Osmotically effective solutes used for the former purpose include magnesium sulfate, magnesium chloride, potassium sulfate, sodium sulfate, lithium sulfate, potassium acid phosphate, d-mannitol, urea, inositol, magnesium succinate, tartaric acid, carbohydrates such as raffinose, sucrose, glucose, α-d-lactose monohydrate, and mixtures thereof. The amount of osmagent in the compartment will generally be from 0.01% to 30% or higher in the first composition, and usually from 0.01% to 40% or higher in the second composition.

The osmotic solute is initially present in excess and it can be in any physical form that is compatible with the beneficial agent, the osmagent, and osmopolymer. The osmotic pressure of saturated solutions of various osmotically effective compounds and for mixtures of compounds at 37° C., in water, is listed in Table 1. In the table, the osmotic pressure π, is in atmospheres, atm. The osmotic pressure is measured in a commercially available osmometer that measures the vapor pressure difference between pure water and the solution to be analyzed and, according to standard thermodynamic principles, the vapor pressure ratio is converted into osmotic pressure difference. In Table 1, osmotic pressures of from 20 atm to 500 atm are set forth. Of course, the invention includes the use of lower osmotic pressures from zero, and higher osmotic pressures than those set forth by way of example in Table 1. The osmometer used for the present measurements is identified as Model 320B, Vapor Pressure Osmometer, manufactured by the Hewlett Packard Co., Avondale, PA.

TABLE 1

COMPOUND OR MIXTURE	OSMOTIC PRESSURE ATM
Lactose-Fructose	500
Dextrose-Fructose	450
Sucrose-Fructose	430
Mannitol-Fructose	415
Sodium Chloride	356

TABLE 1-continued

COMPOUND OR MIXTURE	OSMOTIC PRESSURE ATM
Fructose	355
Lactose-Sucrose	250
Potassium Chloride	245
Lactose-Dextrose	225
Mannitol-Dextrose	225
Dextrose-Sucrose	190
Manitol-Sucrose	170
Dextrose	82
Potassium Sulfate	39
Mannitol	38
Sodium Phosphate Tribasic $12H_2O$	36
Sodium Phosphate Dibasic $7H_2O$	31
Sodium Phosphate Dibasic $12H_2O$	31
Sodium Phosphate Dibasic Anhydrous	29
Sodium Phosphate Monobasic H_2O	28

The osmopolymers suitable for forming the first osmotic composition, and also suitable for forming the second osmotic composition, are osmopolymers that exhibit fluid imbibition properties. The osmopolymers are swellable, hydrophilic polymers which osmopolymers interact with water and aqueous biological fluids and swell or expand to an equilibrium state. The osmopolymers exhibit the ability to swell in water and retain a significant portion of the imbibed water within the polymer structure. The osmopolymers swell or expand to a very high degree, usually exhibiting a 2 to 50 fold volume increase. The osmopolymers can be noncross-linked or cross-linked. The swellable, hydrophilic polymers are in one presently preferred embodiment lightly cross-linked, such cross-links being formed by covalent or ionic bonds. The osmopolymers can be of plant, animal or synthetic origin. The osmopolymers are hydrophilic polymers. Hydrophilic polymers suitable for the present purpose include poly(hydroxyalkyl methacrylate) having a molecular weight of from 30,000 to 5,000,000; poly(vinylpyrrolidone) having molecular weight of from 10,000 to 360,000; anionic and cationic hydrogels; polyelectrolyte complexes; poly(vinyl alcohol) having a low acetate residual, cross-linked with glyoxal, formaldehyde, or glutaraldehyde and having a degree of polymerization from 200 to 30,000; a mixture of methyl cellulose, cross-linked agar and carboxymethyl cellulose; a water insoluble, water swellable copolymer reduced by forming a dispersion of finely divided copolymer of maleic anhydride with styrene, ethylene, propylene, butylene or isobutylene cross-linked with from 0.001 to about 0.5 moles of polyunsaturated cross-linking agent per mole of maleic anhydride in the copolymer; water swellable polymers of N-vinyl lactams, and the like.

Other osmopolymers include polymers that form hydrogels such as Carbopol ® acidic carboxy polymers having a molecular weight of 450,000 to 4,000,000; Cyanamer ® polyacrylamides; cross-linked water swellable indene-maleic anhydride polymers; Goodrite ® polyacrylic acid having a molecular weight of 80,000 to 200,000; Polyox ® polyethylene oxide polymers having a molecular weight of 100,000 to 5,000,000; starch graft copolymers; Aqua-Keeps ® acrylate polymer; diester cross-linked polyglucan, and the like. Representative polymers that form hydrogels are known to the prior art in U.S. Pat. No. 3,865,108 issued to Hartop; U.S. Pat. No. 4,002,173 issued to Manning; U.S. Pat. No. 4,207,893 issued to Michaels; and in *Handbook of Common Polymers*, by Scott and Roff, published by the Chemical Rubber Company, Cleveland, OH. The amount of osmopolymer in the first osmotic composition is about 0.01 to 90%, and the amount of osmopolymer in the second osmotic composition is 15 to 95%. In a presently preferred embodiment, the osmopolymer identified as P_1 comprising the first composition can be different than the osmopolymer identified as P_2 comprising the second composition. The osmopolymer in the first composition can be structurally different than the osmopolymer in the second composition, or the osmopolymers can be substantially structurally identical with the molecular weight of the osmopolymer in the second osmotic composition larger than the molecular weight of the osmopolymer in the first osmotic composition. The osmopolymer P_1 comprising the first composition serves as a pharmaceutically acceptable carrier for the active agent and it contributes to the driving force that cooperates with osmopolymer P_2 comprising the second composition that delivers the agent through the passageway from the device. During operation of the device fluid is imbibed into the device resulting in the viscosity of P_2 being greater than the viscosity of P_1. In this operation P_1 and P_2 operate as a single unit substantially free of a void between the interfaced contacting surfaces of osmopolymer P_1 and P_2 for successful delivery of the beneficial agent from the osmotic device.

Osmopolymer fluid imbibition determination for a chosen polymer can be made by following the procedure described below. A ½ inch round disk, fitted with a ½ inch diameter stainless steel plug, is charged with a known quantity of polymer with the plugs extending out either end. The plugs and the die were placed in a Carver press with plates between 200° F. and 300° F. A pressure of 10,000 to 15,000 psi was applied to the plugs. After 10 to 20 minutes of heat and pressure the electrical heating to the plates was turned off, and tap water circulated through the plates. The resulting ½ inch disks were placed in an air suspension coater charged with 1.8 kg saccharide cores and coated with cellulose acetate having an acetyl content of 39.8% dissolved in 94:6 w/w, CH_2Cl_2/CH_3OH, to yield a 3% w/w solution. The coated systems were dried overnight at 50° C. The coated disks were immersed in water at 37° C. and periodically removed for a gravimetric determination of water imbibed. The initial imbibition pressure was calculated by using the water transmission constant for the cellulose acetate, after normalizing imbibition values for membrane surface area and thickness. The polymer used in this determination was the sodium derivative of Carbopol-934 ® polymer, prepared according to the procedure of B. F. Goodrich Service Bulletin GC-36, "Carbopol ® Water-Soluble Resins", page 5, published by B. F. Goodrich, Akron, OH.

The cumulative weight gain values, y, as a function of time, t, for the water soluble polymer disk coated with the cellulose acetate were used to determine the equation of the line $y=c+bt+at^2$ passing through those points by at least square fitting technique.

The weight gain for the Na Carbopol-934 ® is given by the equation (19) that follows: Weight gain equals $0.359+0.665t-0.00106t^2$ wherein t is elapsed time in minutes. The rate of water flux at any time will be equal to the slope of the line that is given by the following equations (19) and (20):

$$\frac{dy}{dt} = \frac{d(0.359 + 0.665t - 0.00106t^2)}{dt} \quad (19)$$

-continued

$$\frac{dy}{dt} = 0.665 - 0.00212t \quad (20)$$

To determine the initial rate of water flux the derivative is evaluated at t=0, and dy/dt=0.665 μl/min., which is equal to the coefficient b. Then, normalizing the imbibition rate for time, membrane surface area and thickness, and the membrane permeability constant to water, Kπ may be determined according to the following equation (21):

$$K\pi = 0.665\ \mu l/\text{min.} \times \left(\frac{60\ \text{min.}}{\text{hr}}\right) \times \left(\frac{1\ \text{ml}}{1000\ l}\right)\left(\frac{0.008\ \text{cm}}{2.86\ \text{cm}}\right) \quad (21)$$

with $K = 1.13 \times 10^{-4}$ cm²/hr. The π value for NaCl was determined with a Hewlett Packard vapor pressure osmometer to be 345 atm±10%, and the K value for cellulose acetate used in this experiment calculated from NaCl imbibition values was determined to be 1.9×10^{-7} cm²/hr atm.

Substituting these values into the calculated Kπ expression, $(1.9 \times 10^{-7}\text{cm}^2/\text{hr.atm})(\pi) = 1.13 \times 10^{-4}$ cm²hr gives π=600 atm at t=0. As a method for evaluating the efficiency of a polymer with respect to duration of zero order driving force, the percent of water uptake was selected before the water flux values decreased to 90% of their initial values. The value of the slope for the equation of a straight line emanating from the percent weight gained axis will be equal to the initial value of dy/dt evaluated at t=0, with the y intercept c defining the linear swelling time, with $(dy/dt)_0 = 0.665$ and the y intercept=0, which yields y=0.665t+0.359. In order to determine when the value of the cumulative water uptake is 90% below the initial rate, the following expression is solved for t:

$$0.9 = \frac{at^2 + bt + c}{bt + c} = \left(\frac{\Delta W}{w}\right)_{0.9} \quad (22)$$

$$\frac{-0.00106\ t^2 + 0.665\ t + 0.359}{0.665\ t + 0.359} = 0.9, \text{ and} \quad (23)$$

solving for t,

$$-0.00106t^2 + 0.0065t + 0.0359 = 0 \quad (24)$$

$$t = \frac{-0.0665 \pm [(0.0665)^2 - 4(-0.00106)(0.0359)]^{\frac{1}{2}}}{2(-0.00106)}$$

t=62 min and the weight gain is $-0.00106(62)^2 + (0.665)(62) + 0.359 = 38$ μl, with the initial sample weight=100 mg, thus $(\Delta w/w)_{0.9} \times 100 = 38\%$. The results are presented in FIG. 8 for a graphical representation of the values. Other methods available for studying the hydrogel solution interface include rheologic analysis, viscometric analysis, ellipsometry, contact angle measurements, electrokinetic determinations, infrared spectroscopy, optical microscopy, interface morphology and microscopic examination of an operative device.

The expression active agent as used herein, includes any beneficial agent, or beneficial compound, that can be delivered from the device to produce a beneficial and useful result. The agent can be insoluble to very soluble in the exterior fluid that enters the device and it can be mixed with an osmotically effective compound and an osmopolymer. The term active agent includes algicide, antioxidant, air purifier, biocide, bactericide, catalyst, chemical reactant, disinfectant, fungicide, fermentation agent, fertility inhibitor, fertility promoter, germicide, herbicide, insecticide, microorganism attenuator, pesticide, plant growth promoter, plant growth inhibitor, preserative, rodenticide, sterilization agent, sex sterilant, and the like.

In the specification and the accompanying claims, the term beneficial agent also includes drugs. The term drugs includes any physiologically or pharmacologically active substance that produces a local or systemic effect, in animals, including warm blooded mammals, humans and primates; avians; household, sport and farm animals; laboratory animals; fishes; reptiles and zoo animals. The term physiologically, as used herein, denotes the administration of a drug to produce generally normal levels and functions. The term pharmacologically denotes generally variations in response to amount of drug administered to the host. See *Stedman's Medical Dictionary*, 1966, published by Williams and Wilkins, Baltimore, MD. The phrase drug formulation as used herein means the drug is in the compartment mixed with an osmotic solute and/or an osmopolymer and, if applicable, and with a binder and lubricant. The active drug that can be delivered includes inorganic and organic compounds. The term drug includes, for example, muscle relaxants, anti-parkinson agents, analgesics, anti-inflammatory agents, local anesthetics, muscle contractants, anti-microbials, anti-malarials, hormonal agents, contraceptives, sympathomimetics, diuretics, anti-parasitics, neoplastics, hypoglycemics, ophthalmics, electrolytes and diagnostic agents.

Exemplary drugs that are very soluble in water and can be delivered by the devices of this invention include prochlorperazine edisylate, ferrous sulfate, aminocaproic acid, potassium chloride, mecamylamine hydrochloride, procainamide hydrochloride, amphetamine sulfate, benzphetamine hydrochloride, isoproternol sulfate, methamphetamine hydrochloride, phenmetrazine hydrochloride, bethanechol chloride, methacholine chloride, pilocarpine hydrochloride, atropine sulfate, methascopolamine bromide, atropine sulfate, isopropamide iodide, tridihexethyl chloride, phenformin hydrochloride, methylphenidate hydrochloride, oxprenolol hydrochloride, metoprolol tartrate, cimetidine hydrochloride, theophylline cholinate, cephalexin hydrochloride, and the like.

Exemplary drugs that are poorly soluble in water and that can be delivered by the devices of this invention include diphenidol, prochlorperazine maleate, phenoxybenzamine. thiethylperazine maleate, anisindone, diphenadione erythrityl tetranitrate, dizoxin, isofurophate, reserpine, acetazolamide, methazolamide, bendroflumethiazide, chlorpropamide, tolazamide, clormadinone acetate, phenaglycodol, allopurinol, aluminum aspirin, methotrexate, acetyl sulfisoxazole, erthromycin, progestins, esterogenic progestational, corticosteroids, hydrocortisone, hydrocorticosterone acetate, cortisone acetate, triamcinolone, methyltesterone, 17β-estradiol, ethinyl estradiol, ethinyl estradiol 3-methyl ether, pednisolone, 17β-hydroxyprogesterone acetate,

19-nor-progesterone, norgestrel, norethindone, norethiderone, progesterone, norgesterone, norethynodrel, and the like.

Examples of other drugs that can be delivered by the osmotic device include aspirin, indomethacin, naproxen, fenoprofen, sulidac, diclofenac, indoprofen, nitroglycerin, propranolol, metoprolol, valproate, oxprenolol, timolol, atenolol, alprenolol, cimetidine, clonidine, imipramine, levodopa, chloropromazine, reserpine, methyldopa, dihydroxyphenylalanine, pivaloyloxyethyl, ester of α-methyldopa hydrochloride, theophylline, calcium gluconate, ketoprofen, ibuprofen, cephalexin, erythromycin, zomepirac, ferrous lactate, vincamine, diazepam, phenoxybenzamine. The beneficial drugs are known to the art in *Pharmaceutical Sciences*, 1979, 14th Ed., edited by Remington, published by Mack Publishing Co., Easton, PA; *The Drug, The Nurse, The Patient, Including Current Drug Handbook*, 1974–1976, by Falconer, et al., published by Saunder Company, Philadelphia, PA; and *Medicinal Chemistry*, 3rd Ed., Vol. 1 and 2, by Burger, published by Wiley-Interscience, New York.

The drug can be in various forms, such as uncharged molecules, molecular complexes, pharmacologically acceptable salts such as hydrochloride, hydrobromide, sulfate, laurylate, palmitate, phosphate, nitrite, borate, acetate, maleate, tartrate, oleate and salicylate. For acidic drugs, salts of metals, amines or organic cations; for example, quaternary ammonium can be used. Derivatives of drugs such as ester, ethers and amides can be used. Also, a drug that is water insoluble can be used in a form that is a water soluble derivative thereof to serve as a solute, and on its release from the device, is converted by enzymes, hydrolyzed by body pH or other metabolic processes to the original biologically active form. The agent, including drug, can be present in the compartment with a binder, dispersant, wetting agent, suspending agent, lubricant and dye. Representative of these include suspending agents such as acacia, agar, calcium carrageenan, alginic acid, algin, agarose powder, collagen, colloidal magnesium silicate, pectin, gelatin and the like; binders like polyvinyl pyrrolidone, lubricants such as magnesium stearate; wetting agents such as fatty amines, fatty quaternary ammonium salts, and the like. The phrase drug formulation indicates the drug is present in the compartment accompanied by an osmagnet, osmopolymer, a binder, and the like. The amount of beneficial agent in a device generally is about from 0.05 ng to 5 g or more, with individual devices containing, for example, 25 ng, 1 mg, 5 mg, 125 mg, 250 mg, 500 mg, 750 mg, 1.5 g, and the like. The devices can be administered one, twice or thrice daily.

The solubility of a beneficial agent in the fluid can be determined by known techniques. One method consists of preparing a saturated solution comprising the fluid plus the agent as ascertained by analyzing the amount of agent present in a definite quantity of the fluid. A sample apparatus for this purpose consists of a test tube of medium size fastened upright in a water bath maintained at constant temperature and pressure, in which the fluid and agent are placed and stirred by a rotating glass spiral. After a given period of stirring, a weight of the fluid is analyzed and the stirring continued an additional period of time. If the analysis shows no increase of dissolved agent after successive periods of stirring, in the presence of excess solid agent in the fluid, the solution is saturated and the results are taken as the solubility of the product in the fluid. If the agent is soluble, an added osmotically effective compound optionally may be not needed; if the agent has limited solubility in the fluid, then an osmotically effective compound can be incorporated into the device. Numerous other methods are available for the determination of the solubility of an agent in a fluid. Typical methods used for the measurement of solubility are chemical and electrical conductivity. Details of various methods for determining solubilities are described in *United States Public Health Service Bulletin*, No. 67 of the Hygienic Laboratory; *Encyclopedia of Science and Technology*, 1971, Vol. 12, pp 542 to 556, published by McGraw-Hill, Inc.; and *Encyclopedia Dictionary of Physics*, 1962, Vol. 6, pp 547 to 557, published in Pergamon Press, Inc.

The osmotic device of the invention is manufactured by standard techniques. For example, in one embodiment the beneficial agent is mixed with an osmagent and osmopolymer, and pressed into a solid possessing dimensions that correspond to the internal dimensions of the compartment adjacent to the passageway; or the beneficial agent and other formulation forming ingredients and a solvent are mixed into a solid or a semisolid by conventional methods such as ballmilling, calendering, stirring or rollmilling, and then pressed into a preselected shape. Next, a layer of a composition comprising an osmagent and an osmopolymer is laced in contact with the layer of beneficial agent formulation, and the two layers surrounded with a semipermeable wall. The layering of the beneficial agent composition and the osmagent/osmopolymer can be accomplished by conventional two-layer tablet press techniques. The wall can be applied by molding, spraying, or dipping the pressed shapes into wall-forming materials. Another and presently preferred technique that can be used for applying the wall is the air suspension coating procedure. This procedure consists in suspending and tumbling the pressed compositions in a current of air and a wall forming composition until the wall surrounds and coats the two pressed compositions. The procedure is repeated with a different lamina forming composition to form a laminated wall. The air suspension procedure is described in U.S. Pat. No. 2,799,241; *J. Am. Pharm. Assoc.*, 1979, Vol. 48, pp 451 to 459; and, ibid, 1960, Vol. 49, pp 82 to 84. Other standard manufacturing procedures are described in *Modern Plastics Encyclopedia*, 1969, Vol. 46, pp 62 to 70; and in *Pharmaceutical Sciences*, by Remington, 1970, 14th Ed., pp 1626 to 1978, published by Mack Publishing Co., Easton, PA.

Exemplary solvents suitable for manufacturing the laminates and laminae include inert inorganic and organic solvents that do not adversely harm the materials and the final laminated wall. The solvents broadly include members selected from the group consisting of aqueous solvents, alcohols, ketones, esters, ethers, aliphatic hydrocarbons, halogenated solvents, cycloaliphatics, aromatics, heterocyclic solvents, and mixtures thereof. Typical solvents include acetone, diacetone alcohol, methanol, ethanol, isopropyl alcohol, butyl alcohol, methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, methyl propyl ketone, n-hexane, n-heptane, ethylene glycol monoethyl ether, ethylene glycol monoethyl acetate, methylene dichloride, ethylene dichloride, propylene dichloride, carbon tetrachloride, chloroform, nitroethane, nitropropane, tetrachloroethane, ethyl ether, isopropyl ether, cyclohexane, cyclo-octane, benzene, toluene, naphtha, 1,4-dioxane, tetrahydrofuran, diglyme, water and mixtures thereof, such as acetone and water,

acetone and methanol, acetone and ethyl alcohol, methylene dichloride and methanol, and ethylene dichloride and methanol.

DETAILED DESCRIPTION OF EXAMPLES

The following examples are merely illustrative of the present invention, and they should not be considered as limiting the scope of the invention in any way, as these examples and other equivalents thereof will become apparent to those versed in the art in the light of the present disclosure, the drawings and the accompanying claims.

EXAMPLE 1

An osmotic, therapeutic device for the delivering of the drug sodium diclofenac for uses as an anti-inflammatory is prepared by first pressing in a Manesty press an osmotic drug composition containing 75 mg of sodium diclofenac, 300 mg of sorbitol, 30 mg of sodium bicarbonate, 26 mg of pectin, 10 mg of polyvinyl pyrrolidone, and 5 mg of stearic acid, and pressing the composition in a cavity to a solid layer. Next, the cavity is charged with a second and greater force generating composition comprising 122 mg of pectin having a molecular weight of 90,000 to 130,000, 32 mg of mannitol, 20 mg of polyvinyl pyrrolidone, and 2 mg of magnesium stearate and pressed to form a second layer in contacting relation with the first layer. The second layer has a density of 1.28 g/cm^3 and a hardness score of greater than 12 kP. Next, the two layer core is surrounded with a semipermeable wall comprised by coating 85 g of cellulose acetate having an acetyl content of 39.8%, and 15 g of polyethylene glycol 4000, 3 wt/wt percent solid in a wall forming solvent comprising 1,960 ml of methylene chloride and 819 ml of methanol. The coated device is dried for 72 hrs. at 50° C., and then a 0.26 mm diameter passageway is laser drilled through the wall. The semipermeable wall is 0.1 mm thick, the device has an area of 3.3 cm^2, and it has an average rate of drug release of 5.6 mg per hour over a 12 hour period. The cumulative amount released is illustrated in FIG. 9. The small vertical bars represent the minimum and maximum drug release for five systems measured at that time.

EXAMPLE 1A

The procedure of Example 1 is followed for providing an osmotic device wherein the compartment contained a blend of osmopolymers. The compartment contained a first composition weighing 312 mg and consists of 48% sodium diclofenac drug, 38% poly(ethylene oxide)osmopolymer having a molecular weight of 200,000, 10% poly(ethylene glycol)osmopolymer having a molecular weight of 20,000, 2% sodium chloride, and 2% magnesium stearate; and, a second composition weighing 150 mg and consisting of 93% poly(ethylene oxide) having a molecular weight of 5,000,000, 5% sodium chloride, and 2% magnesium stearate.

EXAMPLE 2

In this example, the increase in osmotic pressure for a number of compositions comprising an osmagent and as osmopolymer are made for demonstrating the operative advantage provided by the invention. The measurements are made by measuring the amount of water imbibed across the semipermeable wall of a bag containing an osmagent, or an osmopolymer, or a composition comprising an osmagent and an osmopolymer. The semipermeable wall of the bag is formed of cellulose acetate having an acetyl content of 39.8% The measurements are made by weighing the dry ingredients of the semipermeable bag, followed by weighing the blotted semipermeable bag, after the bag is in a water bath at 37° C. for various lengths of time. The increase in weight is due to water imbibition across the semipermeable wall caused by the osmotic pressure gradient across the wall. The osmotic pressure curves are illustrated in FIG. **10**. In FIG. **10** the curved line with the triangles represents the osmotic pressure for poly(ethylene)oxide having a molecular weight of 5,000,000; the curved line with the circles represents the osmotic pressure for a composition comprising poly(ethylene)oxide having a molecular weight of 5,000,000 and sodium chloride with the ingredients present in the composition in the ratio of 9.5 parts osmopolymer to 0.5 parts osmagent; the curved line with squares represents a composition comprising the same osmopolymer and osmagent in the ratio of 9 parts osmopolymer to one part osmagent; the curved lines with hexagon represents the same composition comprising the osmopolymer and osmagent in the ratio of 8 parts to 2 parts; and, the dashed lines represent the osmagent sodium chloride. The mathematical calculations are made using the formula $dw/dt = A(K\pi)/h$, wherein dw/dt is the rate of water imbibition over time, π is the osmotic pressure, A is the area of the semipermeable wall, h is the semipermeable wall thickness, and K is the permeability coefficient. Also, in FIG. **10**, W_H/W_p is the amount of water imbibed divided by the weight of osmopolymer plus osmagent.

EXAMPLE 3

An osmotic therapeutic device for dispensing sodium diclofenac is prepared by screening through a 40 mesh screen a composition comprising 49% of sodium diclofenac, 44% poly(ethylene)oxide having a molecular weight of 100,000, 2% sodium chloride and 3% hydroxypropylmethylcellulose, and then blending the screened composition with an alcohol solvent used in the ratio of 75 ml of solvent to 100 g of granulation. The wet granulation is screened through a 16 mesh screen, dried at room temperature for 48 hours under vacuum, passed through a 16 mesh screen, and blended with 2% 80 mesh screen magnesium stearate. The composition is compressed as described above.

Next a composition comprising 73.9% of pectin having a molecular weight of 90,000 to 130,000, 5.8% microcrystalline cellulose, 5.8% polyvinyl pyrrolidone, 14.3% sodium chloride and 2% sucrose is passed through a 40 mesh screen, blended with an organic solvent in the ratio of 100 ml of solvent to 100 g of granulation of 25 minutes, passed through a 16 mesh screen, dried for 48 hours at room temperature under vacuum, again passed through a 16 mesh screen, blended with 2% magnesium stearate, and then compressed onto the compressed layer described in the above paragraph. The dual layered drug core is coated by dipping in a wall forming composition comprising 80% cellulose acetate having an acetyl content of 39.8%, 10% polyethylene glycol 4000, and 10% hydroxypropylmethylcellulose. A passageway is drilled through the wall communicating with the drug containing composition. The passageway diameter is 0.38 mm. The cumulative release profile for the device is depicted

in FIG. 11. FIG. 12 depicts the release rate in mg per hour for the osmotic device.

EXAMPLE 4

The procedure of Example 3 is repeated with all conditions as described except that the osmopolymer in the drug composition is polyoxyethylene polyoxypropylene block copolymer having a molecular weight of about 12,500.

EXAMPLE 5

An osmotic device is made by following the above procedures. The device of this example comprises a single composition comprising 50% of sodium diclofenac, 46% of poly(ethylene)oxide having a molecular weight of 100,000, 2% sodium chloride and 2% magnesium stearate. The device has a semipermeable wall comprising 90% cellulose acetate comprising 39.8% acetyl, and 10% polyethylene glycol 4000. The cumulative amount released for this device comprising the single composition is 40% of the device comprising two compositions. The cumulative amount released is illustrated in FIG. 13.

EXAMPLE 6

The in vivo and in vitro mean cumulative releases of diclofenac sodium from an osmotic device comprising a first osmotic composition comprising 75 mg of diclofenac sodium, 67 mg of poly(ethylene)oxide having a molecular weight of 100,000, 3.0 mg of sodium chloride, 4.5 mg of hydroxypropylmethylcellulose and 3.0 mg of magnesium stearate; a second osmotic composition distant from the releasing passageway comprising 51 mg of poly(theylene)oxide having a molecular weight of 5,000,000, 22.5 mg of sodium chloride, and 1.5 mg of magnesium stearate; and, surrounded by a semipermeable wall comprising 90% cellulose acetate having an acetyl content of 39.8% and 10% polyethylene glycol 4000 was measured in vivo and in vitro in laboratory dogs. The amounts of drug released at various times in vivo were determined by administering a series of devices to the animal and measuring the amount released from the corresponding device at the appropriate residence time. The results are depicted in FIG. 14, wherein the circles with the bars are the in vitro means cumulative releases and the triangles with the bars are the in vivo means cumulative releases.

EXAMPLE 7

The procedure of Example 10 is followed for making an osmotic therapeutic delivery system comprising: a first or drug composition weighing 638 mg and consisting of 96% cephalexin hydrochloride, 2% Povidone (polyvinyl pyrrolidone) and 2% magnesium stearate; a second, or osmotic deriving composition weighing 200 mg and consisting of 68.5% poly(ethylene oxide) having a molecular weight of 5×10^6, 29.4% sodium chloride, and 2% magnesium stearate; a semipermeable wall weighing 55.8 mg consisting of 80% cellulose acetate having an acetyl content of 39.8%, 10% polyethylene glycol 4000, and 10% hydroxypropylmethylcellulose; and an osmotic orifice having a diameter of 0.039 mm. The device has an average rate of release of about 54 mg per hour over a period of 9 hours.

The novel osmotic system of this invention used dual means for the attainment of precise release rate of drugs that are difficult to deliver in the environment of use, while simultaneously maintaining the integrity and the character of the system. The novel osmotic system of this invention unexpectedly and unobviously achieves controlled delivery while using at least two molecularly or structurally different polymers that exhibit different osmotic pressure gradients across a semipermeable wall, exhibit different rates of fluid imbibition through the semipermeable wall, exhibit different rates of expansion in the presence of fluid imbibed into the osmotic system, and exhibit different physical and chemical kinetics while in operation acting as a integrated unit for dispensing a beneficial agent at meaningful rates and at useful amounts from the osmotic system. While there has been described and pointed out features and advantages of the invention as applied to the presently preferred embodiments, those skilled in the dispensing art will appreciate that various modifications, changes, additions, and omissions in the system illustrated and described can be made without departing from the spirit of the invention.

We claim:

1. An osmotic device for the delivery at a controlled rate a beneficial agent to an environment of use, the osmotic device comprising:

(a) a wall comprising in at least a part a semipermeable composition permeable to the passage of an exterior fluid present in the environment of use and substantially impermeable to the passage of a beneficial agent, the wall surrounding and forming:

(b) a compartment;

(c) a first composition in the compartment, said first composition comprising a beneficial agent, an osmagent that exhibits an osmotic pressure gradient across the wall against an external fluid, and an osmopolymer that exhibits an osmotic pressure gradient across the wall against an external fluid;

(d) a second composition in the compartment, said second composition comprising an osmagent that exhibits an osmotic pressure gradient across the wall against an external fluid, and an osmopolymer that exhibits an osmotic pressure gradient across the wall against an external fluid; and,

(e) at least one passageway in the wall communicating with the first composition and the exterior of the device for delivering the beneficial agent through the passageway from the device.

2. The osmotic device for the delivery at a controlled rate the beneficial agent according to claim 1, wherein the semipermeable composition is a member selected from the group consisting of cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate and cellulose triacetate.

3. The osmotic device for the delivery at a controlled rate the beneficial agent according to claim 1, wherein the beneficial agent is a member selected from the group consisting essentially of algicide, germicide, herbicide, fungicide, insecticide and pesticide.

4. The osmotic device for the delivery at a controlled rate the beneficial agent according to claim 1, wherein the first composition is in the compartment as a layer, and the second composition is in the compartment as a layer.

5. The osmotic device for the delivery at a controlled rate the beneficial agent according to claim 1, wherein the first composition imbibes external fluid through the wall into the compartment, and the second composition imbibes external fluid through the wall into the compartment.

6. The osmotic device for the delivery at a controlled rate the beneficial agent according to claim 1, wherein the osmopolymer comprising the second composition has a molecular weight greater than the molecular weight of the osmopolymer comprising the first composition.

7. An osmotic device for the controlled delivery of a beneficial drug to a biological environment of use, comprising:

(a) a shaped wall permeable in at least a part to the passage of an exterior fluid present in the environment of use, and substantially impermeable to the passage of drug, the wall surrounding and forming:

(b) a compartment comprising: (1) a composition comprising a dosage amount of a drug, an osmotically effective compound that exhibits an osmotic pressure gradient across the wall against an external fluid, and a polymer that exhibits an osmotic pressure gradient across the wall against an external fluid, and (2) a composition comprising an osmotically effective compound that exhibits an osmotic pressure gradient across the wall against an external fluid, and a polymer that exhibits an osmotic pressure gradient across the wall against an external fluid; and,

(c) at least one passageway in the wall communicating with the exterior of the device and the composition comprising the drug for delivering a therapeutically effective amount of drug from the device at a controlled rate over a prolonged period of time.

8. The osmotic device for the controlled delivery of the beneficial drug to the biological environment of use according to claim 7, wherein the device when in operation in the environment of use, the osmotically effective compound present in composition (1) comprising the drug imbibes fluid through the wall into the compartment and the polymer present in said composition (1) imbibes fluid through the wall into the compartment for osmotically delivering the drug from the osmotic device.

9. The osmotic device for the controlled delivery of the beneficial drug to the biological environment of use according to claim 7, wherein the device when in operation in the environment of use, composition (2) comprising the osmotically effective compound and the polymer imbibes fluid through the wall into the compartment.

10. The osmotic device for the controlled delivery of the beneficial drug to the biological environment of use according to claim 7, wherein the shaped wall is formed of a semipermeable material, selected from the group consisting of cellulose acylate, cellulose diacylate, and cellulose triacylate.

11. The osmotic device for the controlled delivery of the beneficial drug to the biological environment of use according to claim 7, wherein the shaped wall is a laminate comprising a semipermeable lamina and a microporous lamina.

12. The osmotic device for the controlled delivery of the beneficial drug according to claim 7, wherein the device when in operation in the environment of use, (1) the composition comprising drug, osmotically effective compound and polymer imbibes fluid into the compartment and forms a formulation containing drug, compound and polymer, and (2) the composition comprising osmotically effective compound and polymer imbibes fluid into the compartment and forms in situ a formulation containing compound and polymer, whereby through the combined operations of (1) and (2) the formulation containing drug is delivered through the passageway from the compartment to the exterior of the osmotic device over time.

13. The osmotic device for the controlled delivery of the beneficial drug according to claim 7, wherein the polymer comprising composition (1) is water soluble.

14. The osmotic device for the controlled delivery of the beneficial drug according to claim 7, wherein the polymer comprising composition (1) is cross linked.

15. The osmotic device for the controlled delivery of the beneficial drug according to claim 7, wherein the polymer comprising composition (2) is water soluble.

16. The osmotic device for the controlled delivery of the beneficial drug according to claim 7, wherein the polymer comprising composition (2) is cross linked.

17. An osmotic device for the controlled delivery of a beneficial drug formulation to a biological environment of use, comprising:

(a) a shaped wall permeable in at least a part to the passage of an exterior biological fluid and substantially impermeable to the passage of drug formulation, which wall surrounds and forms:

(b) a compartment comprising: (1) a drug formulation, which formulation comprises a drug that is insoluble to very soluble in the biological fluid, an osmotically effective solute that is soluble in the exterior fluid and exhibits an osmotic pressure gradient across the wall against the fluid and a polymer that imbibes fluid and absorbs fluid that enters the compartment; and (2) a delivery formulation, which formulation comprises an osmotically effective solute that is soluble in the exterior fluid and exhibits an osmotic pressure gradient across the wall against the fluid and a polymer that imbibes fluid and absorbs fluid that enters the compartment; and,

(c) at least one passageway in the wall connecting the exterior of the device with the drug formulation for delivering the drug formulation from the device to the environment at a controlled rate over a prolonged period of time.

18. The osmotic device for the delivery of the beneficial drug formulation according to claim 7, wherein the biological environment of use is a human.

19. The osmotic device for the delivery of the beneficial drug formulation according to claim 7, wherein the biological environment of use is the gastrointestinal tract, and the device is shaped and adapted for oral admittance therein.

20. A composition of matter useful for forming a drug delivery system, the composition comprising in combination: (1) a first composition comprising a drug, an osmagent and an osmopolymer; and, (2) a second composition in laminar arrangement with the first composition (1), which second composition (2) comprises an osmagent and an osmopolymer, and wherein compositions (1) and (2) exhibit an osmotic pressure gradient across a semipermeable polymeric film against fluid selected from the group consisting essentially of aqueous and biological fluids.

21. The osmotic device for the delivery at a controlled rate the beneficial agent to the environment of use according to claim 1, wherein the passageway is formed in the environment of use.

22. The osmotic device for the delivery at a controlled rate the beneficial agent to an environment of

use according to claim 1, wherein the wall comprises in at least a part a microporous composition comprising a pore former that is removed during the operation of the device providing at least one passageway.

23. The osmotic device for the delivery of a beneficial drug to a biological environment of use according to claim 7, wherein the passageway is formed in the environment of use.

24. The osmotic device for the controlled delivery of a beneficial drug to a biological environment of use according to claim 7, wherein the wall comprises in at least a part a microporous composition comprising a pore former that is removed during operation of the device.

25. The osmotic device for the controlled delivery of a beneficial drug to a biological environment of use according to claim 7, wherein the wall comprises in at least a part a microporous composition comprising the pore former sorbitol that is removed from the wall during operation of the device.

26. An osmotic device for the controlled delivery of a beneficial drug formulation to a biological environment of use according to claim 17, wherein the passageway in the wall is formed in the environment of use.

27. An osmotic device for the controlled delivery of a beneficial drug formulation to a biological environment of use according to claim 17, wherein the wall comprises in at least a part a microporous composition comprising a pore former that is a member selected from the group consisting of sucrose, glucose, fructose, mannitol, mannose, galactose, aldohexose, altrose, talose, sorbitol, and lactose that is removed from the wall in the environment of use providing a passageway in the wall.

* * * * *

United States Patent [19]

Kuczynski et al.

[11] **Patent Number: 5,024,843**

[45] **Date of Patent: Jun. 18, 1991**

[54] **ORAL HYPOGLYCEMIC GLIPIZIDE GRANULATION**

[75] Inventors: **Anthony L. Kuczynski; Atul D. Ayer; Patrick S.-L. Wong,** all of Palo Alto, Calif.

[73] Assignee: **ALZA Corporation,** Palo Alto, Calif.

[21] Appl. No.: **402,314**

[22] Filed: **Sep. 5, 1989**

[51] **Int. Cl.**[5] **A61K 9/16**; A61K 31/50; A61K 47/38; A61K 47/32

[52] **U.S. Cl.** **424/499**; 424/80; 424/473; 424/501; 514/866

[58] **Field of Search** 424/475, 494, 499

[56] **References Cited**

U.S. PATENT DOCUMENTS

2,799,241	7/1957	Wurster	118/24
3,845,770	11/1974	Theeuwes et al.	128/260
3,916,899	11/1975	Theeuwes et al.	128/260
4,016,880	4/1977	Theeuwes et al.	128/260
4,063,064	12/1977	Saunders et al.	219/121 L
4,088,864	5/1978	Theeuwes et al.	219/121 LM
4,200,098	4/1980	Ayer et al.	128/260
4,285,987	8/1981	Ayer et al.	427/3
4,708,868	11/1987	Brickl et al.	514/255
4,851,232	7/1989	Vrquhart et al.	424/490

OTHER PUBLICATIONS

Martindale, *The Extra Pharmacopoeia,* 29th Ed. (1989), p. 390.

AHFS Drug Information, (1989), pp. 1741–1745.

J. Am. Phar. Assoc., Sci. Ed., vol. 48 (1959), pp. 451–459.

J. Am. Phar. Assoc., Sci. Ed., vol. 49 (1960), pp. 82–84.

Remington's *Pharmaceutical Sciences,* 14th Ed., (1970), pp. 1626–1678.

Primary Examiner—Merrell C. Cashion, Jr.

Assistant Examiner—Edward J. Webman

Attorney, Agent, or Firm—Paul L. Sabatine; Edward L. Mandell; Steven F. Stone

[57] **ABSTRACT**

A dosage form is disclosed comprising the antidiabetic drug glipizide for administering to a patient in need of glipizide therapy.

2 Claims, 2 Drawing Sheets

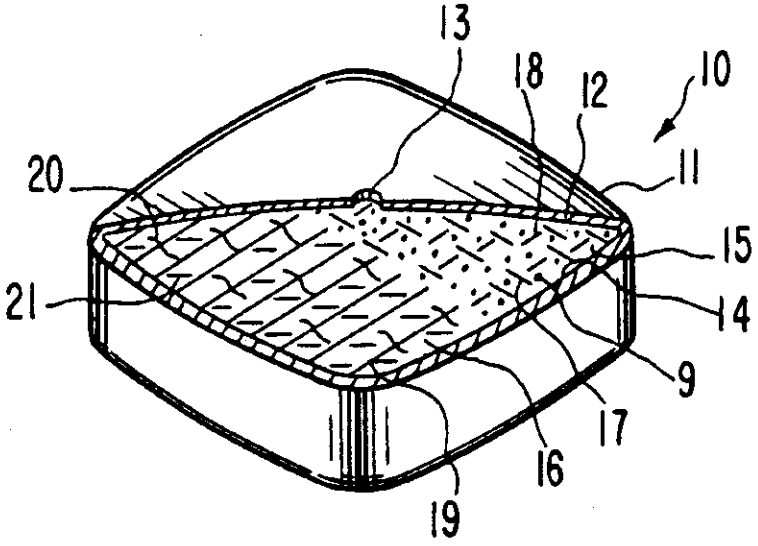


FIG. 1

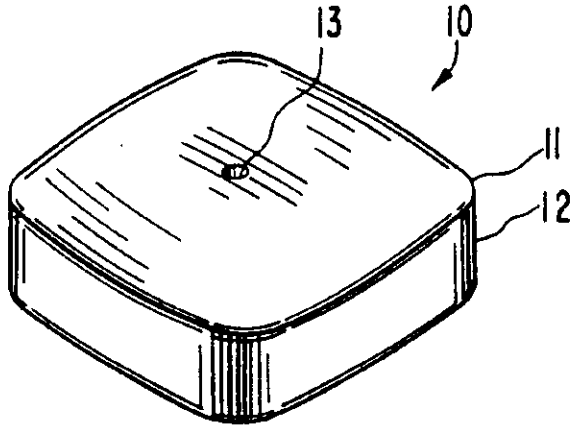


FIG. 2

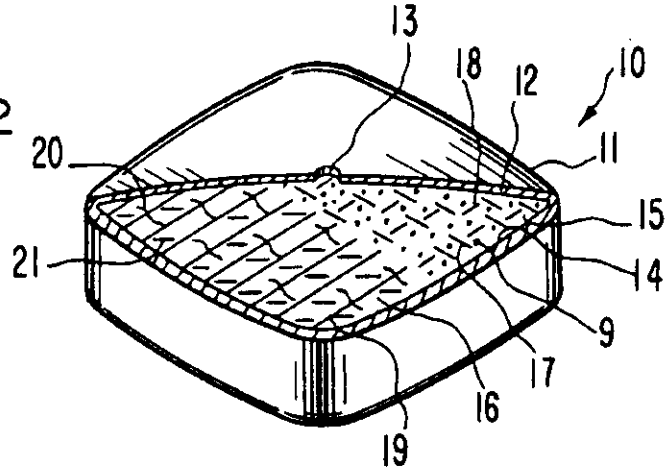


FIG. 3

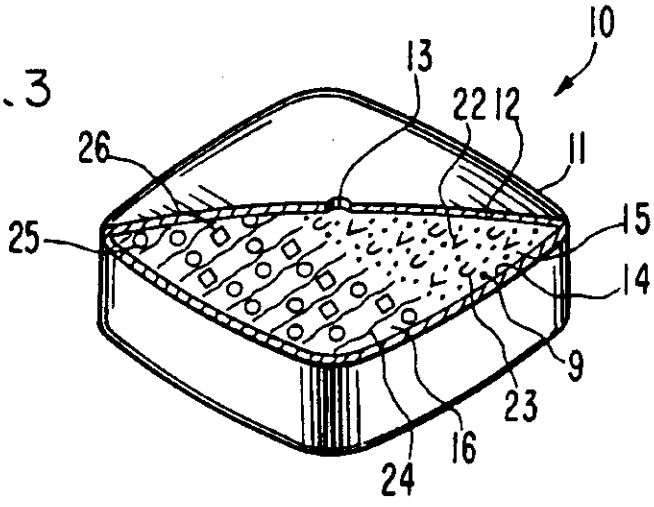


FIG. 4

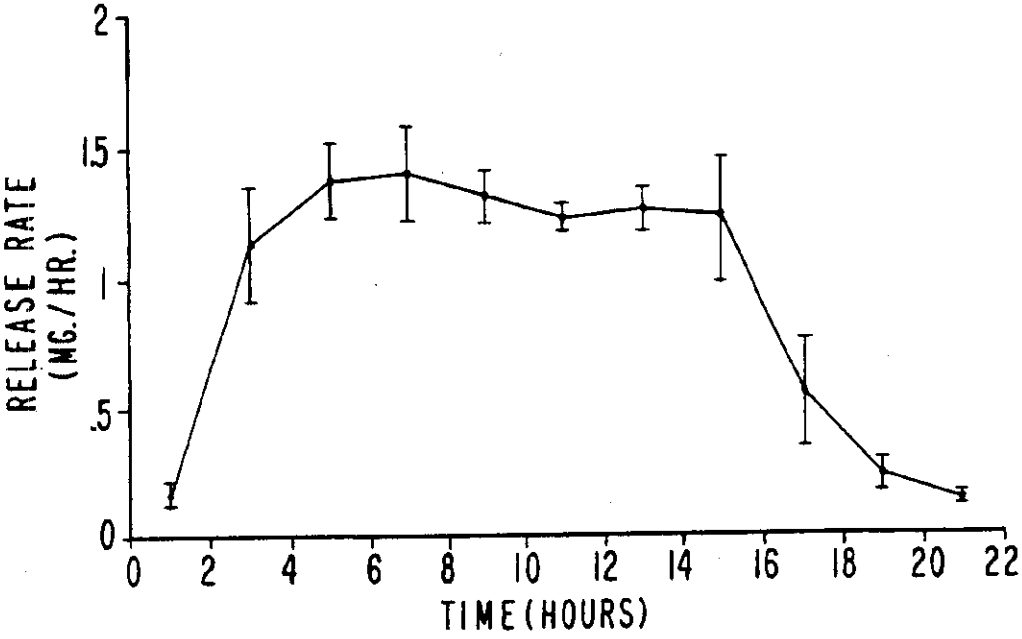
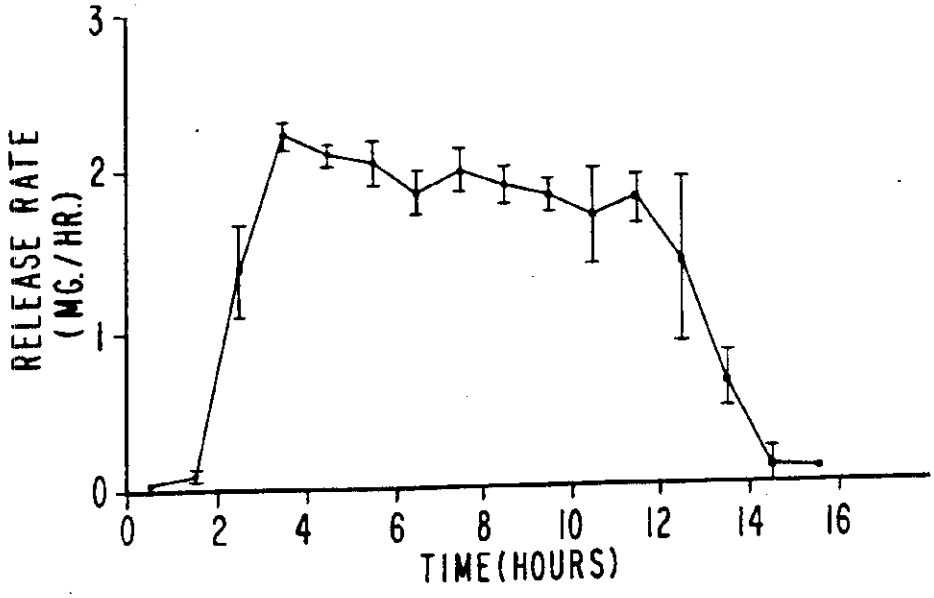

RELEASE RATE (MG./HR.)
2
1.5
1
.5
0
0 2 4 6 8 10 12 14 16 18 20 22
TIME (HOURS)

FIG. 5


RELEASE RATE (MG./HR.)
3
2
1
0
0 2 4 6 8 10 12 14 16
TIME (HOURS)

ORAL HYPOGLYCEMIC GLIPIZIDE GRANULATION

DISCLOSURE OF TECHNICAL FIELD

This invention pertains to a dosage form comprising the hypoglycemic drug glipizide. The invention concerns also a method for administering glipizide to a recipient in need of glipizide therapy.

DISCLOSURE OF BACKGROUND OF THE INVENTION

A clinical need exists for a dosage form for delivering an oral blood-glucose lowering drug to a patient needing this therapy. Glipizide is an oral blood-glucose lowering drug and it is indicated for the control of hyperglycemia and its associated symptomatology in patients with non-insulin dependent diabetes mellitus. Glipizide is useful therapeutically as an oral hypoglycemic drug because it stimulates insulin secretion from the beta cells of pancreatic-islet tissue, it increases the concentration of insulin in the pancreatic vein, and because it exhibits extrapancreatic action such as the ability to increase the number of insulin receptors.

Glipizide is known chemically as N-[2-[4-[[[(cyclohexylamino) carbonyl]amino]sulfonyl]phenyl]ethyl]-5-methylpyrazinecarboxamide. Glipizide is a white, odorless powder with a pKa of 5.9, and it is insoluble in both water and alcohol. These physical and chemical properties of glipizide do not lend the drug to formulation into a dosage form that can administer glipizide at a controlled and known rate per unit time. The properties of glipizide are disclosed in *Martindale The Extra Pharmacoooeia*, 29th Ed., p 390, (1989); and, *AHFS Drug Information*, pp 1741–45, (1989).

In the light of the above presentation, it will be appreciated by those versed in the pharmaceutical dispensing art to which this invention pertains, that a pressing need exists for a rate-controlled dosage form that can deliver the valuable drug glipizide to a patient in clinical need of blood-glucose lowering therapy. The pressing need exists also for an oral dosage form that can deliver glipizide at a controlled rate in a substantially constant dose per unit time for its beneficial therapeutic effects, and remain substantially independent of the changing environment of the gastrointestinal tract. It will be appreciated further by those skilled in the dispensing art, that if such a novel and unique dosage form is made available that can administer glipizide in a rate-controlled dose over time, and simultaneously provide blood-glucose lowering therapy, the dosage form would represent an advancement and a valuable contribution to the medical art.

DISCLOSURE OF OBJECTS OF THE INVENTION

Accordingly, in view of the above presentation, it is an immediate object of this invention to provide a dosage form for delivering glipizide in a rate controlled amount, and which dosage form substantially overcomes the deficiencies and omissions associated with the prior art.

Another object of the present invention is to provide a dosage form for orally administering glipizide in a rate-controlled dose for blood-glucose lowering therapy.

Another object of the invention is to provide a pharmaceutical dosage form that makes available controlled and sustained glipizide therapeutic activity to a patient in need of glipizide therapy.

Another object of the invention is to provide a novel dosage form manufactured as an osmotic device that can administer glipizide to a biological receptor site to produce the desired glipizide pharmacological effects.

Another object of the present invention is to provide a dosage form manufactured as an osmotic dosage form that maintains glipizide in the dosage form until released from the dosage form, thereby substantially reducing and/or substantially eliminating the unwanted influences of the gastrointestinal environment and still provide controlled administration of glipizide over time.

Another object of the present invention is to provide a dosage form that can deliver the aqueous insoluble drug glipizide at a controlled and beneficial known rate over time.

Another object of the present invention is to provide a dosage form adapted for the oral administration of glipizide and which dosage form comprise a first composition and a contacting second composition that operate in combination for the controlled administration of glipizide.

Another object of the present invention is to provide a complete pharmaceutical glipizide regimen comprising a composition comprising glipizide that can be dispensed from a drug delivery dosage form, the use of which requires intervention only for initiation and possibly for termination of the regimen.

Another object of the invention is to provide a method for treating hyperglycemia by orally administering glipizide in a ratecontrolled dose per unit time to a warm-blooded animal in need of hyperglycemia therapy.

Other objects, features and advantages of this invention will be more apparent to those versed in the dispensing arts from the following detailed specification, taken in conjunction with the drawings and the accompanying claims.

BRIEF DISCLOSURE OF THE DRAWINGS

In the drawings, which are not drawn to scale, but are set forth to illustrate various embodiments of the invention, the drawing figures are as follows:

Drawing FIG. 1 is a view of a dosage form designed and shaped for orally administering glipizide to the gastrointestinal tract of a warm-blooded animal, including humans;

Drawing FIG. 2 is an opened view of the dosage form of drawing FIG. 1 illustrating the structure of the dosage form comprising glipizide;

Drawing FIG. 3 is an opened view of the dosage form of drawing FIG. 1 depicting a different internal structure embodiment provided by the invention;

Drawing FIG. 4 is a graph that depicts the release rate pattern from one embodiment of the dosage form provided by the invention; and,

Drawing FIG. 5 is a graph that depicts the release rate pattern for a different embodiment of the dosage form provided by the invention.

In the drawing figures and in the specification like parts in related drawing figures are identified by like numbers. The terms appearing earlier in the specification and in the description of the drawings, as well as embodiments thereof, are further described elsewhere in the disclosure.

DETAILED DISCLOSURE OF THE DRAWING FIGURES

Turning now to the drawing figures in detail, which drawing figures are examples of the dosage forms provided by this invention, and which examples are not to be construed as limiting, one example of the dosage form is illustrated in drawing FIG. 1 and designated by the numeral **10**. In drawing FIG. **1**, dosage form **10** comprises a body **11**, which body member **11** comprises a wall **12** that surrounds and encloses an internal compartment, not seen in drawing FIG. 1. Dosage form **10** comprises at least one exit means **13** for connecting the interior of dosage form **10** with the exterior environment of use.

In drawing FIG. 2, dosage form **10** is seen in opened view. In drawing FIG. 2, dosage form **10** comprises a body member **11** comprising wall **12**, which wall surrounds and defines an internal compartment **14**. Wall **12** comprises at least one exit means **13** that connects internal compartment **14** with the exterior of dosage form **10**. Dosage form **10** can comprise more than one exit means **13**. Wall **12** of dosage form **10** comprises in total, or in at least a part, a composition that is permeable to the passage of an exterior fluid present in the environment, and wall **12** is substantially impermeable to the passage of glipizide and other ingredients present in compartment **14**. The composition comprising wall **12** is semipermeable, it is substantially inert, and wall **12** maintains its physical and chemical integrity during the dispensing life of glipizide from dosage form **10**. The phrase, keeps its physical and chemical integrity, means wall **12** does not lose its structure, and it does not change chemically during the glipizide dispensing life of dosage form **10**.

Wall **12**, in a presently preferred embodiment, comprises 80 weight percent (wt%) to 100 weight percent of a composition comprising a cellulose polymer. The cellulose polymer comprises a member selected from the group consisting of a cellulose ester, cellulose ether, cellulose ester-ether, cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, and cellulose triacetate. Wall **12**, in another preferred manufacture, comprises from 0 weight percent to 25 weight percent of a member selected from the group consisting of hydroxypropylcellulose and hydroxypropylmethylcellulose, and from 0 to 20 weight percent of polyethylene glycol, with the total amount of all wall-forming components comprising wall **12** equal to 100 weight percent.

Internal compartment **14** comprises an internal glipizide lamina **15**, which glipizide lamina can be defined optionally as a glipizide composition **15**. Internal compartment **14** also comprises an internal displacement lamina **16**, which displacement lamina can be defined optionally as a displacement composition **16**. The glipizide lamina **15** and the displacement lamina **16** initially are in laminar arrangement and they cooperate with each other and with dosage form **10** for the effective delivery of glipizide from dosage form **10**.

The glipizide composition **15**, in a presently preferred embodiment, as seen in FIG. 2, comprises about 2.0 mg to 50 mg of glipizide identified by dots **9**; from 100 mg to 320 mg of a polyethylene oxide comprising 80,000 to 350,000 molecular weight and identified by dashes **17**; from 5 mg to 50 mg of hydroxypropylmethylcellulose comprising a 9,200 to 22,000 molecular weight and identified by vertical lines **18**; and from 0 mg to 7.5 mg of a lubricant such as stearic acid, magnesium stearate, and the like.

The displacement lamina **16**, as seen in drawing FIG. **2**, comprises 70 mg to 125 mg of a polyethylene oxide comprising a 4,000,000 to 8,000,000 molecular weight identified as lines **19**; from 20 mg to 50 mg of an osmagent selected from the group consisting of sodium chloride and potassium chloride identified by wavy line **20**; and from 5 mg to 15 mg of a hydroxypropylmethylcellulose having a 9,000 to 25,000 molecular weight identified by vertical slashes **21**. Displacement lamina **16** optionally comprises from 0.1 mg to 5 mg of ferric oxide and from 0.01 mg to 5 mg of a lubricant such as magnesium stearate or stearic acid.

Drawing FIG. 3 depicts in opened section another osmotic dosage form **10** provided by the invention. In drawing FIG. 3, dosage form **10** comprises a body **11**, a wall **12**, which wall **12** surrounds an internal compartment **14** with an exit passageway **13** in wall **12**. Internal compartment **14**, in this dosage form, comprises an internal glipizide lamina **15**, which glipizide lamina **15** comprises 2 mg to 25 mg of aqueous insoluble drug glipizide identified by dots **9**; from 100 mg to 150 mg of a hydroxypropylcellulose comprising a 40,000 to 80,000 molecular weight identified by angle **22**; and from 40 mg to 70 mg of a polyvinylpyrrolidone comprising a 30,000 to 70,000 molecular weight and identified by half circle **23**. Internal compartment **14** comprises a displacement lamina **16** comprising 30 mg to 150 mg of sodium carboxymethylcellulose having 200,000 to 1,000,000 molecular weight identified by wavy lines **24**; from 20 mg to 70 mg of an osmagent selected from the group consisting of sodium chloride and potassium chloride identified by circle **25**; and from 0.5 mg to 10 mg of a hydroxypropylmethylcellulose comprising a 9,200 to 22,000 molecular weight identified by squares **26**. Displacement lamina **16** optionally comprises from 0 mg to 5 mg of ferric oxide and optionally 0 mg to 7 mg of a lubricant.

The expression, "exit means **13**,' as used herein, comprises means and methods suitable for the controlled metered release of glipizide **9** from compartment **14** of dosage form **10**. The exit means **13** comprises at least one passageway, orifice, or the like, through wall **12** for communication with glipizide **9** in compartment **14**. The expression, "at least one passageway,' includes aperture, orifice, bore, pore, or porous element through which glipizide can be released, or hollow fiber, capillary tube, porous overlay, porous insert, and the like. The expression also includes a material that erodes or is fluid-leached from wall **12** in a fluid environment of use to produce at least one pore-passageway of governed release rate pore-size in wall **12**. Representative materials suitable for forming at least one passageway, or a multiplicity of passageways, comprise an erodible polyglycolic acid, or a polylactic acid member in wall **12**, a gelatinous filament, polyvinyl alcohol, leachable materials such as a fluid removable pore forming polysaccharide, salt, oxide, polyol, or the like. A passageway or a plurality of passageways can be formed by leaching a material such as sorbitol, lactose, or the like, from wall **12**. The passageway can have any shape such as round, triangular, square, elliptical, and the like, for assisting in the metered release of glipizide **9** from dosage form **10**. Dosage form **10** can be constructed with one or more passageways in spaced apart relations, or more than one passageway on a single surface of dosage form **10**. Passageways and equipment for forming passageways are

disclosed in U.S. Pat. Nos. 3,845,770 issued 11/74 to Theeuwes et al; 3,916,899 issued 11/75 to Theeuwes et al; 4,016,880 issued 4/77 to Theeuwes et al; 4,063,064 issued 12/77 to Saunders et al; 4,088,864 issued 5/78 to Theeuwes et al; and, passageways formed by leaching are disclosed in U.S. Pat. Nos. 4,200,098 issued 4/80 to Ayer et al; 4,235,236 issued 11/80 to Theeuwes; and, 4,285,987 issued to Ayer et al.

Dosage form 10 of this invention is manufactured by standard techniques. For example, in one manufacture the drug glipizide is mixed with other composition-forming ingredients and the mix then pressed into a solid lamina possessing dimensions that correspond to the internal dimensions of the compartment space adjacent to the passageway. In another embodiment the beneficial drug glipizide and other composition forming ingredients and a solvent are mixed into a solid, or into a semisolid, by conventional methods such as ballmilling, calendering, stirring, or rollmilling, and then pressed into a preselected lamina forming shape. Next, a lamina composition comprising the osmopolymer and the osmagent are placed in contact with the lamina comprising the beneficial drug glipizide, and the two lamina comprising the laminate are surrounded with a semipermeable wall. The lamination of the glipizide composition and the osmopolymer displacement composition can be accomplished by using a two-layer tablet press technique. The wall can be applied by molding, spraying, or dipping the pressed shapes into wall-forming formulations. Another preferred technique that can be used for applying the wall is the air suspension coating procedure. This procedure consists in suspending and tumbling the two layered laminate in a current of air until the wall forming composition surrounds the laminate. The air suspension procedure is described in U.S. Pat. No. 2,799,241; in *J. Pharm. Assoc.. Sci. Ed.*, Vol. 48 pp 451-59 (1959); and *ibid.* Vol. 49, pp 82-84, (1960). Other standard manufacturing procedures are described in *Modern Plastics Encyclooedia.* Vol. 46, pp 62-70, (1969); and in *Pharmaceutical Sciences*, by Remington, 14th Ed., pp 1626-1978, (1970), published by Mack Publishing Co., Easton, PA.

Exemplary solvents suitable for manufacturing the wall, the laminate, and laminae, comprise inert inorganic and organic solvents that do not adversely affect the final wall and the final laminates. The solvents broadly comprise a member selected from the group consisting of aqueous solvents, alcohols, ketones, esters, ethers, aliphatic hydrocarbons, halogenated solvents, cycloaliphatics, aromatics, heterocyclic solvents, and mixtures thereof. Typical solvents comprise acetone, diacetone, alcohol, methanol, ethanol, isopropyl alcohol, butyl alcohol, methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, methylpropyl ketone, n-hexane, n-heptane, ethylene glycol monoethyl ether, ethylene glycol monoethyl acetate, methylene dichloride, ethylene dichloride, propylene dichloride, acetone and water, acetone and methanol, acetone and ethyl alcohol, methylene dichloride and methanol, ethylene dichloride and methanol, and the like.

DETAILED DISCLOSURE OF EXAMPLES OF THE INVENTION

The following examples are merely illustrative of the present invention, and they should not be considered as limiting the scope of this invention in any way, as these examples and other equivalents thereof will become apparent to those versed in the art in the light of the present disclosure, the drawings and the accompanying claims.

EXAMPLE 1

An oral dosage form, adapted, designed and shaped as an osmotic drug delivery system for admittance into the gastrointestinal tract of a patient in need of glipizide is manufactured as follows: first, 369 g of pharmaceutically acceptable hydroxypropylcellulose comprising a 60,000 average molecular weight is passed through a 20 mesh screen, followed by passing through a 40 mesh screen 162 g of pharmaceutically acceptable polyvinylpyrrolidone comprising a 40,000 average molecular weight. Next, the two screened ingredients are blended with 66 g of glipizide to form a homogeneous blend. The blend is suspended in a fluidized bed and sprayed with an atomized spray comprising an ethanol:water (70:30 vol:vol) solution until granules are formed of the three ingredients. The freshly prepared granules then are passed through a 20 mesh screen. Finally, the screened granulation is mixed with 3 g of magnesium stearate in a rollermill for 5 minutes.

Next, a separate hydrogel granulation is prepared as follows: first, 389 g of pharmaceutically acceptable sodium carboxymethylcellulose having 700,000 molecular weight, 174 g of sodium chloride, 30 g of pharmaceutically acceptable hydroxypropylmethylcellulose comprising a 11,200 molecular weight and 6 g of ferric oxide separately are screened through a 40 mesh screen. Then, all the screened ingredients are mixed to produce a homogeneous blend. Next, 300 ml of denatured anhydrous ethanol is added slowly to the blend with continuous mixing for about 5 minutes. The freshly prepared wet granulation is screened through a 20 mesh screen, allowed to dry at room temperature for 16 hours, and again passed through a 20 mesh screen. The screened granulation is mixed with 1.5 g of magnesium stearate in a rollermill for about 5 minutes.

Next, the glipizide granulation, and the hydrogel granulation are compressed into a bilaminate tablet arrangement. First, 200 mg of the glipizide composition is added to a 0.375 inch (9.5 mm) punch and tamped, then, 140 mg of the hydrogel granulation is added to the punch and the two laminae are pressed into a solid, contacting arrangement.

Next, the bilaminate is coated with a semipermeable wall. The semipermeable wall-forming composition comprises 93% cellulose acetate having a 39.8% acetyl content, and 7% polyethylene glycol having a 3350 molecular weight. The wall-forming composition is dissolved in a cosolvent comprising acetone: water (90:10 wt:wt) to onto and around the bilaminate in an Aeromatic ® Air Suspension Coater.

Then, a 25 mil (0.635 mm) exit orifice is mechanically drilled on the glipizide side of the osmotic dosage form. The residual solvent is removed by drying the osmotic system for 48 hours at 50° C. and 50% humidity. The osmotic systems are dried for 1 hour at 50° C. to remove excess moisture. Attached drawing FIG. 4 shows the in vitro release rate profile for glipizide from the finished osmotic system as released in distilled water. The error bars represent the standard deviation added to and subtracted from the mean of five osmotic delivery system. An osmotic dosage form provided by the invention comprises 11 wt% glipizide, 61.50 wt% hydroxypropylcellulose of 60,000 molecular weight, 27.0 wt% polyvinylpyrrolidone of 40,000 molecular weight, 0.5%

magnesium stearate in the glipizide composition; 64.8 wt% sodium carboxymethylcellulose of 700,000 molecular weight, 29 wt% sodium chloride, 5 wt% hydroxypropylmethylcellulose of 11,200 molecular weight and 1.0 wt% ferric oxide, 0.2% magnesium stearate in the hydrogel composition; and, 93.0 wt% cellulose acetate having a 39.8% acetyl content, and 7.0 wt% polyethylene glycol having a 3350 molecular weight in the semipermeable wall formulation.

EXAMPLE 2

A dosage form adapted, designed and shaped as an osmotic drug delivery system is manufactured as follows: first, a glipizide composition is provided by blending together into a homogeneous blend 478 g of pharmaceutically acceptable polyethylene oxide comprising a 200,000 molecular weight, 66 g of glipizide and 54 g of pharmaceutically acceptable hydroxypropylmethylcellulose comprising a 11,200 molecular weight. Then, 425 ml of denatured anhydrous ethanol is added slowly with continuous mixing over 5 minutes. The freshly prepared wet granulation is screened through a 20 mesh screen dried at room temperature for 16 hours, and again screened through a 20 mesh screen. Finally, the screened granulation is mixed with 1.5 g of magnesium stearate in a rollermill for 5 minutes.

Next, a hydrogel composition is prepared as follows: first, 412.5 g of pharmaceutically acceptable polyethylene oxide comprising a 7,500,000 molecular weight, 150 g of sodium chloride and 6 g of ferric oxide separately are screened through a 40 mesh screen. Then, all the screened ingredients are mixed with 30 g of hydroxypropylmethylcellulose comprising a 11,200 molecular weight to produce a homogeneous blend. Next, 300 mg of denatured anhydrous alcohol is added slowly to the blend with continuous mixing for 5 minutes. The freshly prepared wet granulation is passed through a 20 mesh screen, allowed to dry at room temperature for 16 hours, and again passed through a 20 mesh screen. The screened granulation is mixed with 1.5 g of magnesium stearate in a rollermill for 5 minutes.

Next, the glipizide composition and the hydrogel composition are compressed into bilaminate tablets. First, 200 mg of the glipizide is added to a 0.375 inch (9.5 mm) punch and tamped, then, 140 mg of the hydrogel composition is added and the laminae are pressed under a pressure head of 2 tons into a contacting laminated arrangement.

Then, the bilaminate arrangements are coated with a semipermeable wall. The wall forming composition comprises 93% cellulose acetate having a 39.8% acetyl content, and 7% polyethylene glycol having a molecular weight of 3350. The wall-forming composition is dissolved in an acetone:water (90:10 wt:wt) cosolvent to make a 4% solids solution. The wall forming composition is sprayed onto and around the bilaminate in an Aeromatic ® Air Suspension Coater.

Next, a 25 mil (0.635 mm) exit passageway is mechanically drilled through the semipermeable wall to connect the glipizide drug lamina with the exterior of the dosage system. The residual solvent is removed by drying for 48 hours at 50° C. and 50% humidity. Next, the osmotic systems are dried for 1 hour at 50° C. to remove excess moisture. The dosage form produced by this manufacture provides a glipizide composition comprising 11 wt% glipizide, 79.7 wt% polyethylene oxide of 200,000 molecular weight, 9 wt% hydroxypropylmethylcellulose of 11,200 molecular weight, and 0.3 wt% magnesium stearate; a hydrogel composition comprising 68.8 wt% polyethylene oxide comprising a 7,500,000 molecular weight, 25 wt% sodium chloride, 5 wt% hydroxypropylmethylcellulose, 1.0 wt% ferric oxide and 0.2 wt% magnesium stearate; and a semipermeable wall comprising 93 wt% cellulose acetate comprising a 39.8% acetyl content, and 7.0 wt% polyethylene glycol comprising a 3350 molecular weight.

Accompanying drawing FIG. 5 depicts the in vitro release rate profile of glipizide released from the final dosage form for four dosage forms. The error bars represent the standard deviation added to and subtracted from the mean of the dosage form.

DISCLOSURE OF A METHOD OF USING THE INVENTION

An embodiment of the invention pertains to a method for delivering the beneficial drug glipizide orally at a controlled rate to a warm blooded animal in need of glipizide therapy, which method comprises the steps of: (A) admitting into the warm-blooded animal a dosage form comprising: (1) a wall surrounding a compartment, the wall comprising at least in part a semipermeable polymeric composition permeable to the passage of fluid and substantially impermeable to the passage of glipizide; (2) a pharmaceutically acceptable composition in the compartment comprising about 2.5 mg to 50mg of hypoglycemic glipizide for performing an antidiabetic program; (3) a hydrogel composition in the compartment comprising a member selected from the group consisting of a polyethylene oxide having a 4,000,000 to 7,500,000 molecular weight and a sodium carboxymethylcellulose having a 200,000 to 1,000,000 molecular weight for imbibing and absorbing fluid for pushing the glipizide composition from the dosage form; and, (4) at least one passageway in the wall for releasing glipizide; (B) imbibing fluid through the semipermeable wall at a rate determined by the permeability of the semipermeable wall and the osmotic pressure gradient across the semipermeable wall causing the hydrogel composition to expand and swell; and (C) delivering the beneficial glipizide from the dosage form through the exit passage to the warm blooded animal over a prolonged period of time to produce the desired hypoglycemic effect.

In summary, it will be appreciated that the present invention contributes to the art an unexpected and unforseen dosage form that possesses the practical utility for administering aqueous insoluble glipizide from an osmotic dosage form at a dose metered release rate per unit time. While the invention has been described and pointed out in detail with reference to operative embodiments thereof it will be understood that those skilled in the art that various changes, modifications, substitutions and omissions can be made without departing from the spirit of the invention. It is intended, therefore, that the invention embrace those equivalents within the scope of the claims which follow.

We claim:

1. A pharmaceutical granulation comprising granules of 2 mg to 50 mg of substantially aqueous insoluble glipizide, from 100 mg to 320 mg of a polyethylene oxide having a 80,000 to 350,000 molecular weight, and from 5 mg to 50 mg of a hydroxypropylmethylcellulose having a 9,200 to 2,000 molecular weight, which granules are useful for manufacturing an osmotic dosage form for dispensing the glipizide for up to 22 hours

when the dosage form is in gastrointestinal tract of a patient.

2. A pharmaceutical granulation comprising granules of 2 mg to 25 mg of substantially aqueous insoluble glipizide, from 40 mg to 70 mg of a polyvinylpyrrolidone having a 30,000 to 70,000 molecular weight, and from 100 to 150 mg of a hydroxypropylcellulose having a 40,000 to 80,000 molecular weight, and wherein the granules are useful for manufacturing an osmotic dosage form for dispensing the glipizide for up to 22 hours when the dosage form is in the gastrointestinal tract of a patient.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 5,024,843

DATED : June 18, 1991

INVENTOR(S) : Anthony L. Kuczynski, Atul D. Ayer, Patrick S. L. Wong

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 8, line 66, "2,000" should read --22,000--.

Signed and Sealed this

Twenty-third Day of November, 1993

Attest:

BRUCE LEHMAN

Attesting Officer

Commissioner of Patents and Trademarks

US005082668A

United States Patent [19]

Wong et al.

[11] Patent Number: 5,082,668

[45] Date of Patent: Jan. 21, 1992

[54] CONTROLLED-RELEASE SYSTEM WITH CONSTANT PUSHING SOURCE

[75] Inventors: Patrick S. L. Wong, Palo Alto; Brian L. Barclay, Sunnyvale; Joseph C. Deters; Felix Theeuwes, both of Los Altos, all of Calif.

[73] Assignee: Alza Corporation, Palo Alto, Calif.

[21] Appl. No.: 595,140

[22] Filed: Oct. 9, 1990

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 212,552, Jun. 28, 1988, which is a continuation-in-part of Ser. No. 912,712, Sep. 29, 1986, Pat. No. 4,783,337, which is a continuation-in-part of Ser. No. 685,687, Dec. 24, 1984, abandoned, which is a continuation-in-part of Ser. No. 493,760, May 11, 1983, abandoned.

[51] Int. Cl.[5] A61K 9/22

[52] U.S. Cl. 424/473; 424/465

[58] Field of Search 424/473

[56] References Cited

U.S. PATENT DOCUMENTS

4,008,719	2/1977	Theeuwes et al.	128/260
4,014,334	3/1977	Theeuwes et al.	128/260
4,063,064	12/1977	Saunders et al.	219/121
4,077,407	3/1978	Theeuwes et al.	128/260
4,093,708	6/1978	Zaffaroni et al.	424/15
4,111,202	9/1978	Theeuwes	128/260
4,160,020	7/1979	Ayer et al.	424/15
4,186,184	1/1980	Zaffaroni	424/14
4,200,098	4/1980	Ayer et al.	128/260
4,207,893	6/1980	Michaels	128/260
4,210,139	7/1980	Higuchi	128/260
4,285,987	8/1981	Ayer et al.	427/3
4,298,003	11/1981	Theeuwes et al.	128/260
4,320,759	3/1982	Theeuwes	128/260
4,327,725	5/1982	Cortese et al.	128/260
4,350,271	9/1982	Eckenhoff	222/386.5
4,455,143	6/1984	Theeuwes et al.	604/890
4,608,048	8/1986	Cortese et al.	604/890
4,610,686	9/1986	Ayer et al.	604/890
4,612,008	9/1986	Wong et al.	604/892
4,643,731	2/1987	Eckenhoff	604/892

Primary Examiner—Thurman K. Page

Attorney, Agent, or Firm—Paul L. Sabatine; Edward L. Mandell; Jacqueline S. Larson

[57] ABSTRACT

A device is disclosed comprising a wall that surrounds a compartment. The compartment comprises a beneficial agent composition and a push composition. A passageway in the wall connects the compartment with the exterior of the device for delivering the beneficial agent at a rate governed, in combination, by the wall, the beneficial agent composition and the push composition through the passageway of the device over time.

3 Claims, 7 Drawing Sheets

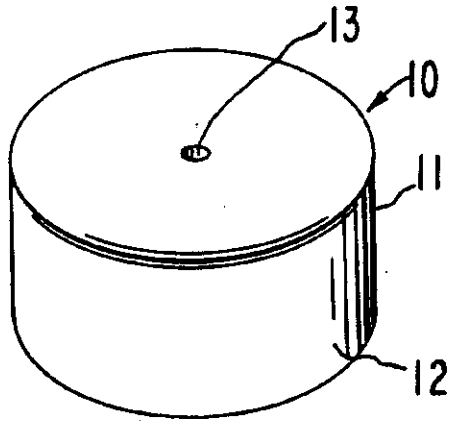


FIG.1

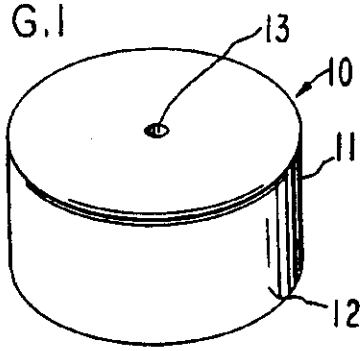


FIG.2

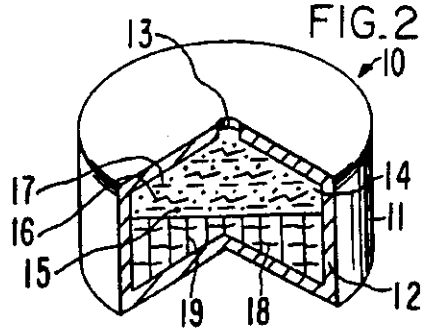


FIG.3

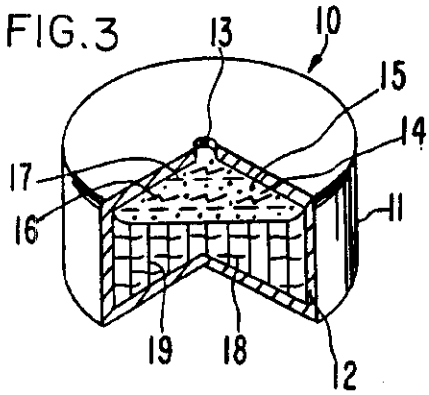


FIG.4

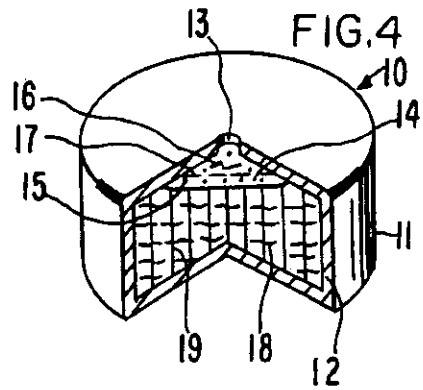


FIG.5

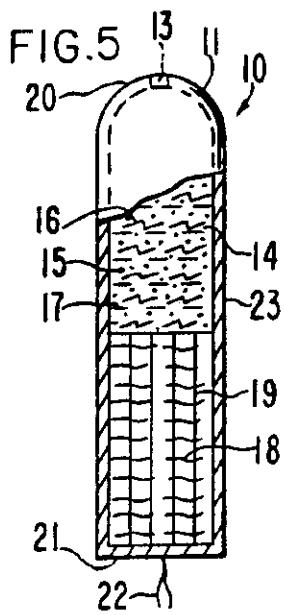


FIG.6

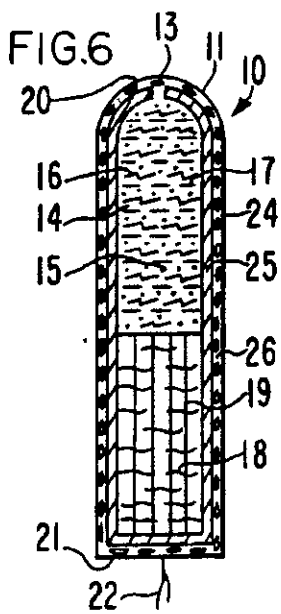


FIG.7

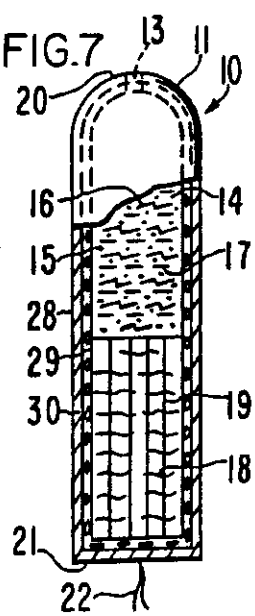


FIG.8

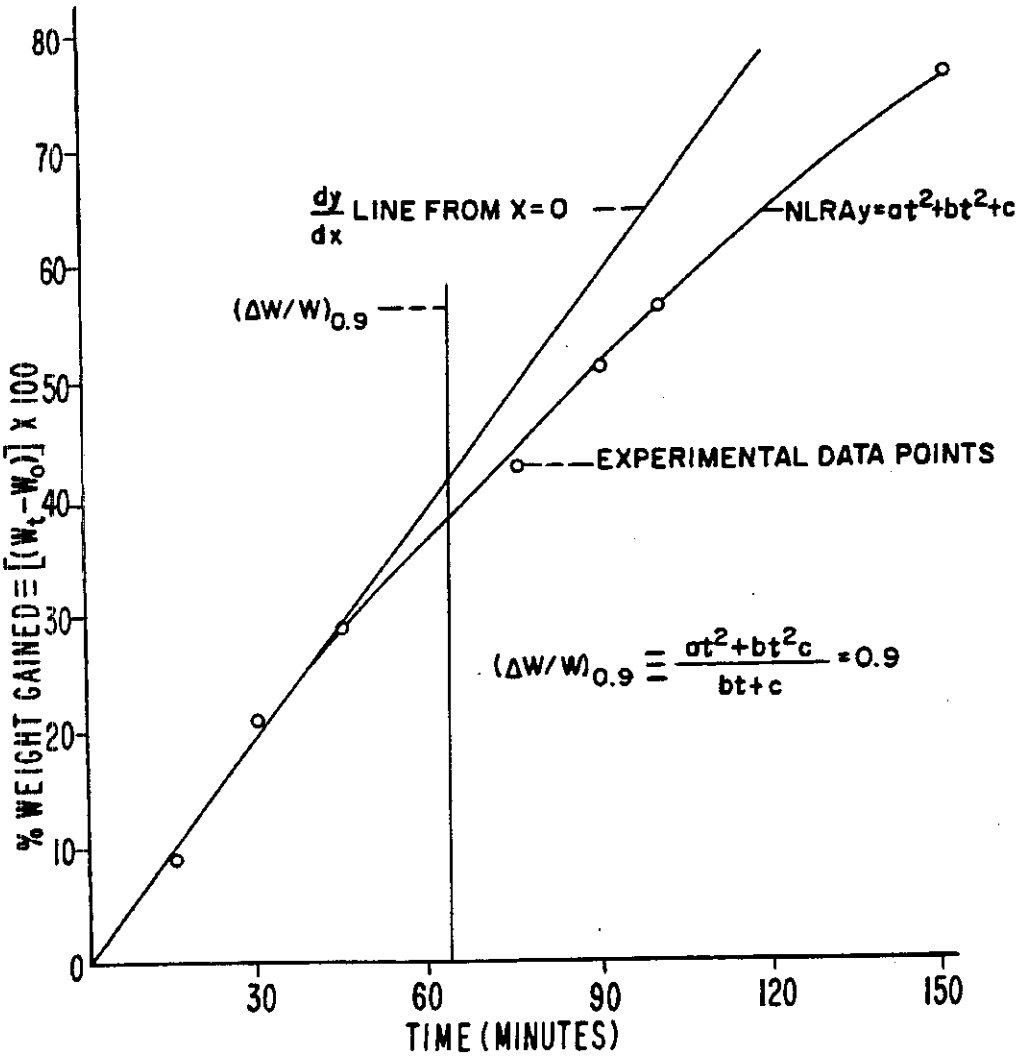

80
70
60
50
40
30
20
10
0
% WEIGHT GAINED = [(W_t - W_o)] X 100
30
60
90
120
150
TIME (MINUTES)
dy/dx LINE FROM X=0
NLRAy=at²+bt²+c
(ΔW/W)0.9
EXPERIMENTAL DATA POINTS
(ΔW/W)0.9 = (at²+bt²c)/(bt+c) = 0.9

FIG. 9

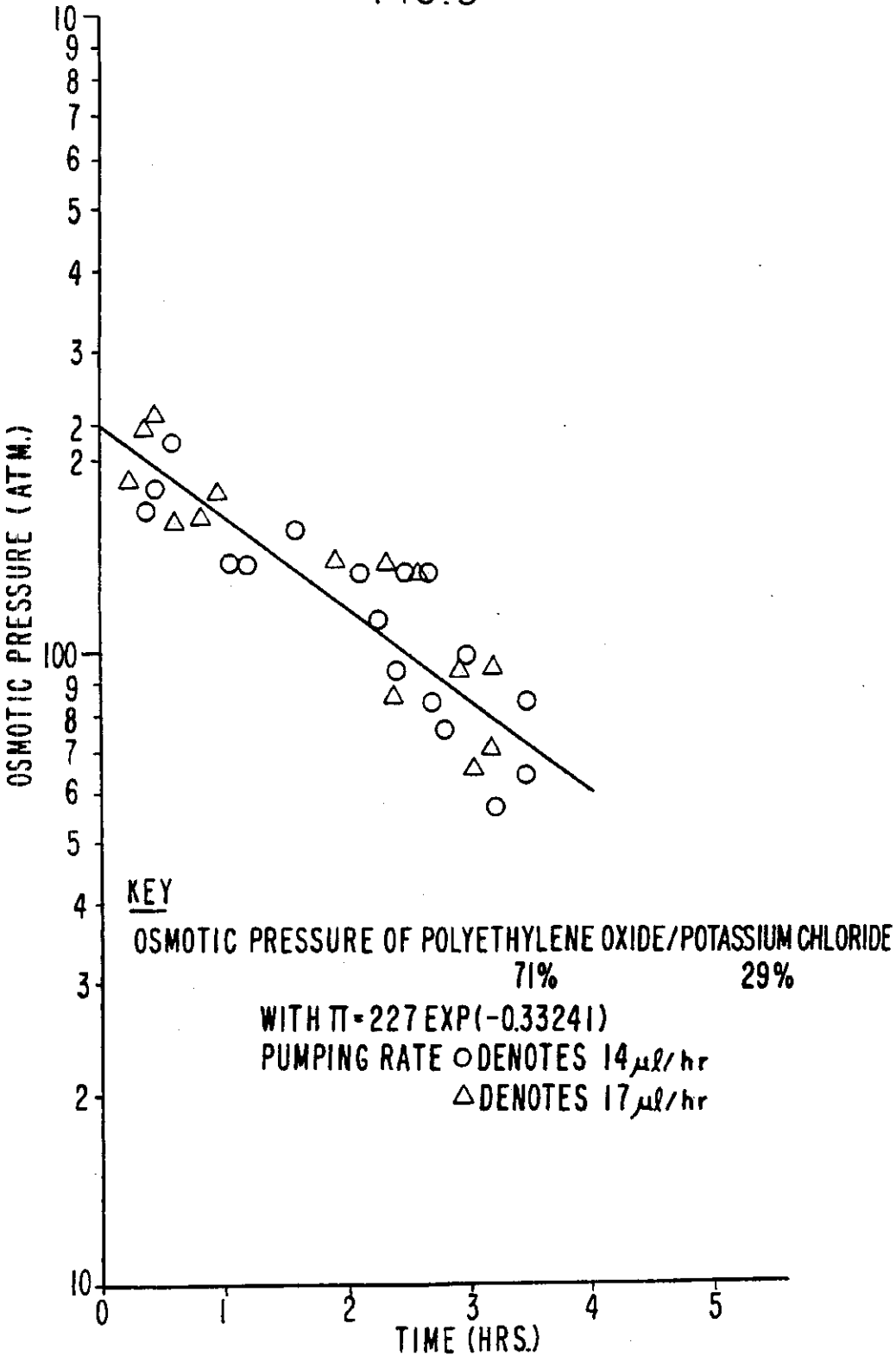
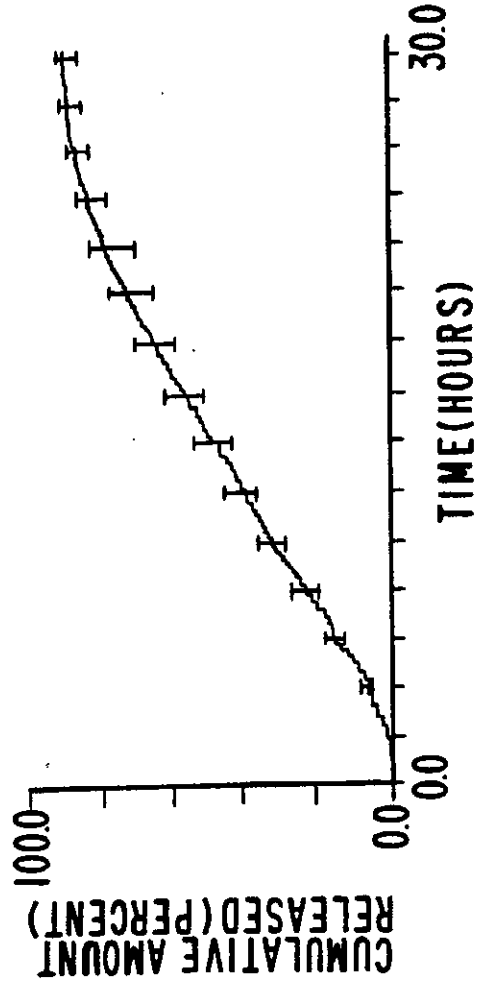

OSMOTIC PRESSURE (ATM.)
10
9
8
7
6
5
4
3
2
2
100
9
8
7
6
5
4
3
2
10
0
1
2
3
4
5
TIME (HRS.)
KEY
OSMOTIC PRESSURE OF POLYETHYLENE OXIDE/POTASSIUM CHLORIDE
71% 29%
WITH π = 227 EXP(-0.33241)
PUMPING RATE ○ DENOTES 14 μl/hr
△ DENOTES 17 μl/hr

FIG. 11


CUMULATIVE AMOUNT RELEASED (PERCENT)
100.0
0.0
0.0
30.0
TIME (HOURS)

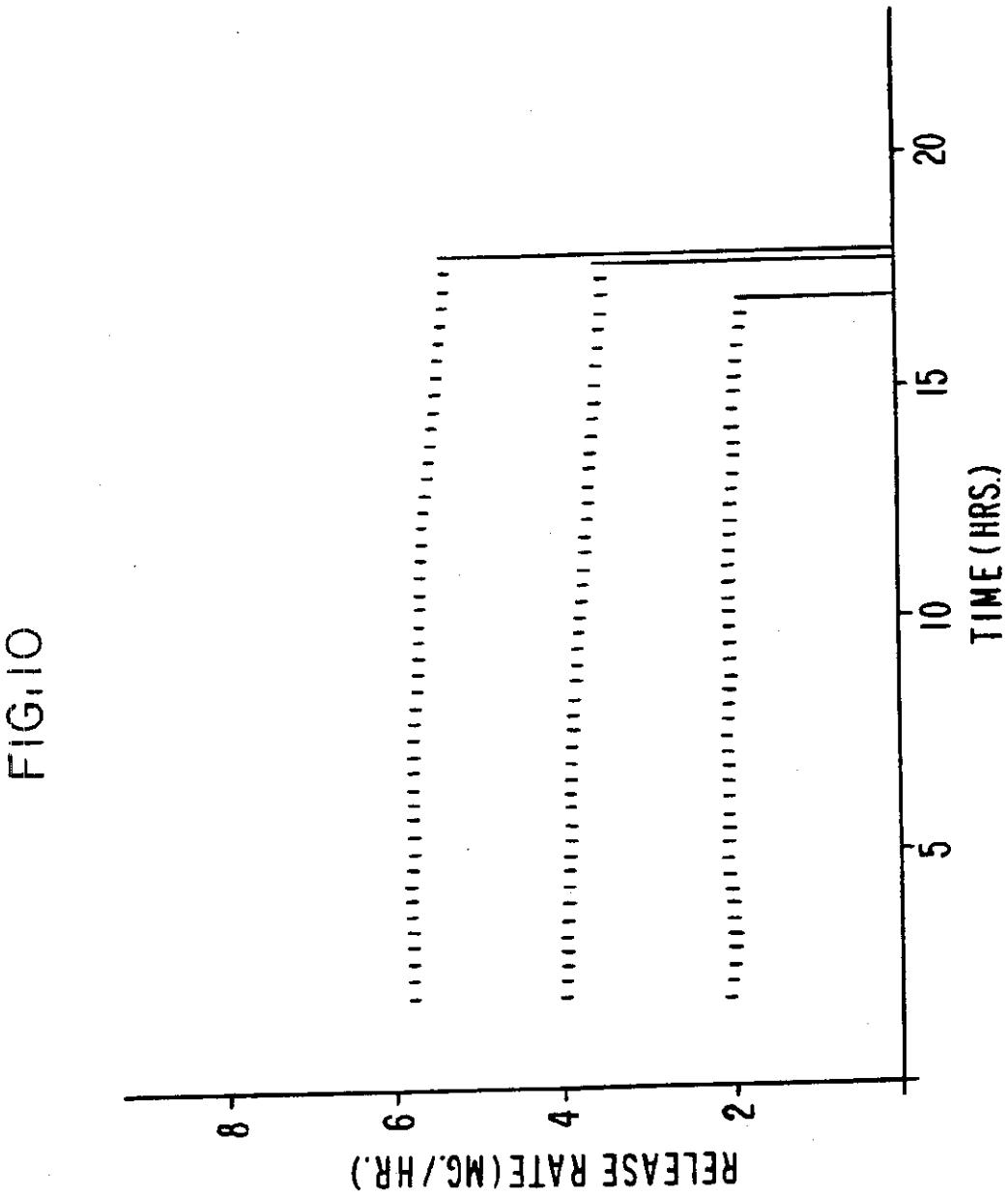


FIG. 10

FIG.12

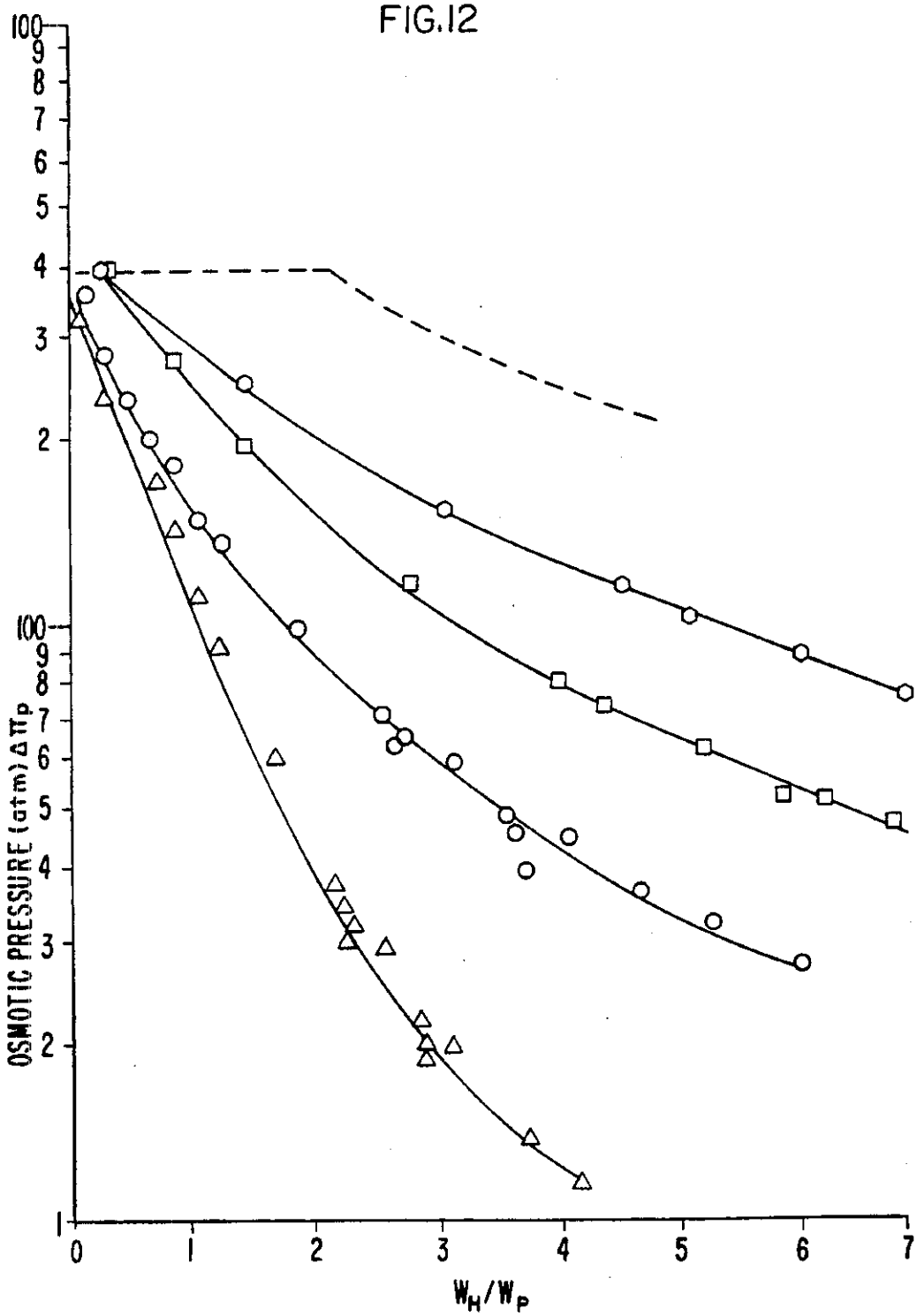
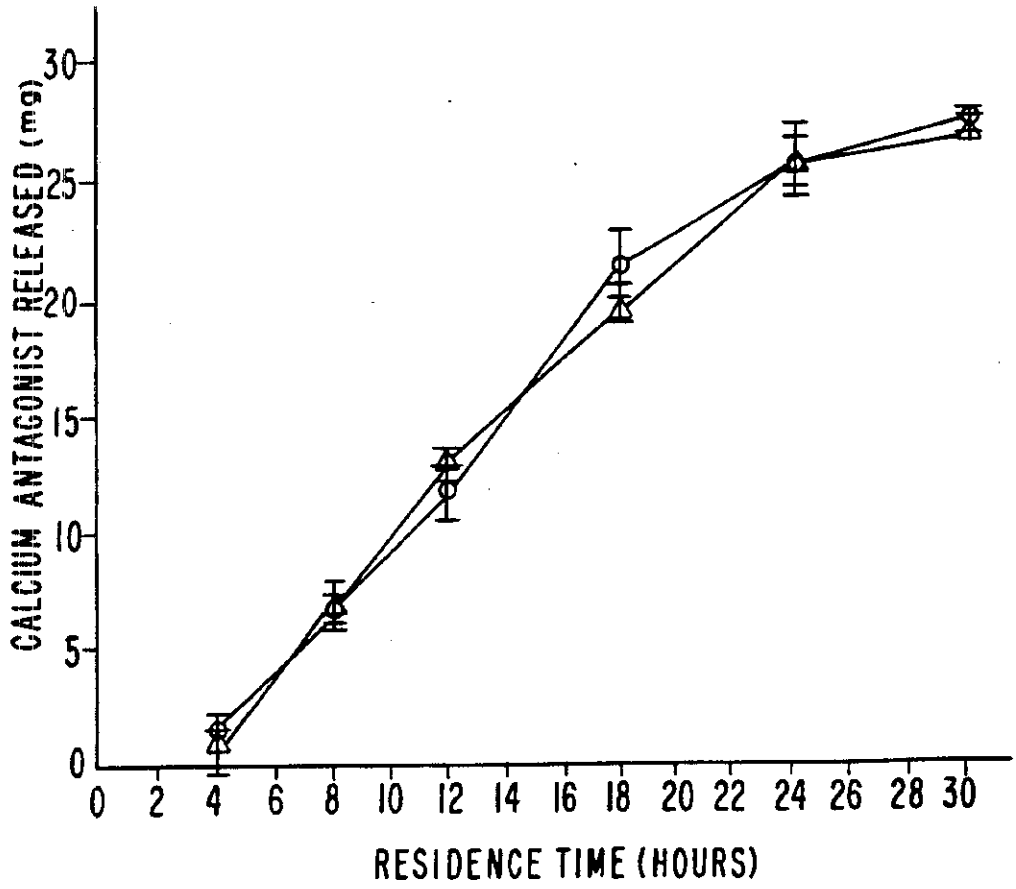

OSMOTIC PRESSURE (atm) Δπp
100
9
8
7
6
5
4
3
2
100
9
8
7
6
5
4
3
2
1
0
1
2
3
4
5
6
7
WH/WP

FIG. 13


CALCIUM ANTAGONIST RELEASED (mg)
0
5
10
15
20
25
30
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30
RESIDENCE TIME (HOURS)

CONTROLLED-RELEASE SYSTEM WITH CONSTANT PUSHING SOURCE

This patent application is a continuation-in-part of U.S. Pat. Appln. Ser. No. 07/212,552, filed on June 28, 1988 which patent application is a continuation-in-part of U.S. Pat. Appln. Ser. No. 06/912,712, filed on Sept. 29, 1986, now U.S. Pat. No. 4,783,337 issued on Nov. 8, 1988, which Appln. Ser. No. 06/912,712 is a continuation-in-part of U.S. Pat. Appln. Ser. No. 06/685,687 filed on Dec. 24, 1984 (now abandoned), which Appln. Ser. No. 06/685,687 is a continuation-in-part of U.S. Pat. Appln. Ser. No. 06/493,760 filed May 11, 1983 (now abandoned), which applications are incorporated herein by reference and benefits are claimed of their filing dates. These patent applications are assigned to the ALZA Corp., of Palo Alto, Calif.

This invention pertains to both a novel and unique delivery system. More particularly, the invention relates to a delivery device comprising a wall that surrounds a compartment comprising: (1) a first composition comprising a beneficial agent, an osmopolymer and optionally an osmagent, said first composition in arrangement with (2) a second composition comprising a constant pushing means for pushing the first composition from the device. The device comprises at least one passageway through the wall that connects the exterior of the device with the compartment for delivering the first composition comprising the beneficial agent from the device. The device in one presently preferred embodiment is useful for delivering (3) beneficial agents that because of their solubilities are difficult to deliver in a known amount at a controlled rate from a delivery device, and for delivering (4) beneficial agents that are therapeutically very active and are dispensed in small amounts, that is in minidoses, at a controlled rate from the dispensing system.

BACKGROUND OF THE INVENTION

Since the beginning of antiquity, both pharmacy and medicine have sought a delivery system for administering a beneficial drug. The first written reference to a delivery system is in the Eber Papyrus, written about 1552 B.C. The Eber Papyrus mentions delivery systems such as anal suppositories, vaginal pessaries, ointments, oral pill formulations, and other delivery systems. About 2500 years passed without any advance in dosage form development, when the Arab physician Rhazes, 865–925 A.D., invented the coated pill. About a century later the Persian Avicenna, 980–1037 A.D., coated pills with gold or silver for increasing patient acceptability and for enhancing the effectiveness of the drug. Also around this time, the first tablet was described in Arabian manuscripts written by al-Zahrawi, 936–1009 A.D. The manuscripts described a tablet formed from the hollow impressions in two facing tablet molds. Pharmacy and medicine waited about 800 years for the next innovation in delivery systems when, in 1883, Mothes invented the capsule for administering drug. The next quantum leap in dosage forms came in 1972 with the invention of the osmotic delivery system by inventors Theeuwes and Higuchi as disclosed in U.S. Pat. Nos. 3,845,770 and 3,916,889.

The osmotic systems disclosed in U.S. Pat. Nos. 3,845,770 and 3,916,889 comprise in at least part a semipermeable wall that surrounds a compartment containing a beneficial agent. The semipermeable wall is permeable to the passage of an external fluid, and it is substantially impermeable to the passage of a beneficial agent. There is at least one passageway through the wall for delivering the beneficial agent from the osmotic system. These systems release a beneficial agent by fluid being imbibed through the semipermeable wall into the compartment at a rate determined by the thickness and permeability of the semipermeable wall and the osmotic pressure gradient across the semipermeable wall to produce an aqueous solution containing a beneficial agent that is dispensed through a passageway from the system. These systems are extraordinarily effective for delivering a beneficial agent that is soluble in the fluid and exhibits an osmotic pressure gradient across the semipermeable wall against the external fluid.

A pioneer advancement in osmotic delivery systems, manufactured in the form of an osmotic device, was presented to the dispensing arts by inventor Felix Theeuwes in U.S. Pat. No. 4,111,202. In this patent, the delivery kinetics of the osmotic device is enhanced for delivering beneficial agents, including drugs, that are insoluble to very soluble in the fluid, by manufacturing the osmotic device with a beneficial agent compartment and an osmagent compartment separated by an internal film. The internal film is movable from a rested to an expanded state. The osmotic device delivers the beneficial agent by fluid being imbibed through the semipermeable wall into the osmagent compartment producing a solution that causes the compartment to increase in volume and act as a driving force that is applied against the film. This force urges the film to expand in the device against the beneficial agent compartment and, correspondingly, diminish the volume of the beneficial agent compartment, whereby beneficial agent is dispensed through the passageway from the osmotic device. While this device operates successfully for its intended use, and while it can deliver numerous useful agents of varying solubilities, its use can be limited because of the manufacturing steps and costs needed for fabricating and placing the movable film in the compartment of the osmotic device.

In the U.S. Pat. No. 4,327,725 patentees Richard Cortese and Felix Theeuwes provided an osmotic dispensing device for delivering beneficial agents that, because of their solubilities in aqueous and biological fluids, are difficult to deliver in meaningful amounts at controlled rates over time. The osmotic devices of this patent comprise a semipermeable wall surrounding a compartment containing a beneficial agent that is insoluble to very soluble in aqueous and biological fluids, and an expandable hydrogel. In operation the hydrogel expands in the presence of external fluid that is imbibed into the device thereby dispensing the beneficial agent through the passageway from the device. This device operates successfully for its intended use, and it delivers many difficult to deliver beneficial agents for their intended purpose.

Now it has been observed that the value of the prior art system described immediately above can be enhanced unexpectedly by the present invention providing an unobvious composition comprising the beneficial agent and a pharmaceutically acceptable carrier gel, which composition cooperates with a separate expanding hydrogel for pushing the beneficial agent from the device, thereby leading to improved administration and to improved therapy. It will be appreciated by those versed in the art, that if such an osmotic device can be provided that exhibits a high level of delivery activity,

such an osmotic device would have a positive value and represent an advancement in the dispensing art. Likewise, it will be immediately appreciated by those versed in the dispensing art that if an osmotic device is made available possessing dual thermodynamic osmotic activity for delivering increased amounts of a beneficial agent accompanied by a pharmaceutically acceptable carrier at a controlled rate, said osmotic device would find practical application in the fields of pharmacy and medicine.

OBJECT OF THE INVENTION

Accordingly, in view of the above presentation, it is an immediate object of this invention to provide a delivery system that can be manufactured by standard manufacturing techniques into osmotic devices of various sizes, shapes and forms that represent a further improvement and advancement in the dispensing art.

Another object of the invention is to provide a delivery system manufactured in the form of an osmotic device for delivering in vivo a beneficial agent including drug that is difficult to delivery and now can be delivered by the device provided by this invention in therapeutically effective amounts over time.

Another object of the invention is to provide a delivery system possessing dual osmotic activity that operates as an integrated unit, which system comprises a compartment containing a first osmotic composition comprising a beneficial agent such as a drug, and an osmopolymer carrier for the agent or drug and optionally an osmagent, and a second osmotic composition comprising an osmopolymer, an optional osmagent and free of agent or drug, with the compositions acting in concert for delivering the drug through a passageway of controlled dimensions from the osmotic device.

Yet another object of the invention is to provide a delivery device having means for high loading of a water insoluble or a slightly water soluble beneficial agent such as a drug and means for delivering the beneficial agent in either instance at a controlled rate and continuously over time to a drug recipient.

Yet another object of the invention is to provide an osmotic device that can deliver a pH dependent beneficial agent by providing a neutral medium for delivering the beneficial agent in a finely dispersed form for increasing its surface area and for maximizing and dissolution rate of the beneficial agent.

Still yet another object of the invention is to provide an osmotic device for delivering a drug having a very low dissolution rate that is the rate limiting step for delivering the drug from the device, but now can be delivered by using an osmotic composition that functions in situ as a carrier that is delivered with the drug, thereby enhancing the drug's delivery from the osmotic device.

Another object of the invention is to provide an osmotic device comprising means for maintaining a high level of osmotic activity of a polymer which polymer is used for delivering a beneficial agent from the osmotic device.

Still a further object of the invention is to provide an osmotic, therapeutic device that can administer a complete pharmaceutical dosage regimen comprising poorly soluble to very soluble agents, at a controlled rate and continuously for a particular time period, the use of which requires intervention only for the initiation and possible termination of the regimen.

Still another object of this invention is to provide an osmotic device, which device can house a small amount of a therapeutic agent and dispense small doses, that is minidoses, of the therapeutic agent at a controlled rate to the gastrointestinal tract throughout the length of the gastrointestinal tract.

Still another object of the invention is to provide an improvement in an osmotic device manufactured with a compartment housing a first drug polymer means and a second drug free polymer means in spaced arrangement that simultaneously maintain their original identity and function as an integrated layered unit for delivering the beneficial drug accompanied by the first drug polymer means in paste or gel ribbon-like form from the osmotic device.

Still a further object of this invention is to provide a delivery device that possesses the ability to deliver drugs over a broad range of drug delivery rates, and can deliver the drugs according to a predetermined drug release rate pattern to a biological recipient over time.

A still further object of the invention is to provide a delivery system that avoids patient compliance problems and uses less drug, minimizes side effects and thereby provides efficiency in treatment for better health.

Other objects, features, aspects and advantages of the invention will be more apparent to those versed in the dispensing art from the following detailed specification taken in conjunction with the figures and the accompanying claims.

BRIEF DESCRIPTION OF THE DRAWINGS

In the drawings, which are not drawn to scale, but are set forth to illustrate various embodiments of the invention, the drawing figures are as follows:

FIG. 1 is an isometric view of a delivery device designed for orally administering a beneficial agent to the gastrointestinal tract;

FIG. 2 is an opened view of the device of FIG. 1 illustrating the structure of the device of FIG. 1;

FIG. 3 is an opened view of the device of FIG. 1 illustrating the device in operation and delivering a beneficial agent from the device;

FIG. 4 is an opened view of the device of FIG. 1 considered with FIG. 3 illustrating the device in operation and comprising more than one passageway for delivering a major amount of a beneficial agent from the device;

FIG. 5 shows a therapeutic device with its wall partially broken away, designed for delivering a beneficial agent into a body passageway, such as the ano-rectal and vaginal passageways;

FIG. 6 shows the device of FIG. 5 with a different wall structure;

FIG. 7 shows the device of FIG. 5 depicting a different wall structure than the wall structure depicted in FIG. 6;

FIG. 8 represents the weight gain as a function of time for a polymer encapsulated in a semipermeable membrane when the encapsulated polymer is placed in water;

FIG. 9 depicts the osmotic pressure of a polymer containing an osmagent that develops osmotic pressure at two different pumping rates;

FIG. 10 depicts the release rate for three delivery systems, the top release rate pattern for a system comprising 99 mg of a drug, the middle line for a system

comprising 66 mg of a drug, and the bottom line for a system comprising, 33 mg of a drug;

FIG. 11 depicts the cumulative amount of drug released from a device comprising two osmopolymer having two different molecular weights;

FIG. 12 depicts the osmotic pressure curves for an osmagent and a number of osmopolymer/osmagent compositions;

FIG. 13 illustrates the in vivo and in vitro cumulatie release for a drug delivered by an osmotic device.

In the drawings and the specification, like parts in related figures are identified by reference numerals. The terms appearing earlier in the specification and in the description of the drawings, as well as embodiments thereof, are further detailed elsewhere in the disclosure.

DETAILED DESCRIPTION OF THE DRAWINGS

Turning now to the drawings in detail, which are examples of various devices provided by the invention, and which examples are not to be construed as limiting, one example of a device is seen in FIG. 1. In FIG. 1, device 10 is seen comprising a body member 11 having a wall 12 and at least one passageway 13 for releasing a beneficial agent from device 10 to a fluid environment of use. The phrase "fluid environment of use" as used for the purpose of this invention denotes the gastrointestinal tract, comprising the stomach and the intestine, and other fluid containing areas in an animal environment.

In FIG. 2, device 10 of FIG. 1 is seen in opened section. In FIG. 2, device 10 comprises a body 11, a wall 12 that surrounds and forms internal compartment 14, that communicates through a passageway 13 with the exterior of device 10. Wall 12 comprises totally a semipermeable composition or at least in part a semipermeable composition. When wall 12 comprises at least in part a semipermeable composition the remainder of the wall is comprised of a non-semipermeable composition. Compartment 14 contains a first composition comprising a beneficial agent 15, represented by dots, which agent 15 can be from insoluble to very soluble in fluid imbibed into compartment 14, an optional osmagent 16, represented by irregular lines, that is soluble in fluid imbibed into compartment 14 and exhibits an osmotic pressure gradient across semipermeable wall 12 against an external fluid and an osmopolymer 17, represented by horizontal dashes, that imbibes and/or absorbs fluid into compartment 14 and exhibits an osmotic pressure gradient across semipermeable wall 12 against an exterior fluid present in the environment of use. Wall 12 comprises a semipermeable composition that is substantially permeable to the passage of the exterior fluid, and it is substantially impermeable to the passage of agent 15, osmagent 16 and osmopolymer 17. Semipermeable wall 12 is non-toxic and it maintains its physical and chemical integrity during the delivery life of agent 15 from device 10.

Compartment 14 also houses a second composition that is distant from passageway 13 and in spaced relation with the first composition. The second composition contributes an expandable driving force that pushes and acts in cooperation with the first composition for delivering the maximum amount of beneficial agent 15 from device 10. The second composition comprises an optional osmagent 18, represented by wavy lines, that is soluble in fluid imbibed into compartment 14 and exhibits an osmotic pressure gradient across semipermeable wall 12 against an external fluid, blended with a presently preferred osmopolymer 19, represented by vertical lines, that imbibes fluid into compartment 14 and exhibits an osmotic pressure gradient across semipermeable wall 12 against external fluid. Osmopolymer 17 and osmopolymer 19 are hydrophilic water soluble or lightly cross-linked water soluble polymers, and they possess osmotic properties such as the ability to imbibe external fluid through the semipermeable wall, exhibit an osmotic pressure gradient across the semipermeable wall against the external fluid, and swell or expand in the presence of the fluid in the compartment. Osmopolymers 17 and 19 preferably are mixed with an optional osmagent 16 and an optional osmagent 18, respectively, for imbibing the optimal maximum volume of external fluid into compartment 14. This imbibed fluid is available to osmopolymers 17 and 19 to optimize the volumetric rate and for total expansion of osmopolymer 17 and 19. That is, osmopolymers 17 and 19 absorb fluid imbibed into compartment 14 by the osmotic imbibition action of osmopolymers 17 and 19 supplemented by the osmotic imbibition action of optional osmagents 16 and 18 for effecting the optimal maximum expansion of osmopolymers 17 and 19 from a rested to an enlarged, that is, an expanded state.

In operation, the delivery of beneficial agent 15 from osmotic device 10 is carried out, in one presently preferred embodiment, by (1) imbibition of fluid by the first composition to form a fluidic composition in situ and delivery of the suspension through the passageway; and concurrently by (2) imbibition of fluid by the second composition causing the second composition to swell and cooperate with the first composition for driving the agent formulation through at least one, or more than one, passageways. The agent formulation is preferably delivered as a ribbon, which is a viscous or paste-like strip. According to the operation described, the device may be considered as a cylinder, with the second composition expanding like the movement of a piston for aiding in delivering the beneficial agent composition from the device. For the purpose of the present analysis, the volume rate delivered by the device F_t is composed of two sources: the water imbibition rate by the first composition F, and the water imbibition rate by the second composition Q wherein:

$$F_t = F + Q \tag{1}$$

Since the boundary between the first composition and the second composition hydrates very little during the functioning of the device, there is insignificant water migration between the compositions. Thus, the water imbibition rate of the second composition, Q, equals the expansion of its volume:

$$\frac{dv_p}{dt} = Q \tag{2}$$

The total delivery rate from the osmotic device is then,

$$\frac{dm}{dt} = F_t \cdot C = (F + Q)C \tag{3}$$

wherein C is the concentration of beneficial agent in the delivered slurry or solution. Conservation of the osmotic device volume, V, and the surface area, A, gives equations (4) and (5):

$$V = V_d + V_p \quad (4)$$

$$A = A_d + A_p \quad (5)$$

wherein V_d and V_p equal the volumes of the first composition and the second composition, respectively; and wherein A_d and A_p equal the surface area in contact with the wall by the first composition and the second composition, respectively. In operation, both V_p and A_p increase with time, while V_d and A_d decrease with time as the device delivers beneficial agent.

The volume of the second composition that expands with time when fluid is imbibed into the compartment is given by equation (6):

$$V_p = f\frac{W_H}{W_p} \quad (6)$$

wherein W_H is the weight of fluid imbibed by the second composition, W_p is the weight of the second composition initially present in the device, W_H/W_p is the ratio of fluid to initial solid of the second composition, and

$$V_p = \left(1 + \frac{W_H}{W_p}\right)\frac{W_p}{\rho} \quad (7)$$

wherein ρ is the density of the second composition corresponding to W_H/W_p. Thus, based on the geometry of a cylinder, where r is the radius of the cylinder, the area of imbibition is related to the volume of the swollen second composition as follows:

$$A_p = \pi r^2 + \frac{2}{r}\,\frac{W_p}{\rho}\,(1 + W_H/W_p) \quad (8)$$

The fluid imbibition rates into each composition are:

$$A_d = A - A_p \quad (9)$$

The fluid imbibiion rates into each composition are:

$$F = \left(\frac{k}{h}\right)(A_d \cdot \Delta\pi_d) \quad (10)$$

$$Q = \left(\frac{k}{h}\right)(A_p \cdot \Delta\pi_p) \quad (11)$$

wherein k equals the osmotic permeability of the wall, h equals the wall thickness, $\Delta\pi_d$ and $\Delta\pi_p$ are the osmotic gradients for the first composition and the second composition respectively. The total delivery rate, therefore, is equation (12):

$$\frac{dm}{dt} = \frac{k}{h}\,C\left(\left[A - \pi r^2 - \frac{2}{r}\,\frac{W_p}{\rho}\,(1 + W_H/W_p)\right]\Delta\pi_d + \left[\pi r^2 + \frac{2}{r}\,\frac{W_p}{\rho}\,(1 + W_H/W_p)\right]\Delta\pi_d\right) \quad (12)$$

FIGS. 3 and 4 illustrate the osmotic device in operation as described for FIGS. 1 and 2. In FIGS. 3 and 4, for osmotic device 10, fluid is imbibed by the first composition at a rate determined by the permeability of the wall and the osmotic pressure gradient across the wall. The imbibed fluid continuously forms a composition comprising a beneficial agent and the gel, which composition is released by the combined operations of the first composition and the second composition device 10. These operations include the composition being osmotically delivered through the passageway due to the continuous formation of the composition, and by the swelling and increasing volume of the different second composition, is represented by the increase in height of the vertical lines in FIGS. 3 and 4. This latter swelling and increase in volume applies pressure against the first composition thereby aiding the first composition and simultaneously causing delivery of beneficial agent through the osmotic passageway to the exterior of the device. The device can comprise more than one passageway, a passageway made as a microporous insert, or drug releasing pores formed by leaching a leachable pore-former thereby providing pore-passageways for releasing drug to the exterior of the device. Thus, the osmotic device provided by this invention can be viewed as a single unit construction device comprising two compositions containing two polymeric structures acting in concert for effective drug administration to a patient.

The first composition and the second composition act together to substantially insure that delivery of beneficial agent from the compartment is controlled and constant over a prolonged period of time by two methods. First, the first composition imbibes external fluid across the wall, thereby forming a dispensalbe composition, which is substantially delivered at non-zero order rate, without the second composition present, since the driving force decays with time. Second, the second composition operating by imbibing external fluid across the wall continuously and, consequently, increases in volume as well as imbibition area, thereby exerting a force which can be constant, increasing or decreasing with time (depending on the osmotic formulation) against the first composition and diminishing the volume of beneficial agent first composition, thusly directing beneficial agent to the passageway at a controlled rate from the compartment. Additionally, as the first composition is squeezed out, that is, delivered from device 10, the osmotic composition closely contacts the internal wall and generates a constant osmotic pressure and, therefore, effects a constant delivery rate in conjunction with the second composition. The swelling and expansion of the second composition, with its accompanying increase in volume, along with the simultaneous corresponding reduction in volume of the first composition, assures the delivery of beneficial agent through the osmotic passageway at a controlled rate over time.

Device 10 of FIGS. 1 through 4 can be made into many embodiments including the presently preferred embodiments for oral use for releasing a locally or systemically acting therapeutic agent in a gastrointestinal tract. Oral system 10 can have various conventional shapes and sizes, such as round with a diameter of 3/16 inches to § inches. In these forms system 10 can be adapted for administering beneficial agent to numerous animals, including warm blooded animals, humans, avians, reptiles and pisces.

FIGS. 5, 6 and 7 show another embodiment provided by this invention. FIGS. 5, 6 and 7 show an osmotic device 10 designed for placement in a body passageway,

such as a vagina, or the ano-rectal canal. Device **10** has an elongated, cylindrical, self-sustaining shape with a curved lead end **20**, a trailing end **21**, and it is optionally equipped with manually controlled strings **22** for easily removing device **10** from the biological passageway. Device **10** is structurally identical with the device described above in FIGS. **1** through **4**, and it operates in a like manner. In FIG. **5**, device **10** is depicted with a semipermeable wall **23**, in FIG. **6** with a laminated wall **24** compri sing an inner semipermeable lamina **25** adjacent to compartment **14** and an external microporous lamina **26** distant from compartment **14**. Micro porous lamina **26** can have preformed pores, or its pores can be formed when device **10** is in the environment of use, such as by leaching a leachable material from the lamina. The pores of lamina **26** are of controlled porosity size, and they can function as pore-passageways for the release of beneficial agent **15** from device **10**. In FIG. **6**, a pore controlled-releasing-passageway and a laser controlled-releasing-passageway function as the composite passageway **13** for releasing agent **15** from device **10**. In FIG. **7**, device **10** comprises a laminated wall **28** formed of a microporous lamina **29** next to compartment **14**, and a semipermeable lamina **30** facing the environment of use and in laminar arrangement with microporous lamina **29**. The semipermeable lamina used for manufacturing these osmotic devices is permselective since it is permeable to the passage of fluid and substantially impermeable to the passage of agent, osmagent and osmopolymer. The micropores of lamina **29** can align with the passage way of lamina **30** for releasing drug from device **10**. Device **10** delivers a beneficial agent for absorption by the vaginal mucosa, or the anorectal mucosa, to produce an in vivo local or systemic effect over a prolonged period of time.

The devices of FIGS. **1** through **7** can be used for delivering numerous beneficial agents including drugs at a controlled rate independent of the drug pH dependency, or where the dissolution rate of the agent can vary between low and high in fluid environments, such as gastric fluid and intestinal fluid. The osmotic devices also provide for low/high loading of agents of low solubility and their delivery at meaningful, therapeutic amounts. While FIGS. **1** through **7** are illustrative of various devices that can be made according to the invention, it is to be understood these devices are not to be construed as limiting, as the devices can take a wide variety of shapes, sizes and forms adapted for delivering beneficial agents to the environment of use. For example, the devices include buccal, implant, rumen, artificial gland, cervical, intrauterine, ear, nose, dermal, vaginal, percutaneous, subcutaneous, anal, and like delivery devices. The devices also can be sized, shaped, structured and adapted for delivering an active agent in streams, aquariums, fields, factories, reservoirs, laboratory facilities, hot houses, transportation means, naval means, military means, hospitals, veterinary clinics, nursing homes, farms, zoos, sickrooms, chemical reactions, and other environments of use.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the practice of this invention it has now been found that delivery device **10** can be manufactured with a first composition and a different second composition mutually housed in cooperative relationship in the compartment of the device. The compartment is formed by a wall comprising a material that does not adversely affect the beneficial agent, osmagent, osmopolymer, and the like. The wall is permeable to the passage of an external fluid such as water and biological fluids, and it is substantially impermeable to the passage of agents, osmagents, osmopolymers, and the like. The wall comprises a material that does not adversely affect an animal, or host, or the components comprising the device, and the selectively semipermeable materials used for forming the wall are non-erodible and they are insoluble in fluids. Typical materials for forming the wall are, in one embodiment, cellulose esters, cellulose ethers and cellulose ester-ethers. These cellulosic polymers have a degree of substitution, D.S., on the anhydroglucose unit, from greater than 0 up to 3 inclusive. By degree of substitution is meant the average number of hydroxyl groups originally present on the anhydroglucose unit comprising the cellulose polymer that are replaced by a substituting group. Representative materials include a member selected from the group consisting of cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, mono-, di- and tricellulose alkanylates; mono-, di- and tricellulose aroylates, and the like. Exemplary polymers include cellulose acetate having a D.S. up to 1 and an acetyl content up to 21%; cellulose acetate having an acetyl content of 32% to 39.8%; cellulose acetate having a D.S. of 1 to 2 and an acetyl content of 21% to 35%; cellulose acetate having a D.S. of 2 to 3 and an acetyl content of 35% to 44.8%, and the like. More specific cellulosic polymers include cellulose propionate having a D.S. of 1.8 and a propyl content of 39.2% to 45% and a hydroxyl content of 2.8% to 5.4%; cellulose acetate butyrate having a D.S. of 1.8, an acetyl content of 13% to 15% and a butyryl content of 34% to 39%; cellulose acetate butyrate having an acetyl content of 2% to 29%, a butyryl content of 17% to 53% and a hydroxyl content of 0.5% to 4.7%; cellulose triacylates having a D.S. of 2.9 to 3 such as cellulose trivalerate, cellulose trilaurate, cellulose tripalmitate, cellulose trisuccinate, and cellulose triocta noate; cellulose diacylates having a D.S. of 2.2 to 2.6 such as cellulose disuccinate, cellulose dipalmitate, cellulose dioctanoate, cellulose dipentanoate, co-esters of cellulose such as cellulose acetate butyrate and cellulose acetate propionate, and the like.

Additional polymers include ethyl cellulose of various degree of etherification with ethoxy content of from 40% to 55%, acetaldehyde dimethyl cellulose acetate, cellulose acetate ethyl carbamate, cellulose acetate methyl carbamate, cellulose acetate dimethyl aminoacetate, semipermeable polyamides; semipermeable polyurethanes; semipermeable sulfonated polystyrenes; semipermeable cross-linked selective polymers formed by the coprecipitation of a polyanion and a polycation as disclosed in U.S. Pat. Nos. 3,173,876; 3,276,586; 3,541,005; 3,541,006, and 3,546,142; semipermeable polymers as disclosed by Loeb and Sourirajan in U.S. Pat. No. 3,133,132; semipermeable lightly cross-linked polystyrene derivatives; semipermeable cross-linked poly(-sodium styrene sulfonate); semipermeable cross-linked poly(vinylbenzyltrimethyl ammonium chloride); water permeable membrane exhibiting a fluid permeability of 2.5×10^{-8} to 2.5×10^{-4} (cm^2/hr·atm) expressed per atmosphere of hydrostatic or osmotic pressure difference across the wall. The polymers are known to the art in U.S. Pat. Nos. 3,845,770; 3,916,899; and 4,160,020; and in *Handbook of Common Polymers* by Scott, J. R.

and Roff, W. J., (1971), published by CRC Press, Cleveland, Ohio.

The laminated wall comprising a semipermeable lamina and a microporous lamina are in laminar arrangement and they act in concert to form an integral laminated wall that maintains its physical and chemical integrity and does not separate into the original lamina throughout the operative agent release history of the osmotic device. The semipermeable lamina is made from the semipermeable polymeric materials, the semipermeable homopolymers, and the semipermeable copolymers presented above, and the like.

Microporous lamina suitable for manufacturing a wall or a laminated osmotic device generally comprises preformed microporous polymeric materials, and polymeric materials that can form a microporous lamina in the environment of use. The microporous materials in both embodiments are laminated to form the laminated wall. The preformed materials suitable for forming the microporous lamina are essentially inert, they maintain their physical and chemical integrity during the period of agent release and they can be described generically as having a sponge like appearance that provides a supporting structure for a semipermeable lamina and also provides a supporting structure for microscopic sized interconnected pores or voids. The microporous materials can be isotropic wherein the structure is homogeneous throughout a cross sectional area, or they can be anisotropic wherein the structure is non-homogeneous throughout a cross sectional area. The pores can be continuous pores that have an opening on both faces of a microporous lamina, pores interconnected through tortuous paths of regular and irregular shapes, including curved, curved-linear, randomly oriented continuous pores, hindered connected pores and other porous paths discernible by microscopic examination. Generally, microporous lamina are defined by the pore size, the number of pores, the tortuosity of the microporous path and the porosity which relates to the size and the number of pores. The pore size of a microporous lamina is easily ascertained by measuring the observed pore diameter at the surface of the material under the electron microscope. Generally, materials possessing from 5% to 95% pores and having a pore size of from 10 angstroms to 100 microns can be used for making a microporous lamina.

The pore size and other parameters characterizing the microporous structure also can be obtained from flow measurements, where a liquid flux, J, is produced by a pressure difference ΔP, across the lamina. The liquid flux through a lamina with pores of uniform radius extended through the lamina and perpendicular to its surface with area A given by relation (13):

$$J = \frac{N\pi r^4 \Delta P}{8\eta \Delta x} \tag{13}$$

wherein J is the volume transported per unit time and lamina area containing N number of pores of radius r, η is the viscosity of the liquid and ΔP is the pressure difference across the lamina with thickness Δx. For this type of lamina, the number of pores N can be calculated from relation (14), wherein ϵ is the porosity defined as the ratio of void volume to total volume of the lamina; and A is the cross sectional area of the lamina containing N pores.

$$N = \frac{\epsilon A}{\pi r^2} \tag{14}$$

The pore radius then is calculated from relation (15):

$$r = \left[8\eta \frac{\Delta x \cdot \tau}{\Delta P \cdot \epsilon} J' \right]^{\frac{1}{4}} \tag{15}$$

wherein J' is the volume flux through the lamina per unit area pro duced by the pressure difference ΔP across the lamina, η, ϵ and Δx have the meaning defined above and τ is the tortuosity defined as the ratio of the diffusional path length in the lamina to the lamina thickness. Relations of the above type are discussed in *Transport Phenomena In Membranes*, by Lakshminatayanaiah, N. Chapter 6, (1969), published by Academic Press, Inc., New York.

As discussed in this reference, supra, on page 336, in Table 6.13, the porosity of the lamina having pores with radius r can be expressed relative to the size of the transported molecule having a radius a, and as the ratio of molecular radius to pore radius a/r decreases, the lamina becomes porous with respect to this molecule. That is, when the ratio a/r is less than 0.3, the lamina becomes substantially microporous as expressed by the osmotic reflection coefficient σ which decreases below 0.5. Microporous lamina with a reflection coefficient σ in the range of less than 1, usually from 0 to 0.5, and preferably less than 0.1 with respect to the active agent are suitable for fabricating the system. The reflection coefficient is determined by shaping the material in the form of a lamina and car rying out water flux measurements as a function of hydrostatic pressure difference and as a function of the osmotic pressure difference caused by the active agent. The osmotic pressure difference creates a hydrostatic volume flux, and the reflection coefficient is expressed by relation (16):

$$\sigma = \frac{\text{osmotic volume flux}}{\text{hydrostatic volume flux}} \tag{16}$$

Properties of microporous materials are described in *Science*, Vol. 170, pp 1302–1305, (1970); *Nature*, Vol. 214, page 285, (1967); *Polymer Engineering and Science*, Vol. 11, pp 284–288, (1971); U.S. Pat. Nos. 3,567,809 and 3,751,536; and in *Industrial Processing With Membranes*, by Lacey, R. E., and Loeb, Sidney, pp 131–134, (1972).

Microporous materials having a preformed structure are commercially available and they can be made by art known methods. The microporous materials can be made by etching, nuclear tracking, by cooling a solution of flowable polymer below the freezing point whereby solvent evaporates from the solution in the form of crystals dis persed in the polymer and then curing the polymer followed by removing the solvent crystals, by cold or hot stretching at low or high temperatures until pores are formed, by leaching from a polymer a soluble component by an appropriate solvent, by ion exchange reaction, and by polyelectrolyte process. Process for repairing microporous materials are described in *Synthetic Polymer Membranes*, by R. E. Kesting, (1971), Chapters 4 and 5, published by McGraw Hill, Inc; *Chemical Reviews*, "Ultrafiltration", Vol. 18, pp 373 to 455, (1934); *Polymer Eng. and Sci.*, Vol. 11, No. 4, pp

284-288, (1971); *J. Appl. Poly. Sci.*, Vol. 15, pp 811-829, (1971); and in U.S. Pat. Nos. 3,565,259; 3,615,024; 3,751,536; 3,801,692; 3,852,224, and 3,849,528.

Microporous materials useful for making the wall or the lamina include microporous polycarbonates comprised of linear polyesters of carbonic acid in which carbonate groups recur in the polymer chain; microporous materials prepared by the phosgenation of a dihydroxyl aromatic, such as bisphenol A; microporous poly(vinyl chloride); microporous polyamides such as polyhexamethylene adipamide; microporous modacrylic copolymers including those formed from 60% vinyl chloride and 40% acrylonitrile; styrene acrylic copolymers; porous polysulfones characterized by diphenylene sulfone groups in a linear chain thereof; poly(vinylidene) halides; polychloroethers; acetal polymers; polyesters prepared by esterification of a dicarboxylic acid or anhydride with an alkylene polyol; poly(alkylenesulfides); phenolic polyesters; microporous poly(saccharides); microporous polymers having substituted and unsubstituted anhydroglucose units exhibiting a higher permeability to the passage of water and biological fluids than a semipermeable lamina; asymmetric porous polymers; cross linked olefin polymers; hydrophobic or hydrophilic microporous homopolymers, copolymers or interpolymers having a reduced bulk density; and materials described in U.S. Pat. Nos. 3,597,752; 3,643,178; 3,654,066; 3,709,774; 3,718,532; 3,803,061; 3,852,224; 3,853,601; and 3,852,388, in British Patent No. 1,126,849, and in *Chem. Abst.*, Vol. 71 4274F, 22572F, 22573F, (1969).

Additional microporous materials include microporous poly(urethanes); microporous cross linked, chain extended poly(urethanes); microporous poly(urethanes) in U.S. Pat. No. 3,524,753; microporous poly(imides); microporous poly(benzimidazoles); regene rated microporous proteins; semi-solid cross linked microporous poly(vinylpyrrolidone); microporous materials prepared by diffusion of multivalent cations into polyelectrolyte sols as in U.S. Pat. No. 3,565,259; anisotropic microporous materials of ionically associated polyelectrolytes; porous polymers formed by the coprecipitation of a polycation and a polyanion as described in U.S. Pat. Nos. 3,276,589; 3,541,055; 3,541,066 and 3,546,142; deriva tives of poly(styrene), such as microporous poly(sodium styrenesulfonate) and microporous poly(-vinyl benzyltrimethyl-ammonium chloride), the microporous materials disclosed in U.S. Pat. Nos. 3,615,024, U.S. Pat. Nos. 3,646,178, 3,852,224, and the like.

Further, the micropore forming material used for the purpose of the invention includes the embodiment wherein the microporous wall or the lamina is formed in situ by a pore former being removed by dissolving, extracting, eroding, or leaching it to form the microporous lamina during the operation of the system. The pore former can be a solid or a liquid. The term, "liquid," for this invention, embraces semi-solids and viscous fluids. The pore formers can be inorganic or organic. The pore formers suitable for the invention include pore formers that can be extracted, dissolved or leached without any chemical change in the polymer. The pore forming solids have a size of about 0.1 to 200 micrometers and they include alkali metal salts such as sodium chloride, sodium bromide, potassium chloride, potassium sulfate, potassium phosphate, sodium benzoate, sodium acetate, sodium citrate, potassium nitrate, and the like. The alkali earth metal salts include calcium phosphate, calcium nitrate, and the like. The transition metal salts include ferric chloride, ferrous sulfate, zinc sulfate, cupric chloride, manganese fluoride, manganese fluorosilicate, and the like. The pore formers include organic compounds such as polysaccharides. The polysaccharides include the sugars: sucrose, glucose, fructose, mannose, galactose, aldohexose, altrose, talose, lactose, monosaccharides and disaccharides; and polyalcohols such as mannitol and sorbitol. Also, organic aliphatic and aromatic oils and solids, including diols and polyols, as exemplified by polyhydric alcohols, poly(alkylene glycols), polyglycols, alkylene glycols, poly(alpha-omega)-alkylene diols esters or alkylene glycols and the like; water soluble cellulosic polymers such as hydroxyloweralkyl cellulose, hydroxypropylmethylcellulose, methylcellulose, methylethyl cellulose, hydroxyethylcellulose and the like: water soluble polymers such as sodium carboxymethylcellulose and the like. The pore-formers on their removal from the lamina form channels through the lamina. These can serve as pore-passageways for effective release of agent from the system. In a preferred embodiment the nontoxic, pore forming agents are selected from the group consisting of inorganic and organic salts, carbohydrates, polyalkylene glycols, poly (alpha-omega)-alkylenediols, esters of alkylene glycols, glycols, alcohols, hydric alcohols, and water soluble polymers used for forming a microporous lamina in a biological environment. Generally, for the purpose of this invention, when the polymer forming the microporous lamina contains more than 15% by weight of a pore former, the polymer is a precursor microporous lamina that on removing the pore former yields a lamina which is substantially microporous.

The expression, "passageway," as used herein comprises means and methods suitable for releasing the agent or drug from the osmotic system. The expression, "passageway," includes aperture, orifice, hole, porous element, hollow fiber, capillary tube, microporous insert, pore, microporous overlay, or bore, and the like, through the semipermeable lamina, the microporous lamina, or through the laminated wall. The passageway can be formed by mechanical drilling, laser drilling, eroding an erodible element, extracting, dissolving, bursting or leaching a passageway former from the wall. One description of a presently preferred passageway an the maximum and minimum dimensions for such a passageway, are disclosed in U.S. Pat. Nos. 3,845,770 and 3,916,899. The osmotically calibrated passageway has a maximum cross sectional area, A_s, defined by the relation (17) as follows:

$$A_{s(max)} = \frac{L}{F} \times \frac{Q_p}{t} \times \frac{1}{DS} \quad (17)$$

wherein L is the length of the passageway Q_p/t is the mass delivery rate of the agent, D is the diffusion coefficient of the agent, S is the solubility of the agent in the fluid, and F is from 2 to 1000, said passageway having a minimum area A_s defined by relation (18) as follows:

$$A_{s(min)} = \left[\frac{L_v}{t} \times 8 \times \frac{\pi \eta}{\Delta P} \right]^{\frac{1}{4}} \quad (18)$$

wherein L is the length of the passageway, v/t is the agent solution volume delivery rate, π is 3.14; η is the viscosity of agent solution or suspension dispensed from

the device and ΔP is the hydrostatic pressure difference between the inside and the outside of the compartment having a value up to 20 atmospheres. In addition, one or more passageways can be introduced into the device. The number of passageways can be large, but should satisfy the condition that the delivery rate is substantially governed by the imbibition flux of water across the surrounding wall.

The passageway can be a pore formed by leaching sorbitol, and the like, from a wall, as disclosed in U.S. Pat. No. 4,200,098. This patent discloses pores of controlled size-porosity formed by dissolving, extracting or leaching a material from a wall, such as sorbitol from cellulose acetate. The pore-passageways extend from the inside to the outside of the wall for effective release of beneficial agent including a drug to the exterior of the system. In U.S. Pat. No. 4,285,987 a composite delivery system is disclosed comprising a first device that surround a second device. The first comprises a cellulose acetate wall comprising leachable sorbitol for forming a pore for releasing osmotically active potassium chloride from an osmotic core. The second device releases drug through a laser drilled passageway. The patent thereby discloses drug released through passageways formed by different techniques.

The osmotically effective compounds that can be used for the purpose of this invention include inorganic and organic compounds that exhibit an osmotic pressure gradient across a semipermeable wall, or across a microporous, or a laminated wall, against an external fluid. The osmoticlly effective compounds, along with the osmopolymers, imbibe fluid into the osmotic device thereby making available in situ fluid for imbibition and/or absorption by an osmopolymer to enhance its expansion, and/or for forming a solution or suspension containing a beneficial agent for its delivery through a passageway form the osmotic device.

The osmotically effective compounds are known also as osmotically effective solutes, and also as osmagents. The osmotically effective compounds are used by mixing them with a beneficial agent, or with an osmopolymer for forming a solution, or suspension containing the beneficial agent that is osmotically delivered from the device. The expression, "limited solubility," as used herein means the agent has a solubility of about less than 5% by weight in the aqueous fluid present in the environment. The osmotic solutes are used by homogeneously or heterogeneously mixing the solute with the agent or osmopolymer and then charging them into the reservoir. The solutes and osmopolymers attract fluid into the reservoir producing a solution of solute in a gel which is delivered from the system concomitantly transporting undissolved and dissolved beneficial agent to the exterior of the system. Osmotically effective solutes used for the former purpose include magnesium sulfate, magnesium chloride, potassium sulfate, sodium sulfate, lithium sulfate, potassium acid phosphate, d-mannitol, urea, inositol, magnesium succinate, tartaric acid, carbohydrates such as raffinose, sucrose, glucose, alpha-d-lactose monohydrate, sorbitol, and mixtures thereof. The amount of osmagent in the compartment will generally be from 0.01% to 30% or higher in the first composition, and usually from 0.01% to 40% or higher in the second composition.

The osmotic solute is preferably initially present in excess and it can be in any physical form that is compatible with the beneficial agent, the device, and the osmopolymer. The osmotic pressure of saturated solutions of various osmotically effective compounds and for mixtures of compounds at 37° C., in water, are listed in Table 1. In the table, the osmotic pressure π, is in atmospheres, atm. The osmotic pressure is measured in a commercially available osmometer that measures the vapor pressure difference between pure water and the solution to be analyzed and, according to standard thermodynamic principles, the vapor pressure ratio is converted into osmotic pressure difference. In Table 1, osmotic pressures of from 20 atm to 500 atm are set forth. Of course, the invention includes the use of lower osmotic pressures from zero, and higher osmotic pressures than those set forth by way of example in Table 1. The osmometer used for the present measurements is identified as Model 320B, Vapor Pressure Osmometer, manufactured by the Hewlett Packard Co., Avondale, Pa.

TABLE 1

COMPOUND OR MIXTURE	OSMOTIC PRESSURE ATM
Lactose-Fructose	500
Dextrose-Fructose	450
Sucrose-Fructose	430
Mannitol-Fructose	415
Sodium Chloride	356
Fructose	355
Lactose-Sucrose	250
Potassium Chloride	245
Lactose-Dextrose	225
Mannitol-Dextrose	225
Dextrose-Sucrose	190
Manitol-Sucrose	170
Dextrose	82
Potassium Sulfate	39
Mannitol	38
Sodium Phosphate Tribasic $12H_2O$	36
Sodium Phosphate Dibasic 7 H_2O	31
Sodium Phosphate Dibasic $12H_2O$	31
Sodium Phosphate Dibasic Anhydrous	29
Sodium Phosphate Monobasic H_2O	28

The osmopolymers suitable for forming the first drug containing osmotic composition, and also suitable for forming the second drug free osmotic composition, are osmopolymers that exhibit fluid imbibition properties. The osmopolymers are swellable, hydrophilic hydrogel polymers which osmopolymers interact with water and aqueous biological fluids and swell or expand to an equilibrium state. The osmopolymers exhibit the ability to swell in water and retain a significant portion of the imbibed water within the polymer structure. The osmopolymers swell or expand to a very high degree, usually exhibiting a 2 to 50 fold volume increase. The osmopolymers can be noncross-linked or cross-linked. The swellable, hydrophilic polymers are, in one presently preferred embodiment, lightly cross-linked, such cross-links being formed by covalent bonds, hydrogen bonds, ionic bonds or residue crystalline regions after swelling. The osmopolymers can be of plant, animal or synthetic origin. The osmopolymers are hydrophilic polymers. Hydrophilic polymers suitable for the present purpose include poly(hydroxy-alkyl methacrylate) having a molecular weight of from 30,000 to 5,000,000; anionic and cationic hydrogels; polyelectrolyte complexes; poly(vinyl alcohol) having a low acetate residual, cross-linked with glyoxal, formaldehyde, or glutaraldehyde and having a degree of polymerization from 200 to 30,000; a mixture of methylcellulose, cross-linked agar and carboxymethyl cellulose; a mixture of hydroxypropyl methylcellulose and sodium carboxymethylcel-

lulose, hydroxypropyl-methylcellulose and sodium carboxymethyl cellulose; a water insoluble, water swellable copolymer reduced by forming a dispersion of finely divided copolymer of maleic anhydride with styrene, ethylene, propylene, butylene or isobutylene crosslinked with from 0.001 to about 0.5 moles of saturated cross-linking agent per mole of maleic anhydride in copolymer; water swellable polymers of N-vinyl lactams; polyoxyethylene-polyoxypropylene gel; polyoxybutylene-polyethylene block copolymer gel; carob gum, polyacrylic gel; polyester gel; polyurea gel; polyether gel; polyamide gel; polyimide gel; polypeptide gel; polyamino acid gel; polycellulosic gel; polygum gel; initially dry hydrogels that generally imbibe and absorb water which penetrates the glassy hydrogel and lowers its glass transition temperature, and the like.

Other osmopolymers include hydrogels such as Carbopol ® acidic carboxy polymers, a polymer of acrylic acid crosslinked with a polyallyl sucrose, also known as carboxypolymethylene and carboxyvinyl polymer having a molecular weight of 250,000 to 4,000,000; Cyanamer ® polyacrylamides; cross-linked water swellable indene-maleic anhydride hydrogel polymers; Goodrite ® polyacrylic acid having a molecular weight of 80,000 to 200,000; Polyox ® polyethylene oxide polymers having a molecular weight of 100,000 to 5,000,000 and higher; starch graft copolymers; Aqua-Keeps ® acrylate polymer polysaccharides composed of condensed glucose units such as diester cross-linked polyglucan; and the like. Representative polymers that form hydrogels are known to the prior art in U.S. Pat. No. 3,865,108 issued to Hartop; U.S. Pat. No. 4,002,173 issued to Manning; U.S. Pat. No. 4,207,893 issued to Michaels; and in *Handbook of Common Polymers*, by Scott and Roff, published by the Chemical Rubber Company, Cleveland, Ohio. The amount of osmopolymer in the first composition is about 10% to 90%, and the amount of osmopolymer in the second composition is 20% to 100%, with the total weight of all ingredients in a composition equal to 100%. In a presently preferred embodiment, the osmopolymer identified as P_1 comprising the first composition is different than the osmopolymer identified as P_2 comprising the second composition. The osmopolymer in the first composition can be structurally different than the osmopolymer in the second composition. Or, the osmopolymer's molecular weight in the second osmotic composition is larger than the molecular weight of the osmopolymer in the first composition. The osmopolymer P_1 comprising the first composition comprising the beneficial agent serves as a pharmaceutically acceptable carrier for transporting the active agent from the device in the form of a paste or gel-like ribbon, and it also contributes to the driving force that cooperates with osmopolymer P_2 comprising the second composition that delivers the agent through the passageway from the device. The phrase, "pharmaceutically acceptable carrier," as used for the purpose of this invention, means the drug is mixed with a gel and is transported with the gel from the device. During operation of the device fluid is imbibed into the device resulting in the viscosity of P_2 being greater than the viscosity of P_1. In this operation P_1 and P_2 operate as a single unit substantially free of a void between their interfaced contacting surfaces of osmopolymer P_1 and P_2 for successful delivery of the beneficial agent from the osmotic device.

Osmopolymer fluid imbibition determination for a chosen polymer can be made by following the procedure described below. A round die having an inner diameter of ½ inch, fitted with a ½ inch diameter stainless steel plug, is charged with a known quantity of polymer with the plugs extending out either end. The plugs and the die were placed in a Carver press with plates between 200° F. and 300° F. A pressure of 10,000 to 15,000 psi was applied to the plugs. After 10 to 20 minutes of heat and pressure the electrical heating to the plates was turned off, and tap water circulated through the plates. The resulting ½ inch disks were placed in an air suspension coater charged with 1.8 kg saccharide cores, placebo cores, made of any sugar such as lactose, and so forth, and coated with cellulose acetate having an acetyl content of 39.8% dissolved in 94:6 w/w, CH_2Cl_2/CH_3OH, to yield a 3% w/w solution. The coated systems were dried overnight at 50° C. The coated disks were immersed in water at 37° C. and periodically removed for a gravimetric determination of water imbibed. The initial imbibition pressure was calculated by using the water transmission constant for the cellulose acetate, after normalizing imbibition values for membrane surface area and thickness. The polymer used in this determination was the sodium derivative of Carbopol-934 ® polymer, prepared according to the procedure of B. F. Goodrich Service Bulletin GC-36, "Carbopol ® Water-Soluble Resins," page 5, published by B. F. Goodrich, Akron, Ohio.

The cumulative weight gain values, y, as a function of time, t, for the water soluble polymer disk coated with the cellulose acetate were used to determine the equation of the line $y=c+bt+at^2$ passing through those points by at least square fitting technique.

The weight gain for the sodium salt of Carbopol-934 ® is given by the equation (19) that follows: Weight gain equals $0.359+0.665t-0.00106t^2$ wherein t is elapsed time in minutes. The rate of water flux at any time will be equal to the slope of the line that is given by the following equations (19) and (20):

$$\frac{dv}{dt} = \frac{d(0.359 + 0.665t - 0.00106t^2)}{dt} \quad (19)$$

$$\frac{dv}{dt} = 0.665 - 0.00412t \quad (20)$$

To determine the initial rate of water flux the derivative is evaluated at t=0, and dy/dt 0.665 μl/min., which is equal to the coefficient b. Then, normalizing the imbibition rate for time, membrane surface area and thickness, and the membrane permeability constant to water, $K\pi$ may be determined according to the following equation (21):

$$K\pi = 0.665\ \mu l/min \times \left(\frac{60\ min}{hr}\right) \times \left(\frac{1\ ml}{1000\ \mu l}\right)\left(\frac{0.008\ cm}{2.86\ cm^2}\right) \quad (21)$$

with $K\pi = 1.13\times10^{-4}$ cm²/hr. The π value for NaCl was determined with a Hewlett Packard vapor pressure osmometer to be 345 atm±10%, and the K value for cellulose acetate used in this experiment calculated from NaCl imbibition values was determined to be 1.9×10^{-7} cm²/hr·atm.

Substituting these values into the calculated $K\pi$ expression, $(1.9\times10^{-7}/cm^2/hr\ \ atm)(\pi) = 1.13\times10^{-4}$ cm²hr gives $\pi = 600$ atm at t=0. As a method for evaluating the efficiency of a polymer with respect to duration of zero order driving force, the percent of water

uptake was selected before the water flux values decreased to 90% of their initial values. The value of the slope for the equation of a straight line emanating from the percent weight gained axis will be equal to the initial value of dy/dt evaluated at t=0, with the y intercept c defining the linear swelling time, with (dy/dt) 0=0.665 and the y intercept=0, which yields y=0.665t+0.359. In order to determine when the value of the cumulative water uptake is 90% below the initial rate, the following expression is solved for t:

$$0.9 = \frac{at^2 + bt + c}{bt + c} = \frac{\Delta W}{w}\,0.9 \tag{22}$$

$$\frac{0.00106\,t^2 + 0.665\,t + 0.359}{0.665\,t + 0.359} = 0.9 \tag{23}$$

and solving for t,

$$-0.00106\,t^2 + 0.0065\,t + 0.0359 = 0$$

$$t = \frac{-0.0665 + [(0.0665)^2 - 4(-0.00106)(0.0359)]^{\frac{1}{2}}}{2(-0.00106)} \tag{24}$$

t=62 min and the weight gain is $-0.00106(62)^2+(0.665)(62)+0.359$ 38 μl, with the initial sample weight=100 mg, thus (Δw/w) $0.9\times100=38\%$. The results are presented in FIG. 8 for a graphical representation of the values. Other methods available for studying the hydrogel solution interface include rheologic analysis, viscometric analysis, ellipsometry, contact angle measurements, electrokinetic determinations, infrared spectroscopy, optical microscopy, interface morphology and microscopic examination of an operative device.

The expression, "beneficial agent," as used herein, includes any beneficial agent, or beneficial compound, that can be delivered from the device to produce a beneficial and useful therapeutic result. The beneficial agent can be insoluble to very soluble in the exterior fluid that enters the device and it optionally can be mixed with an osmotically effective compound and an osmopolymer. The term, "beneficial agent," includes algicide, antioxidant, air purifier, biocide, bactericide, catalyst, chemical reactant, disinfectant, fungicide, fermentation agent, fertility inhibitor, fertility promoter, germicide, plant growth promoter, plant growth inhibitor, preserative, rodenticide, sterilization agent, sex sterilant, and the like.

In the specification and the accompanying claims, the term, "beneficial agent," also includes drug. The term, "drug," includes any physiologically or pharmacologically active substance that produces a local or systemic effect, in animals, including warm-blooded mammals, humans and primates; avians; household, sport and farm animals; laboratory animals; fishes; reptiles and zoo animals. The term, "physiologically," as used herein, denotes the administration of a drug to produce generally normal levels and functions. The term, "pharmacologically," denotes generally variations in response to the amount of drug administered to the host. See *Stedman's Medical Dictionary*, (1966), published by Williams and Wilkins, Baltimore, MD. The phrase, "drug formulation," as used herein, means the drug is in the compartment mixed with the osmopolymer and, if applicable, with a binder and optional lubricant. The active drug that can be delivered includes inorganic and organic compounds without limitation, including drugs that act on the peripheral nerves, adrenergic receptors, cholinergic receptors, nervous system, skeletal muscles, cardiovascular system, smooth muscles, blood circulatory system, synaptic sites, neuroeffector junctional sites, endocrine system, hormone systems, immunological system, reproductive system, skeletal system, autacoid systems, alimentary and excretory systems, inhibitory of autocoid systems, alimentary and excretory systems, inhibitory of autocoids and histamine systems. The active drug that can be delivered for acting on these recipients include anticonvulsants, analgesics, anti-inflammatories, calcium antagonists, anesthetics, antimicrobials, antimalarials, antiparasitic, antihypertensives, antihistamines, antipyretics, alpha-adrenergic agnoist, alpha-blockers, biocides, bactericides, bronchial dilators, beta-adrenergic blocking drugs, contraceptives, cardiovascular drugs, calcium channel inhibitors, depressants, diagnostics, diuretics, electrolytes, hypnotics, hormonals, hyperglycemics, muscle contractants, muscle relaxants, opthalmics, psychic energizers, parasympathomimetics, sedatives, sympathomimetics, tranquilizers, urinary tract drugs, vaginal drugs, vitamins, nonsteroidal anti-inflammatory drugs, angiotensin converting enzymes, polypeptide drugs, and the like.

Exemplary drugs that are very soluble in water and can be delivered by the osmotic devices of this invention include prochlor perazine edisylate, ferrous sulfate, aminocaproic acid, potassium chloride, mecamylamine hydrochloride, procainamide hydrochloride, amphetamine sulfate, benzphetamine hydrochloride, isoproteronol sulfate, methamphetamine hydrochloride, phenmetrazine hydrochloride, bethanechol chloride, methacholine chloride, pilocarpine hydrochloride, atropine sulfate, scopolamine bromide, isopropamide iodide, tridihexethyl chloride, phenformin hydrochloride, methylphenidate hydrochloride, cimetidine hydrochloride, theophylline cholinate, cephalexin hydrochloride, and the like.

Exemplary drugs that are poorly soluble in water and that can be delivered by the devices of this invention include diphenidol, meclizine hydrochloride, prochlorperazine maleate, phenoxybenzamine, thiethylperazine maleate, anisindone, diphenadione erythrityl tetrani trate, digoxin, isoflurophate, acetazolamide, methazolamide, bendro-flumethiazide, chlorpropamide, tolazamide, chlormadinone acetate, phenaglycodol, allopurinol, aluminum aspirin, methotrexate, acetyl sulfisoxazole, erythromycin, progestins, sterogenic, progestational, corticosteroids, hydrocortisone hydrocorticosterone acetate, cortisone acetate, triamcinolone, methyltesterone, 17 beta-estradiol, ethinyl estradiol, ethinyl estradiol 3-methyl ether, pednisolone, 17 beta-hydroxyprogesterone acetate, 19-nor-progesterone, norgestrel, norethindrone, norethisterone, norethiederone, progesterone, norgesterone, norethynodrel, and the like.

Examples of other drugs that can be delivered by the osmotic device include aspirin, indomethacin, naproxen, fenoprofen, sulindac, indoprofen, nitroglycerin, isosorbide dinitrate, propranolol, timolol, atenolol, alprenolol, cimetidine, clonidine, imipramine, levodopa, chloropromazine, methyldopa, dihydroxyphenylalanine, pivaloyloxyethyl ester of alpha-methyldopa hydrochloride, theophylline, calcium gluconate, ketoprofen, ibuprofen, cephalexin, erythromycin, haloperidol, zomepirac, ferrous lactate, vincamine, diazepam, phenoxybenzamine, diltiazem, milrinone, captopril,

madol, quanbenz, hydrochlorothiazide, ranitidine, flurbiprofen, fenbufen, fluprofen, tolmetin, alolofenac, mefenamic, flufenamic, difuninal, nimodipine, nitrendipine, nisoldipine, nicardipine, felodipine, lidoflazine, tiapamil, gallopamil, amlodipine, mioflazine, lisinolpril, enalapril, captopril, ramipril, endlapriat, famotidine, nizatidine, sucralfate, etintidine, tertatolol, minoxidil, chlordiazepoxide, chlordiazepoxide hydrochloride, diazepan, amitriptylin hydrochloride, impramine hydrochloride, imipramine pamoate, enitabas, and the like. The beneficial drugs are known to the art in *Pharmaceutical Sciences*, 14th Ed., edited by Remington, (1979) published by Mack publishing Co., Easton, Pa.; *The Drug, The Nurse, The Patient, Including Current Drug Handbook*, by Falconer, et al., (1974–1976) published by Saunders Company, Philadelphia, Pa.; *Medicinal Chemistry*, 3rd Ed., Vol. 1 and 2, by Burger, published by Wiley-Interscience, New York; and in *Physicians' Desk Reference*, 38th Ed., (1984) published by Medical Economics Co., Oradell, N.J.

The drug can be in various forms, such as uncharged molecules, molecular complexes, pharmacologically acceptable salts such as hydrochloride, hydrobromide, sulfate, laurate, palmitate, phosphate, nitrite, borate, acetate, maleate, tartrate, oleate and salicylate. For acidic drugs, salts of metals, amines or organic cations; for example, quarternary ammonium can be used. Derivatives of drugs such as ester, ethers and amides can be used. Also, a drug that is water insoluble can be used in a form that is water soluble derivative thereof to serve as a solute, and on its release from the device, is converted by enzymes, hydrolyzed by body pH or other metabolic processes to the original biologically active form. The agent, including drug, can be present in the compartment with a binder, dispersant, wetting agent, suspending agent, lubricant and dye. Representative of these include suspending agents such as acacia, agar, calcium carrageenan, alginic acid, algin, agarose powder, collagen, colloidal magnesium silicate, pectin, gelatin and the like; binders like polyvinyl pyrrolidone, lubricants such as magnesium stearate; wetting agents such as fatty amines, fatty quaternary ammonium salts, and the like. The phrase, "drug formulation," indicates the drug is present in the compartment accompanied by an osmagent, osmopolymer, a binder, and/or the like. The amount of beneficial agent in a device generally is about from 0.05 ng to 5 g or more, with individual devices containing, for example, 25 ng, 1 mg, 5 mg, 10 mg, 25 mg, 125 mg, 250 mg, 500 mg, 750 mg, 1.0 g, 1.2 g, 1.5 g, and the like. The devices can be administered one, twice or thrice daily.

The solubility of a beneficial agent in the fluid can be determined by known techniques. One method consists of preparing a saturated solution comprising the fluid plus the agent as ascertained by analyzing the amount of agent present in a definite quantity of the fluid. A sample apparatus for this purpose consists of a test tube of medium size fastened upright in a water bath maintained at constant temperature and pressure, in which the fluid and agent are placed and stirred by a rotating glass spiral. After a given period of stirring, a weight of the fluid is analyzed and the stirring continued and additional period of time. If the analysis shows no increase of dissolved agent after successive periods of stirring, in the presence of excess solid agent in the fluid, the solution is saturated and the results are taken as the solubility of the product in the fluid. If the agent is soluble, an added osmotically effective compound option ally may be not needed; if the agent has limited solubility in the fluid, then an osmotically effective compound can be incorporated into the device. Numerous other methods are available for the determination of the solubility of an agent in a fluid. Typical methods used for the measurement of solubility are chemical and electrical conductivity. Details of various methods for determining solubilities are described in the *United States Public Health Service Bulletin*, No. 67 of the Hygienic Laboratory; *Encyclopedia of Science and Technology*, Vol. 12, pp 542 to 556, (1971) published by McGraw-Hill, Inc.; and *Encyclopedia Dictionary of Physics*, Vol. 6, pp 547 to 557, (1962) published in Pergamon Press, Inc.

The device of the invention is manufactured by standard techniques. For example, in one embodiment the beneficial agent is mixed with an osmagent and osmopolymer, and pressed into a solid possessing dimensions that correspond to the internal dimensions of the compartment adjacent to the passageway; or the beneficial agent and other formulation forming ingredients and a solvent are mixed into a solid or a semisolid by conventional methods such as ballmilling, calendering, stirring or rollmilling, and then pressed into a preselected shape. Next, a layer of a composition comprising an osmagent and an osmopolymer is laced in contact with the layer of beneficial agent formulation, and the two layers surrounded with a semipermeable wall. The layering of the beneficial agent composition and the osmagent/osmopolymer can be accomplished by conventional two layer tablet press techniques. The wall can be applied by molding, spraying, or dipping the pressed shapes into wall-forming materials. Another and presently preferred technique that can be used for applying the wall is the air suspension coating procedure. This procedure consists in suspending and tumbling the pressed compositions in a current of air and a wall forming composition until the wall surrounds and coats the two pressed compositions. They form a laminated wall. The air suspension procedure is described in U.S. Pat. No. 2,799,241; *J. Am. Pharm. Assoc.*, Vol. 48, pp 451 to 459 (1979); and, *ibid*, Vol. 49, pp 82 to 84 (1960). Other standard manufacturing procedures are described in *Modern Plastics Encyclopedia*, Vol. 46, pp 62 to 70 (1969); and in *Pharmaceutical Science*, by Remington, 14th Ed., pp 1626 to 1978 (1970), published by Mack Publishing Co., Easton, Pa.

Exemplary solvents suitable for manufacturing the wall, the laminates and laminae, include inert inorganic and organic solvents, that do not adversely harm the materials and the final wall or the final laminated wall. The solvents broadly include members selected from the group consisting of aqueous solvents, alcohols, ketones, esters, ethers, aliphatic hydrocarbons, halogenated solvents, cycloaliphatics, aromatics, heterocyclic solvents, and mixtures thereof. Typical solvents include acetone, diacetone alcohol, methanol, ethanol, isopropyl alcohol, butyl alcohol, methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, methyl propyl ketone, n-hexane, n-heptane, ethylene glycol monoethyl ether, ethylene glycol monoethyl acetate, methylene dichloride, ethylene dichloride, propylene dichloride, carbon tetrachloride, chloroform, nitroethane, nitropropane, tetrachloroethane, ethyl ether, isopropyl ether, cyclohexane, cyclo-octane, benzene, toluene, naphtha, 1,4-dioxane, tetrahydrofuran, diglyme, aqueous and nonaqueous mixtures thereof, such as acetone and water, acetone and metha-

nol, acetone and ethyl alcohol, methylene dichloride and methanol, and ethylene dichloride and methanol.

DETAILED DESCRIPTION OF EXAMPLES

The following examples are merely illustrative of the present invention, and they should not be considered as limiting the scope of the invention in any way, as these examples and other equivalents thereof will become apparent to those versed in the art in the light of the present disclosure, the drawings and the accompanying claims.

EXAMPLE 1

The operation of a device **10** manufactured according to the invention is set forth in this example. The volume imbibition rate of the push formulation composition is equal to the volume rate of water imbibition (dV/dt)p into the osmotic push agent formulation composition expressed by equation (25) as follows:

$$\left(\frac{dV}{dt}\right)_p = \frac{k}{h} A_p \cdot \Delta\pi \tag{25}$$

where k is the water permeability of the semipermeable wall, h is the thickness of the wall, A_p is the wall surface of the push compartment exposed to the osmotic process, and $\Delta\pi$ is the osmotic pressure difference of the push formulation across the wall. The geometrical shape considered here is as shown in FIG. **5**, with flat bottom and cylindrical body. The volume rate of water imbibition can be related to the total surface area for water transport A from the end and cylindrical sections from equations (26) and (27):

$$A_p = \Delta r^2 + 2\,rl \tag{26}$$

where l is the height of the osmotic formulation.

$$A_p = \pi r^2 + \frac{2}{r} V \tag{27}$$

where V is the volume of osmotic formulation. The volume expansion of the osmotic driving member equals

$$V = V_o + V_H \tag{28}$$

where V_o and V_H are, respectively, the volumes of dry osmotic agent formulation and water imbibed. Alternatively, (28) can be written

$$V = \frac{W_o}{\rho_o} + \frac{W_H}{\rho_H} \tag{29}$$

where ρ_o is the density of dry osmotic agent formulation, W_o and W_H are the weights of osmotic agent and water imbibed, and ρ_H is the density of water.

Rearranging terms within the equations, the following equation results:

$$V = \frac{W_o}{\rho_o}\left(1 + \frac{W_H}{W_o} \cdot \frac{\rho_o}{\rho_H}\right) \tag{30}$$

and

-continued

$$A_p = \pi r^2 + \frac{2}{r} \frac{W_o}{\rho_o}\left(1 + \frac{W_H}{W_o} \cdot \frac{\rho_o}{\rho_H}\right) \tag{31}$$

Therefore, the volume rate of water imbibition is expressed by:

$$\left(\frac{dV}{dt}\right)_p = \frac{k}{h}\left(\pi r^2 + \frac{2}{r}\left(1 + \frac{\rho_o}{\rho_H} \frac{W_H}{W_o}\right)\frac{W_o}{\rho_o}\right)\Delta\pi \tag{32}$$

The release rate of drug from the dispenser can be written as shown in equation (3) where F and Q are respectively the volume flow into the drug and osmotic push compartment.

$$\frac{dm}{dt} = (F + Q)\, C_d \tag{33}$$

Here C_d is the concentration of drug in the dispensed formulation. Equation (33) considered in conjunction with (32), allow for numerous delivery rates and drug programs derived from system 10 geometry and the osmotic pressure $\Delta\pi$ programmed in the dispenser as a function of time.

For development of the example, equation (34) will be substituted in the subsequent equations.

$$H = \frac{W_H}{W_o} \tag{34}$$

The composition of the driving push composition is formulated with an osmotically active polymer composition as shown in FIG. **9** which exhibits an osmotic pressure as a function of hydration as shown for membranes of two pumping rates. The osmotic pressure can be described by equations (35) and (36).

$$\Delta\pi = 180\ atm\ for\ H \leqq 0.15 \tag{35}$$

$$\Delta\pi = 227 \exp(-0.332\,H)\ for\ H > 0.15 \tag{36}$$

Substituting equation (36) and equation (37) in equation (25) equation (38) results as follows:

$$A_p(H)\pi r^2 + \frac{2}{r}\left(1 + \frac{\rho_o}{\rho_H} H\right)\frac{W_o}{\rho_o} \tag{37}$$

$$\left(\frac{dV}{dt}\right)_p = \frac{k}{h} \cdot A_p(H) \cdot \Delta\pi(H) \tag{38}$$

In addition, equation (39) holds for the volume of absorbed water V_H

$$V_H = \frac{W_H}{\rho_H} = H \cdot \frac{W_o}{\rho_H} \tag{39}$$

Since the volume of formulation displaced equation (40) is related to H by equation (39),

$$\left(\frac{dV}{dt}\right)_p = \frac{dV_H}{dt} \tag{40}$$

it follows that equation (41) results

$$\frac{dH}{dt} = \frac{\rho H}{W_o} \cdot \frac{k}{h} \cdot A_p(H) \cdot \Delta\pi(H) = f(H) \quad (41)$$

The solution of this differential equation will result in H(t) which can be substituted in equation (38) to yield the release rate. The solution to equation (41) was solved by numerical integration, resulting in the simulations for the release rates given by the numerical integration of equation (41) is obtained from equation (42) as follows:

$$= \int_o^H \frac{dH}{f(H)} = \int_o^t dt \quad (42)$$

The final value at shutdown for system 10 for H_f and t_f is given by equation (43):

$$H_f \frac{\rho H}{\rho dc} \cdot \frac{W_{dc}}{W_o} \quad (43)$$

Here π_{dc} and W_{dc} are the density and weight of the drug composition. The function H(t) is obtained by finding the time t_i associated with the hydration value H_i. The final value of H, H_f equation (43) can be reached after m equal steps ΔH, such that equation (44) results, and also equation (45).

$$\Delta H_j = \frac{H_f}{m} \quad (44)$$

$$H(ti) = \sum_{j=i}^{i} \Delta Hj \quad (45)$$

The time t_i associated with H_i is calculated from equation (46) where $\overline{f(Hj)}$ average value of expression (41) between the start and end of the interval i:

$$t_i = \sum_{j=1}^{i} \Delta t_j \quad (46)$$

Here Δt_j is given by (47)

$$\Delta t_j = \frac{\Delta H_j}{F(H)_j} \quad (47)$$

From equations (39), (40), and (47), it follows then that the volume push rate

$$\left(\frac{dV}{dt}\right)_p (t)$$

as a function of time is given by equation (48).

$$\left(\frac{\Delta V}{\Delta t}\right)_p (t) = \frac{W_o}{\rho H} \cdot \frac{\Delta H_i}{\Delta t_i} \quad (48)$$

The concentration C_d of drug in the dispensed formulation can be written as shown in equation (49) where C_o is the

$$C_d = C_o F_D \quad (49)$$

concentration of solids dispensed and F_D the fraction of drug in the dispensed formulation. This fraction of drug F_D can assume to be equal to the fraction of drug formulated in the drug compartment in the dry state if the drug formulation is dispensed uniformly; π_{dc} is the density of the drug formulation.

These push-pull systems operate favorably in a region where the drug compartment formulates drug in suspension at a constant rate and wherein the push compartment dispenses this formulation at a constant rate. Such condition is achieved when the majority of semisolid drug formulation is dispensed such that the total drug delivery rate can be expressed by equation (50).

$$\frac{dm}{dt} = \left(\frac{dV}{dt}\right)_p F_D \cdot \rho dc \quad (50)$$

The influx of water in the drug compartment

$$F = \left(\frac{dV}{dt}\right)_D$$

is responsible for converting the solid drug formulation into a fluid form of drug concentration C_d. The volume flux F adds to the osmotic driving flux

$$Q = \left(\frac{dV}{dt}\right)_p$$

yield equation (51).

$$\frac{dm}{dt} = (Q + F) \cdot C_d \quad (51)$$

By equating equations (33) and (51) and considering equation (49), the concentration of dispensed solids C_o can be found to be given by equation (52), also C_o can

$$C_o = \frac{Q \cdot \rho dc}{F + Q} \quad (52)$$

be verified independently.

Based on the above description, three push-pull osmotic systems were designed to deliver a water soluble drug with parameters as listed in Table 2. The density of the push and drug compartment was respectively 1.4 and 1.2 gr/ml. The osmotic pressure in the drug compartment was 70 atm. The volume was allowed to swell 25 percent till hydration H=0.15, and the diameter and system area during that time decreased by about 15 percent. The release rate from these systems achieved a release rate as shown in FIG. 10 based on equations (48) and (50). The concentration of dispensed solids achieved a range of 500 to 900 mg/ml.

TABLE 2

Design Parameters For Insoluble Drug			
Diameter (cm)	0.79	1.03	1.19
Drug content (mg)	33	66	99
Weight of drug layer (mg)	165	330	495
Weight of push layer (mg)	82.5	165	247.5
Membrane thickness (cm)	12×10^{-3}	11×10^{-3}	9.9×10^{-3}
Membrane	6.35×10^{-7}	6.35×10^{-7}	6.35×10^{-7}

TABLE 2-continued

Design Parameters For Insoluble Drug			
permeability (cm^2/hr atm)			
Total system area A (cm^2)	1.9	3.1	4.1

EXAMPLE 2

An osmotic delivery device manufactured in the appearance of an osmotic tablet shaped, sized and adapted for oral admittance into the gastrointestinal tract is made as follows: a first osmotic drug composition is prepared by screening 355 g of poly(ethylene oxide), having an approximate molecular weight of 200,000, through a 40 mesh stainless steel screen, then 100 g of a calcium antagonist is passed through the 40 mesh screen, 25 g of hydroxypropylmethylcellulose is passed through the 40 mesh screen and, finally, 10 g of potassium chloride is passed through the 40 mesh screen. Next, all the screened ingredients are added to the bowl of a laboratory blender and the ingredients dry blended for 15 to 20 minutes to produce a homogeneous blend. Then, a granulation fluid is prepared comprising 250 ml of ethanol and 250 ml of isopropyl alcohol, and the granulating fluid added to the blending bowl; first, 50 ml is sprayed into the bowl with constant blending, then 350 ml of the granulation fluid is added slowly to the bowl and the wet mass blended for another 15 to 20 minutes. Then, the wet granules are passed through a 16 mesh screen and dried at room temperature for 24 hours. Next, 10 g of magnesium stearate is added to the dry granules, and the ingredients roll-mixed for 20 to 30 minutes on a standard two-roll mill.

Next, a second osmotic composition is prepared as follows: first, 170 g of poly(ethylene oxide) having a molecular weight of 5,000,000 is screened through a 40 mesh screen, then 72.5 g of sodium chloride is passed through the 40 mesh screen, and the ingredients added to a mixing bowl and blended for 10 to 15 minutes. Then, a granulation fluid is prepared by mixing 350 ml of methanol and 150 ml of isopropyl alcohol, and the granulation fluid added to the blending bowl in two steps. First, 50 ml of the granulation fluid is sprayed into the bowl with constant blending; then 350 ml of the granulation fluid is slowly added to the bowl and the wet blend mixed for 15 to 20 minutes to a homogeneous blend. Then, the wet blend is passed through a 16 mesh screen, spread on a stainless steel tray and dried at room temperature of 22.5° C. for 24 hours. The dried blend is passed through a 16 mesh screen, then roll milled with 5 g of magnesium stearate on a two-roll mill for 20 to 30 minutes.

A number of drug cores are prepared by pressing the two compositions on a Manesty Layerpress. The drug containing composition is fed into the cavity mold of the press and tamped into a solid layer. Then, the second osmotic composition is fed into the cavity overlaying the tamped layer and compressed into a solid layer to form a two-layered drug core.

The drug cores next are coated with a semipermeable wall forming composition comprising 95 g of cellulose acetate having an acetyl content of 39.8% and 5 g of poly(ethylene glycol) 4000 in a solvent comprising 1960 ml of methylene chloride and 820 ml of methanol. The drug cores are coated with the semipermeable wall forming composition until the wall surrounds the drug core. A Wurster air suspension coater is used to form the semipermeable wall. The coated cores are then spread on a tray and the solvent evaporated in a circulating air oven at 50° C. for 65 hours. After cooling to room temperature, a 0.26 mm diameter passageway is laser drilled through the semipermeable wall connecting the exterior of the osmotic device with the composition containing the drug. The osmotic device weighed 262 mg and it contained 30 mg of drug in the first composition weighing 150 mg, the second composition weighed 75 mg and the semipermeable wall weighed 37 mg. The first composition of the osmotic device comprises 30 mg of the calcium antagonists, 106 mg of poly-(ethylene oxide), 3 mg of potassium chloride, 7.5 mg of hydroxypropylmethylcellulose and 3 mg of magnesium stearate. The second osmotic composition comprises 51 mg of poly(ethylene oxide), 22 mg of sodium chloride and 1.5 mg of magnesium stearate. The device has a diameter of 8 mm, a surface area of 1.8 cm^2 and the semipermeable wall is 0.17 mm thick. The cumulative amount of drug released is depicted in FIG. 11.

EXAMPLE 3

Osmotic delivery systems are prepared having a first composition comprising 25 to 1000 mg of a calcium channel blocker 100 to 325 mg of poly(ethylene oxide) having a molecular weight of 200,000, 2 to 10 mg of potassium chloride, 5 to 30 mg of hydroxypropylmethylcellulose, and 2 to 10 mg of magnesium stearate; and a second composition comprising 30 to 275 mg of poly-(ethylene oxide) having a molecular weight of 5,000,000, 20 to 75 mg of sodium chloride and 1 to 5 mg of magnesium stearate. The procedure of Example 1 is repeated for preparing osmotic devices having the following compositions: (a) an osmotic device having a first composition comprising 60 mg of the calcium channel blocker, 212 mg of poly(ethylene oxide), 6 mg of potassium chloride, 15 mg of hydroxypropylmethylcellulose and 6 mg of magnesium stearate; and a second composition comprising 102 mg of poly(ethylene oxide), 44 mg of sodium chloride, and 3 mg of magnesium stearate; and, (b) an osmotic device having a first composition comprising 90 mg of the calcium channel blocker, 318 mg of poly(ethylene oxide), 9 mg of potassium chloride, 22.5 mg of hydroxypropylmethylcellulose, and 146 mg of poly(ethylene oxide), 66 mg of sodium chloride, and 4.5 mg of magnesium stearate. In an embodiment, the osmotic device described in (a) and (b) further comprise a pulse coated layer of drug carried on the outer semipermeable wall. The pulse coat comprises 30 mg of the calcium channel blocker and hydroxypropylmethylcellulose. In operation in the fluid environment of use, the pulse coat provides instant drug availability for instant drug therapy.

EXAMPLE 4

An osmotic delivery system is prepared according to the procedure described above for administering a therapeutically effective amount of a member selected from the group consisting of nimodipine, nitrendipine, nisoldipine, nicardipine, felodipine, diltiazem, lidoflazine, tiapamil, gallopamil, amlodipine, and mioflazine.

EXAMPLE 5

An oral osmotic delivery device useful for the management of cardiovascular diseases is prepared according to the mode and manner of the invention. The device comprises a first composition, a drug composition,

comprising 33 mg of a calcium antagonists, 122 mg of poly(ethylene oxide) having a molecular weight of 100,000, 8.25 mg of hydroxypropylmethylcellulose and 1.65 mg of magnesium stearate; and a second composition, a push composition, comprising 52.8 mg of poly(ethylene oxide) having a molecular weight of 5,000,000; 23.9 mg of sodium chloride, 4.13 mg of hydroxypropylmethylcellulose and 0.83 mg of magnesium stearate. The first and second composition are surrounded by a semipermeable wall comprising 95% cellulose acetate having an acetyl content of 39.8% and 5% poly(ethylene glycol) 4000. The osmotic device has at least one osmotic passageway 0.35 mm in diameter in the semipermeable wall connecting the drug composition with the exterior of the osmotic device. The device delivers 1.7 mg/hr of the drug over a prolonged period of 24 hours.

EXAMPLE 6

The procedure of Examples 2 to 4 is repeated for preparing osmotic devices containing from 5 mg to 150 mg of the drug. A series of osmotic devices are prepared containing 5 mg, 10 mg, 30 mg, 60 mg and 90 mg, up to 150 mg. These devices can comprise in the first composition from 50 mg to 750 mg of an osmopolymer and, optionally, 1 mg to 15 mg of an osmagent, and in the second composition from 20 mg to 320 mg of osmopolymer and 10 mg to 80 mg of osmagent. The devices have at least one osmotic passageway of 5 to 30 mils in diameter for delivering the drug. Individual devices can be prepared by following the procedures that have a rate of release of 0.25 mg, 0.5 mg, 0.6 mg, 0.8 mg, 1.3 mg, 2.7 mg and 3.0 mg per hour for 24 hours. The osmotic device is indicated for the management of plasma levels and it is indicated for treating cardiovascular conditions.

EXAMPLE 7

The procedures of the above examples are followed with all conditions as previously described except that the drug in the drug composition is an orally administered drug indicated for the management of cardiovascular diseases and it is a member selected from the group consisting of fendiline, diltiazem, perhexiline, and prenylamine.

EXAMPLE 8

An osmotic therapeutic device for the controlled and the continuous oral release of the beneficial calcium channel blocker drug verapamil is made as follows: 90 mg of verapamil, 50 mg of sodium carboxylvinyl polymer having a molecular weight of 200,000 and sold under the trademark Carbopol ® polymer, 3 mg of sodium chloride, 7.5 mg of hydroxypropylmethylcellulose and 3 mg of magnesium stearate are mixed thoroughly as described in Example I, and pressed in a Manesty ® press with a 5/16 inch punch using a light pressure to produce a layer of the drug composition. Next, 51 mg of the carboxyvinyl polymer having a molecular weight of 3,000,000 and sold under the trademark Carbopol ® polymer, 22 mg of sodium chloride and 2 mg of magnesium stearate are blended thoroughly and added to the Manesty press, and pressed to form a layer of expandable, osmotic composition in contact with the layer of osmotic drug composition.

Next, a semipermeable wall is formed by blending 170 g of cellulose acetate, having an acetyl content of 39.8%, with 900 ml of methylene chloride and 400 ml of methanol, and spray coating the two layered compartment forming member in an air suspension machine until 5.1 mil thick semipermeable wall surrounds the compartment. The coated device is dried for 72 hours at 50° C. and then a 8 mil osmotic passageway is laser drilled through the semipermeable wall to connect the layer containing drug with the exterior of the device for releasing drug over a prolonged period of time.

EXAMPLE 9

An osmotic therapeutic drug delivery device is prepared by following the procedure of Example 6, with all manufacturing conditions as described heretofore, except that in the present example the drug composition comprises 90 mg of verapamil, 50 mg of sodium carboxyvinyl polymer having a molecular weight of 200,000, 7.5 mg of hydroxypropylmethylcellulose and 3 mg of magnesium stearate.

EXAMPLE 10

An osmotic, therapeutic device for the delivery of the drug ketoprofen for uses as an anti-inflammatory is prepared by first pressing in a Manesty press an osmotic drug composition containing 75 mg of ketoprofen, 300 mg of sorbitol, 30 mg of sodium bicarbonate, 26 mg of pectin, 10 mg of polyvinyl pyrrolidone, and 5 mg of stearic acid, and tamping the composition in a cavity to a single layer. Next, the cavity is charged with a second and greater force generating composition comprising 122 mg of pectin having a molecular weight of 90,000 to 130,000, 32 mg of mannitol, 20 mg of polyvinyl pyrrolidone, and 2 mg of magnesium stearate and pressed to form a second layer in contacting relation with the first layer. The second layer had a density of 1.28 g/cm^3 and a hardness score of greater than 12 kP. Next, the two layer core is surrounded with a semipermeable wall comprising 85 g of cellulose acetate having an acetyl content of 39.8%, and 15 g of polyethylene glycol 4000, 3 (wt/wt) percent solid in a wall forming solvent comprising 1960 ml of methylene chloride and 819 ml of methanol. The coated device is dried for 72 hours at 50° C., and then a 0.26 mm diameter passageway is laser drilled through the wall. The semipermeable wall is 0.1 mm thick, the device has an area of 3.3 cm^2, and it releases drug over a 12 hour period.

EXAMPLE 11

The procedure of Example 10 is followed for providing an osmotic device wherein the compartment contained a blend of osmopolymers. The compartment contained a first composition weighing 312 mg and consists of 48% ketoprofen drug, 38% poly(ethylene oxide) osmopolymer having a molecular weight of 200,000, 10% poly (ethylene glycol) osmopolymer having a molecular weight of 20,000, 2% sodium chloride and 2% magnesium stearate; and a second composition weighing 150 mg and consisting of 93% poly(ethylene oxide) having a molecular weight of 5,000,000, 5% sodium chloride and 2% magnesium stearate.

EXAMPLE 12

In this example, the increase in osmotic pressure for a number of compositions comprising an osmagent and an osmopolymer are measured for demonstrating the operative advantage provided by the invention. The measurements are made by measuring the amount of water imbibed across the semipermeable wall of a bag containing an osmagent, or an osmopolymer, or a composition

comprising an osmagent and an osmopolymer. The semipermeable wall of the bag is formed of cellulose acetate having an acetyl content of 39.8%. The measurements are made by weighing the dry ingredients of the semipermeable bag, followed by weighing the blotted semipermeable bag, after the bag is in a water bath at 37° C. for various lengths of time. The increase in weight is due to water imbibition across the semipermeable wall caused by the osmotic pressure gradient across the wall. The osmotic pressure curves are illustrated in FIG. 10. In FIG. 11 the curved line with the triangles represents the osmotic pressure for poly(ethylene oxide) having a molecular weight of 5,000,000; the curved line with the circles represents the osmotic pressure for a composition comprising poly(ethylene oxide) having a molecular weight of 5,000,000 and sodium chloride with the ingredients present in the composition in the ratio of 9.5 parts osmopolymer to 0.5 parts osmagent; the curved line with squares represents a composition comprising the same osmopolymer and osmagent in the ratio of 9 parts osmopolymer to one part osmagent; the curved lines with hexagon represents the same composition comprising the osmopolymer an osmagent in the ratio of 8 parts to 2 parts; and, the dashed lines represent the osmagent sodium chloride. The mathematical calculations are made using the formula $dw/dt = K\Delta\pi A/h$, wherein dw/dt is the rate of water imbibition over time, A is the area of the semipermeable wall, and K is the permeability coefficient. Also, in FIG. 12, W_H/W_p is the amount of water imbibed divided by the dry weight of osmopolymer plus osmagent.

EXAMPLE 13

An osmotic therapeutic device for dispensing naproxen is prepared by screening through a 40 mesh screen a composition comprising 49% of naproxen, 46% poly(ethylene oxide) having a molecular weight of 100,000, and 3% hydroxypropylmethylcellulose, and then blending the screened composition with an alcohol solvent used in the ratio of 75 ml of solvent to 100 g of granulation. The wet granulation is screened through a 16 mesh screen, dried at room temperature for 48 hours under vacuum, and blended with 2% magnesium stearate that has been passed through an 80 mesh screen. The composition is compressed as described above.

Next, a composition comprising 73.9% of pectin having a molecular weight of 90,000 to 130,000, 5.8% microcrystalline cellulose, 5.8% polyvinyl pyrrolidone, 14.3% sodium chloride and 2% sucrose is passed through a 40 mesh screen, blended with an organic solvent in the ratio of 100 ml of solvent to 100 g of granulation for 25 minutes, passed through a 16 mesh screen, dried for 48 hours at room temperature under vacuum, again passed through a 16 mesh screen, blended with 2% magnesium stearate and then compressed onto the compressed layer described in the above paragraph. The dual layered drug core is coated by dipping in a wall forming composition comprising 80% cellulose acetate having an acetyl content of 39.8%, 10% polyethylene glycol 3350, and 10% hydroxypropylmethylcellulose. An osmotic passageway is drilled through the wall communicating with the drug containing composition. The osmotic diameter is 0.38 mm.

EXAMPLE 14

The procedure of Example 11 is repeated with all conditions as described, except that the osmopolymer in the drug composition is polyoxyethylene polyoxypropylene block copolymer having a molecular weight of about 12,500.

EXAMPLE 15

The in vivo and in vitro mean cumulative release of a calcium antagonist from an osmotic device comprising a composition adjacent to the passageway comprising 30 mg of the drug, 106.5 mg of poly(ethylene oxide) having a molecular weight of 200,000, 3 mg of potassium chloride, 7.5 mg of hydroxypropylmethylcellulose, and 3 mg of magnesium stearate; a composition distant from the passageway comprising 52 mg of poly(ethylene oxide) having a molecular weight of 5,000,000, 22 mg of sodium chloride and 1.5 mg of magnesium stearate; and a semipermeable wall comprising 95% cellulose acetate having an acetyl content of 39.8% and 5% hydroxypropylmethylcellulose is measured in vivo in laboratory dogs and in vitro in the laboratory. The amounts of drug released at various times in vivo were determined by administering a series of devices to the animals and measuring the amount released from the corresponding device at the appropriate residence time. The results are depicted in FIG. 13. In FIG. 13 the circles represent the in vivo cumulative release and the triangles represent the in vitro mean cumulative release.

EXAMPLE 16

The procedure of Example 12 is followed for making an osmotic therapeutic delivery system comprising: a first drug composition weighing 638 mg and consisting of 96% cephalexin hydrochloride, 2% granular core starch and 2% magnesium stearate; a second, or osmotic driving composition weighing 200 mg and consisting of 68.5% poly(ethylene oxide) having a molecular weight of 5,000,000, 29.5% sodium chloride, and 2% magnesium stearate; a semipermeable wall weighing 55.8 mg consisting of 80% cellulose acetate having an acetyl content of 39.8%, 10% polyethylene glycol 4000, and 10% hydroxypropyl methylcellulose; and an osmotic orifice having a diameter of 0.39 mm. The device has an average rate of release of about 54 mg per hour over a period of 9 hours.

EXAMPLE 17

The procedures described above are followed in this example for manufacturing an osmotic device for delivering the antipsychotic drug haloperidol to the gastrointestinal tract of a human. The osmotic delivery system comprises a first or drug composition comprising 11 mg of haloperidol, 245 mg of poly(ethylene oxide) having a molecular weight of about 100,000, 13.8 mg of hydroxypropylmethylcellulose and 5.5 mg of magnesium stearate; and, a second composition, initially in laminar arrangement with the first composition, which second composition consists essentially of 122 mg of poly(ethylene oxide) having a molecular weight of about 5,000,000, 56 mg of sodium chloride, 10 mg of hydroxypropylmethyl cellulose and 0.95 mg of magnesium stearate. The two compositions are surrounded by a semipermeable wall comprising 22.5 mg of cellulose acetate having an acetyl content of 39.8% and 2.5 mg of poly(ethylene glycol) 3350. The device has an osmotic pas-

sageway of 0.36 mm. The device delivers about 0.8 mg per hour over a 14 hours time period.

EXAMPLE 18

The procedure of Example 17 is repeated for preparing a series of osmotic devices housing a drug composition containing from 1 mg to 125 mg of haloperidol for dispensing a dosage of 0.1 mg, 1 mg, 2 mg, or 10 mg per hour over a prolonged period of at least 12 hours, or a cumulative dosage of 0.01 mg/kg/day to 0.075 mg/kg/day. The osmotic devices can be administered once, twice or thrice a day.

EXAMPLE 19

The procedure set forth above is repeated for providing an osmotic device for dispensing the nonsteroidal, anti-inflammatory, antipyretic, analgesic drug ibuprofen. The oral osmotic device comprises a first lamina composition consisting of 198 mg of ibuprofen and a second lamina composition consisting of 132 mg of poly(ethylene oxide) having a molecular weight of 5,000,000. The laminae compositions are surrounded by a semipermeable wall consisting essentially of 48.1 mg of cellulose acetate having an acetyl content 32%. The device has an osmotic passageway connecting the first lamina composition with the exterior of the device. The device has an average rate of release of 12.7 mg per hour over a 12 hour dispensing period. Similar osmotic devices are prepared containing 50 mg, 150 mg, 200 mg, 300 mg, 400 mg, 500 mg, and 600 mg for the anti-inflammatory, analgesic and antipyretic activities.

EXAMPLE 20

The procedures described above are followed for providing an osmotic device housing the non-steroidal drug, with anti-inflammatory, antipyretic and analgesic properties, indomethacin. The compartment of the device houses a first layer comprising 50 mg of indomethacin, 8.3 mg of hydroxypropyl methyl cellulose, 3.3 mg of magnesium stearate and 105 mg of poly(ethylene oxide) having a molecular weight of 100,000; and a second layer consisting of 52.5 mg of poly(ethylene oxide) having a molecular weight of 5,000,000, 24.2 mg of sodium chloride, 4.2 mg of hydroxypropylmethylcellulose and 1.67 mg of magnesium stearate. The device has a semipermeable wall comprising 95% (19.0 mg) cellulose acetate having an acetyl content of 39.8%, and 5% (1 mg) poly(ethylene glycol) 4000. The device has an osmotic passageway of 0.36 mm diameter for release of indomethacin. The device delivers 93% of the indomethacin over 18 hours. Similar devices are provided housing 25 mg and 75 mg of indomethacin for administering b.i.d. or t.i.d. for establishing steady-state plasma levels.

EXAMPLE 21

The procedures described above are followed for providing an osmotic device comprising a drug layer of 80 mg of isosorbide di-nitrate, 80 mg of lactose, 208 mg of poly(ethylene oxide) having a molecular weight of 200,000, 19.5 mg of hydroxypropylmethylcellullose and 3.9 mg of magnesium stearate, and a second expandable layer of 239 mg of poly(ethylene oxide) having a molecular weight of 5,000,000, 13 mg of hydroxypropylmethylcellulose, and 5.2 mg of magnesium stearate. The device has a semipermeable wall comprising 80% (36 mg) cellulose acetate having an acetyl content of 39.8%, 10% (4.5 mg) poly(ethylene glycol) 4000, and 10% (4.5 mg) hydroxypropylmethyl cellulose. The device has an osmotic passageway with a diameter of 0.51 mm and is clinically indicated for the relaxation of smooth muscle and treating angina pectoris.

EXAMPLE 22

The procedures described above are followed for making an osmotic device comprising a drug layer of 250 mg of alpha-methyldopa, levo-3-(3,4-dihydroxyphenyl)-2-methylalamine, 97.2 mg of poly(ethylene oxide) having a molecular weight of 200,000, 18.5 mg of hydroxypropyl methylcellulose and 8.7 mg of magnesium stearate, and a second layer of 226.6 mg of poly(ethylene oxide) having a molecular weight of 5,000,000, 12.3 mg of hydroxypropylmethylcellulose, and 4.9 mg of magnesium stearate. The device has a semipermeable wall comprising 65 weight percent (wt %), (15.5 mg), of cellulose acetate having an acetyl content of 39.8%, 17.5 wt % (4.2 mg), poly(ethylene glycol) 3350, and 17.5 wt % (4.2 mg) of hydroxypropylmethylcellulose. The device has an osmotic passageway of 0.51 mm communicating with the drug lamina for dispensing the drug from the device. The drug is indicated as an antihypertensive possessing decarboxylose inhibitor action in animals and in man. Similar devices can be prepared housing 125 mg to 500 mg of the drug.

EXAMPLE 23

The procedures described above are followed for providing an osmotic device comprising a first drug layer comprising 50 mg of hydrochlorothiazide, 189 mg of poly(ethylene oxide) having a molecular weight of 200,000, 1.0 mg of hydroxypropylmethylcellulose, and 2.5 mg of magnesium stearate; and a second expandable push layer comprising 280 mg of poly(ethylene oxide) having a molecular weight of 5,000,000, 15.4 mg of hydroxypropylmethylcellulose, and 0.2 mg of magnesium stearate. The device has a semipermeable wall comprising 95 wt % (54.4 mg) of cellulose acetate having an acetyl content of 39.8% and 5 wt % (2.9 mg) of poly(ethylene glycol) 3350. The device has an osmotic passageway with a diameter of 0.51 mm in the semipermeable wall communicating with the drug. Clinically, hydrochlorothiazide is a diuretic-antihypertensive. The osmotic device can contain from 12.5 to 250 mg given in 1 to 3 doses daily.

EXAMPLE 24

The procedures described above are followed for providing an osmotic device comprising a first drug layer comprising of 6 mg of an alpha adrenoreceptor blocker, 135 mg of poly(ethylene oxide) having a molecular weight of 100,000, 7.5 mg of hydroxypropylmethylcellulose, and 3.0 mg of magnesium stearate; and an expandable push layer initially in close contacting arrangement comprising 47.3 mg of poly(ethylene oxide) having a molecular weight of 5,000,000, 21.8 mg of sodium chloride, 3.8 mg of hydroxypropylmethylcellulose, and 1.5 mg of magnesium stearate. The device has a semipermeable wall comprising 95 wt % (25 mg) of cellulose acetate having an acetyl content of 39.8%, and 5 wt % (1.32 mg) of poly(ethylene glycol) 4000. The device has an osmotic passageway of 0.37 mm. The device, after a start-up of about 1 hour, delivers about 0.24 mg per hour over a period of 26 hours. Devices containing from 1 mg to 125 mg of drug can be prepared for their vasodilator effect as related to blockade

of postsynaptic alpha-adrenoceptors. The device also can be used for the treatment of hypertension.

EXAMPLE 25

The procedure of Example 24 repeated for providing osmotic devices containing in the first layer from 1 mg to 15 mg of a blocking alpha adrenoreceptor from 25 mg to 375 mg of osmopolymer and, optionally, from 0.5 mg to 7.5 mg of osmagents and a second layer comprising 15 mg to 250 mg of osmopolymer and, optionally, from 10 mg to 75 mg of osmagent.

EXAMPLE 26

The procedure of Example 24 Is followed for providing an osmotic device comprising: a first layer composition weighing 150.70 mg comprising 4 wt % of a blocking alpha-adrenoreceptor drug, 89 wt % Polyox® N-10 poly(ethylene oxide) having a molecular weight of 100,000, 5 wt % hydroxypropylmethylcellulose, and 2 wt % magnesium stearate; a second layer composition weighing 150.70 mg comprising 92 wt % Polyox® Coagulant poly(ethylene oxide) having a molecular weight of 5,000,000, 5 wt % hydroxypropylmethylcellulose, 1 wt % ferric oxide, and 2 wt % magnesium stearate. The osmotic device semipermeable wall weighed 23.70 mg comprising 95 wt % cellulose acetate having an acetyl content of 39.8% and 5 wt % poly(ethylene glycol) 4000. The osmotic passageway has a diameter of 0.370 mm connecting the exterior of the device with the drug layer.

EXAMPLES 27–28

The procedures described above are repeated with all procedures as previously described, except that the osmotic device contained an alpha-adrenergic blocking drug selected from the the group consisting of trimazosin, phenoxybenzamine hydrochloride and phentolamine hydrochloride.

EXAMPLES 29–30

The procedures described above are repeated with all procedures as described, except that in the present devices the first composition in the compartment contained from 1 mg to 125 mg of a member selected from the group consisting essentially of anhydrous theophylline, salbutamol base, diazepam and furosemide.

EXAMPLES 31–34

The procedures for manufacturing an osmotic device for dispensing an angiotensin converting enzyme drug through at least one pore in a cellulose acylate wall of the device is manufactured as describe herein with the angiotensin converting enzyme inhibitor a member selected from the group consisting of lisinopril, enalapril, captopril, ramipril and enalapriat.

EXAMPLES 35–40

The procedures for manufacturing an osmotic device for administering a gastrointestinal histamine receptor antagonists in a therapeutically effective amount for treating ulcers through at least one pore-passageway of a cellulosic wall is followed with the manufacture as set forth with the drug selected from the group consisting of famotidine, cimetidine, ranitidine, nizatidine and etintidine, from 100 mg to 450 mg every 12 to 24 hours one to three times daily.

EXAMPLE 41

A dosage form for administering the beneficial, gastrointestinal administrable drug, salbutamol hydrochloride, is made according to the above procedures. The wall in the present example is applied in an air suspension machine and it comprises a microporous wallforming composition. The microporous composition comprises 45% by weight of cellulose acetate having an acetyl content of 39.8%, 45% by weight of sorbitol, and 10% by weight of polyethylene glycol 400. In operation, in the fluid environment of the gastrointestinal tract, the sorbitol is leached from the wall providing thereby a plurality of microporous passageways of controlled porosity for release of the drug salbutamol hydrochloride from the dosage forms.

EXAMPLE 42

A dosage form for administering the beneficial gastrointestinal administrable drug, theophylline isopropanolamine is made according to the above procedures. The wall in the present example is applied in an air suspension machine and it comprises a microporous wallforming composition. The microporous composition comprises 55% by weight of cellulose acetate having an acetyl content of 39.8%, 40% by weight of sorbitol and 5% by weight of polyethylene glycol 400. In operation, in the fluid environment of the gastrointestinal tract, the sorbitol is leached from the wall providing a plurality of micropores. The micropores of controlled porosity provide fluid access through the wall to the osmopolymers. The osmopolymers act in concert to deliver the drug through a preformed passageway in the wall to the drug formulation.

The novel osmotic system of this invention uses dual means for the attainment of precise release rate of drugs that are difficult to deliver in the environment of use, while simultaneously maintaining the integrity and the character of the system. While there has been described and pointed out features and advantages of the invention as applied to the presently preferred embodiments, those skilled in the dispensing art will appreciate that various modifications, changes, additions, and omissions in the system illustrated and described can be made without departing from the spirit of the invention.

We claim:

1. An improvement in a device for delivering a beneficial agent composition to a fluid environment of use, wherein the device comprises:

(a) a wall comprising a composition that is permeable to the passage of fluid and is substantially impermeable to the passage of agent, which wall surrounds and forms;

(b) a compartment, and wherein the improvement comprises;

(c) a beneficial agent composition comprising a beneficial agent and 10% to 90% of an osmopolymer in the compartment, which beneficial agent composition is delivered substantially as a ribbon, at a rate expressed by

$$\frac{dm}{dt} = \left(\frac{dV}{dt}\right)_i \cdot C_D \text{ wherein } \frac{dm}{dt}$$

is the does of beneficial agent delivered in unit time,

$$\left(\frac{dV}{dt}\right)_t$$

is the total volume of the agent composition delivered in unit time, and C_D is the amount of beneficial agent mixed with the osmopolymer composition delivered from the device;

(d) a push composition in contact with the beneficial agent composition in the compartment, which push composition, in the presence of fluid that enters the device, increases in dimension and pushes the beneficial agent composition from the device; and,

(e) exit means in the wall for delivering the beneficial agent composition from the device, at a controlled rate over time.

2. An improvement in a device for delivering a beneficial agent to a fluid environment of use, wherein the device comprises:

(a) a wall comprising a composition that is permeable to the passage of fluid and is substantially impermeable to the passage of agent, which wall surrounds and defines;

(b) a compartment, and wherein the improvement comprises;

(c) a beneficial agent composition in the compartment comprising 10% to 90% of an osmopolymer and an osmagent that exhibit fluid influx, which beneficial agent composition is delivered substantially as a ribbon, and when the device is in operation in a fluid environment, a fluid influx

$$F = \left(\frac{dV}{dt}\right)_D,$$

wherein dV is the volume influxed in unit time dt;

(d) a push composition in contact with the beneficial agent composition in the compartment, said push composition exhibiting, when the device is in operation, a fluid influx

$$Q = \left(\frac{dV}{dt}\right)_p$$

wherein dV is the volume influxed in unit time dt; and,

(e) at least one exit orifice in the wall for delivering the beneficial agent by the cooperating operation of beneficial agent composition and the push composition acting together for delivering the beneficial agent through said orifice.

3. An improvement in a device for delivering a beneficial agent to a fluid environment of use, wherein the device comprises:

(a) a wall comprising a composition that is permeable to the passage of fluid and is substantially impermeable to the passage of agent, which wall surrounds;

(b) a compartment, and wherein the improvement comprises:

(c) a beneficial agent composition in the compartment that is delivered substantially as a ribbon, which composition comprises 10% to 90% of means for absorbing fluid that enters the compartment at a rate

$$F = \left(\frac{dV}{dt}\right)_A$$

for providing at least a fraction of the composition comprising fluid in unit time dt;

(d) a push composition in contact with the beneficial agent composition in the compartment, which push composition absorbs fluid that enters the compartment at a rate

$$Q = \left(\frac{dV}{dt}\right)_p$$

for providing at least in part a fraction of the push needed for pushing the beneficial agent compoition from the device at a rate comprising

$$\frac{dm}{dt} = \left(\frac{dV}{dt}\right)_p \cdot F_D \cdot \rho_{dc}$$

wherein F_D is the fraction of beneficial agent in the agent composition and ρ_{dc} is the density of the beneficial agent composition; and,

(e) at least one exit pore passageway in the wall for delivering the beneficial agent composition from the device, at a rate governed by the wall, the beneficial agent composition and the push composition interacting to deliver the beneficial agent through the orifice.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,082,668

DATED : January 21, 1992

INVENTOR(S) : Patrick S.L. Wong, Brian L. Barclay, Joseph C. Deters, Felix Theeuwes

It is certified that error appears in the above-indentified patent and that said Letters Patent is hereby corrected as shown below:

Title page, in field [*], please add "Notice: The portion of the term of this patent subsequent to September 16, 2003, has been disclaimed."

Signed and Sealed this

Twenty-fourth Day of December, 1996

Attest:

BRUCE LEHMAN

Attesting Officer

Commissioner of Patents and Trademarks

United States Patent [19]

Kuczynski et al.

[11] **Patent Number: 5,091,190**

[45] **Date of Patent: * Feb. 25, 1992**

[54] **DELIVERY SYSTEM FOR ADMINISTRATION BLOOD-GLUCOSE LOWERING DRUG**

[75] Inventors: **Anthony L. Kuczynski; Atul D. Ayer; Patrick S. Wong,** all of Palo Alto, Calif.

[73] Assignee: **ALZA Corporation,** Palo Alto, Calif.

[*] Notice: The portion of the term of this patent subsequent to Jun. 18, 2008 has been disclaimed.

[21] Appl. No.: **652,717**

[22] Filed: **Feb. 8, 1991**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 650,822, Jan. 22, 1991, and a continuation-in-part of Ser. No. 402,314, Sep. 5, 1989, Pat. No. 5,024,843.

[51] **Int. Cl.**[5] **A61K 9/24**

[52] **U.S. Cl.** **424/473**; 424/488; 514/866

[58] **Field of Search** 424/473

[56] **References Cited**

U.S. PATENT DOCUMENTS

2,799,241	7/1957	Wurster	118/24
2,909,462	10/1959	Warfield et al.	167/56
3,845,770	11/1974	Theeuwes et al.	128/260
3,916,899	11/1975	Theeuwes et al.	128/260
4,016,880	2/1983	Theeuwes et al.	128/260
4,063,064	12/1977	Saunders et al.	219/121 L
4,088,864	5/1978	Theeuwes et al.	219/121 LM
4,200,098	4/1980	Ayer et al.	128/260
4,285,987	8/1981	Ayer et al.	427/3
4,708,868	11/1987	Brikl et al.	924/80
4,803,076	2/1989	Ranade	424/438
4,851,232	7/1989	Urquhart et al.	424/469
5,002,772	3/1991	Curatolo	424/438

OTHER PUBLICATIONS

Martindale, *The Extra Pharmacopoeia,* 29th Ed. (1989) p. 390.

AHFS Drug Information, (1989) pp. 1741–1745.

J. Am. Phar. Assoc. Sci. Ed., vol. 48 (1959) pp. 451–459.

J. Am. Phar. Assoc., Sci. Ed., vol. 49 (1960) pp. 82–84.

Remington's *Pharmaceutical Sciences,* 14th Ed., (1970) pp. 1626–1678.

Primary Examiner—Thurman K. Page

Assistant Examiner—D. Gabrielle Phelan

Attorney, Agent, or Firm—Paul L. Sabatine; Edward L. Mandell; Jacqueline S. Larson

[57] **ABSTRACT**

A dosage form is disclosed comprising the antidiabetic drug glipizide for administering to a patient in need of glipizide therapy.

2 Claims, 2 Drawing Sheets

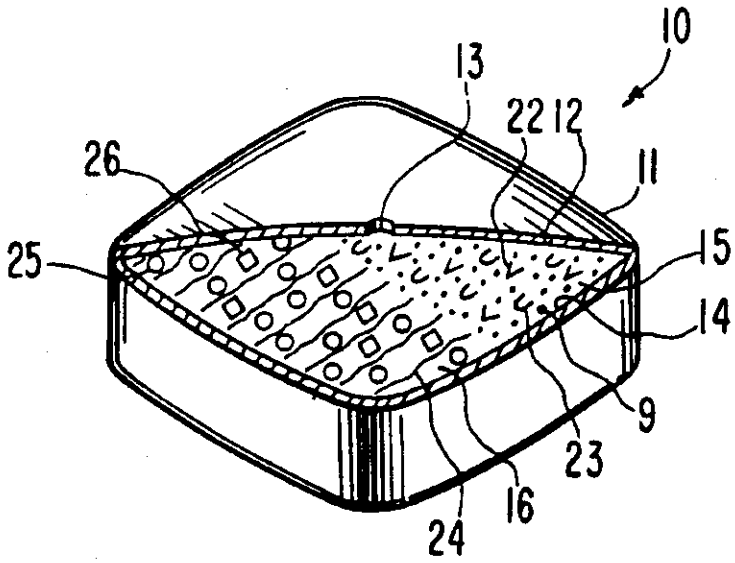


FIG. 1

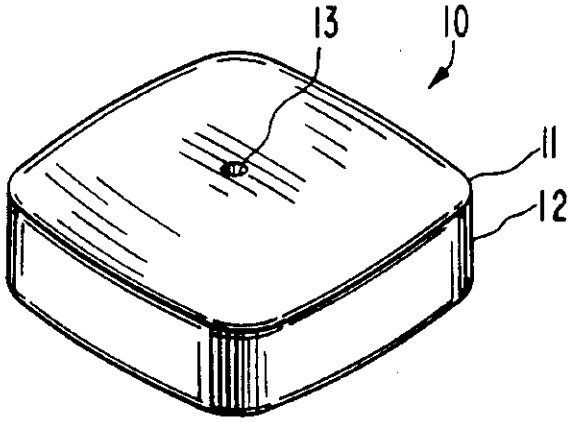


FIG. 2

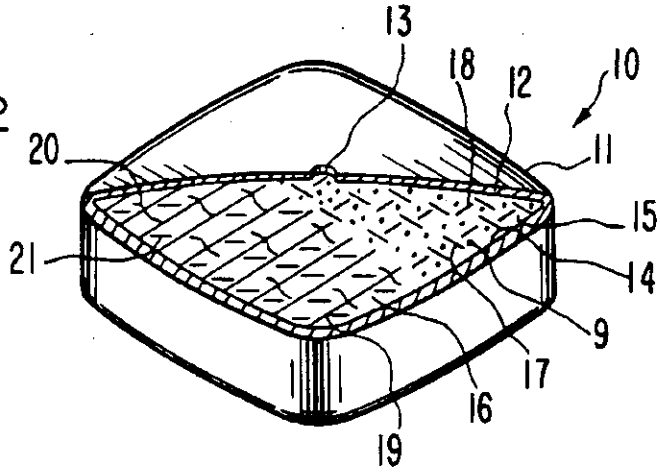


FIG. 3

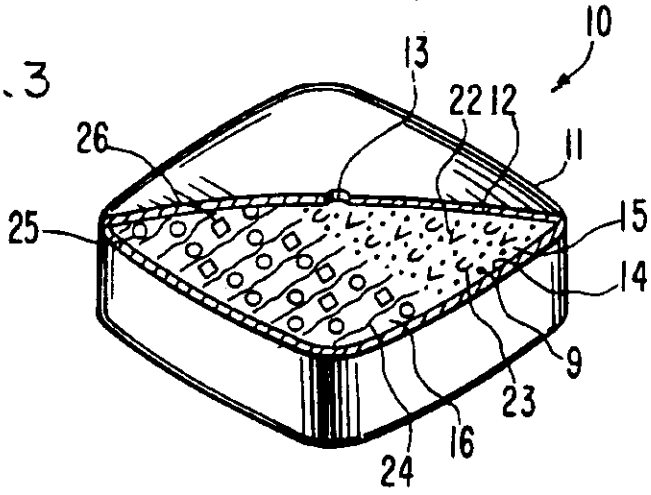


FIG. 4

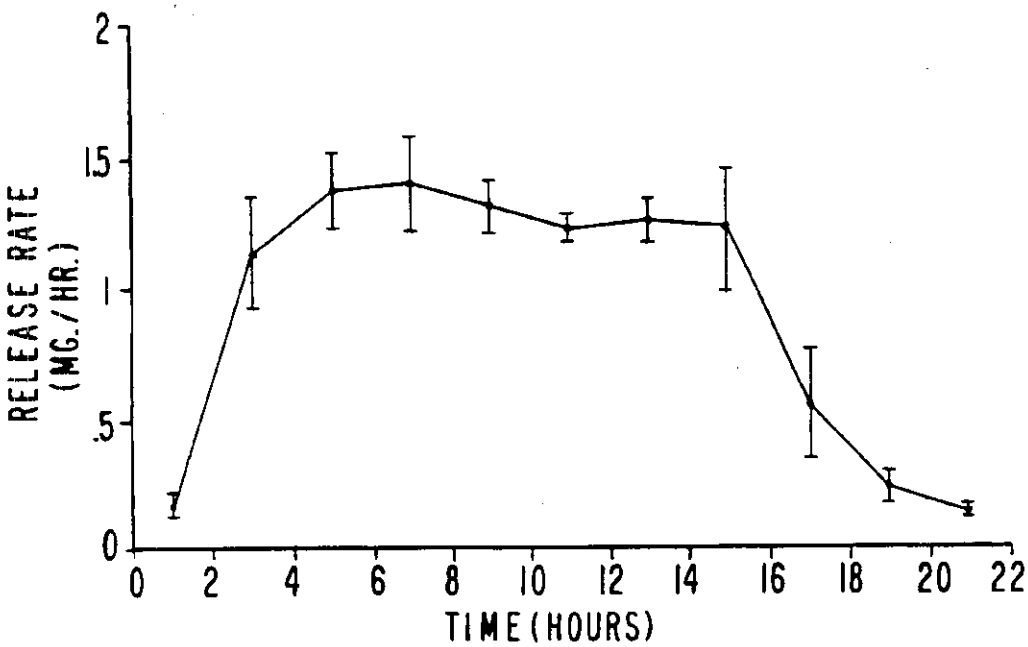
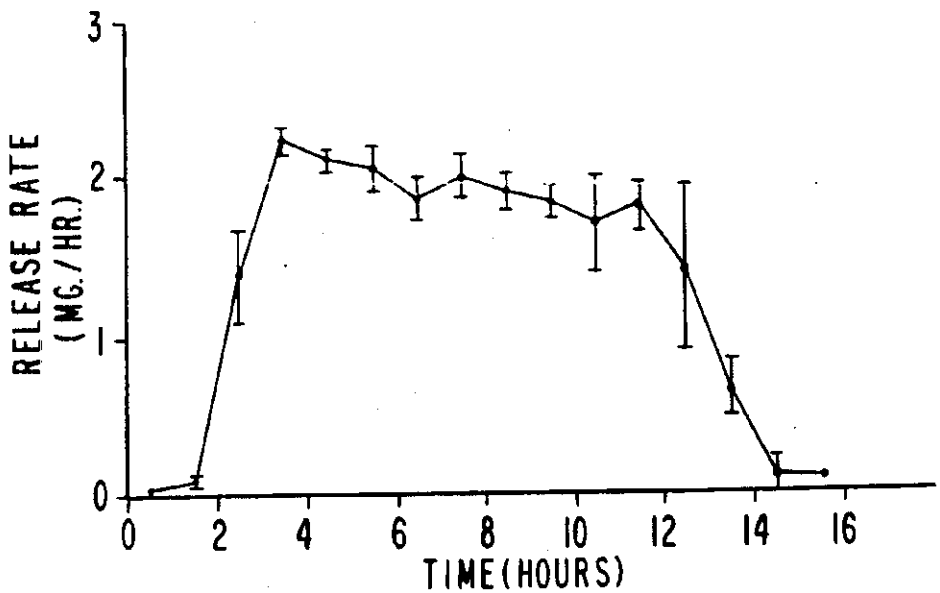

RELEASE RATE (MG./HR.)
2
1.5
1
.5
0
0 2 4 6 8 10 12 14 16 18 20 22
TIME (HOURS)

FIG. 5


RELEASE RATE (MG./HR.)
3
2
1
0
0 2 4 6 8 10 12 14 16
TIME (HOURS)

DELIVERY SYSTEM FOR ADMINISTRATION BLOOD-GLUCOSE LOWERING DRUG

CROSS-REFERENCE TO CO-PENDING APPLICATION

This application is a continuation-in-part with U.S. application Ser. No. 07/402 314, filed Sept. 5, 1989, now U.S. Pat. No. 5,024,843 issued Jun. 18, 1991 and is co-pending with an application now U.S. Ser. No. 07/650,822, filed Jan. 22, 1991.

DISCLOSURE OF TECHNICAL FIELD

This invention pertains to a dosage form comprising the hypoglycemic drug glipizide. The invention concerns also a method for administering glipizide to a recipient in need of glipizide therapy.

DISCLOSURE OF BACKGROUND OF THE INVENTION

A clinical need exists for a dosage form for delivering an oral blood-glucose lowering drug to a patient needing this therapy. Glipizide is an oral blood-glucose lowering drug and it is indicated for the control of hyperglycemia and its associated symptomatology in patients with non-insulin dependent diabetes mellitus Glipizide is useful therapeutically as an oral hypoglycemic drug because it stimulates insulin secretion from the beta cells of pancreatic-islet tissue, it increases the concentration of insulin in the pancreatic vein, and because it exhibits extrapancreatic action such as the ability to increase the number of insulin receptors.

Glipizide is known chemically as N-[2-[4-[[[(cyclohexylamino) carbonyl]amino]sulfonyl]phenyl]ethyl]-5-methylpyrazinecarboxamide. Glipizide is a white, odorless powder with a pKa of 5.9, and it is insoluble in both water and alcohol These physical and chemical properties of glipizide do not lend the drug to formulation into a dosage form that can administer glipizide at a controlled and known rate per unit time. The properties of glipizide are disclosed in *Martindale The Extra Pharmacopoeia* 29th Ed., p 390, (1989); and, AHFS Drug Information, pp 1741–45, (1989).

In the light of the above presentation, it will be appreciated by those versed in the pharmaceutical dispensing art to which this invention pertains, that a pressing need exists for a rate-controlled dosage form that can deliver the valuable drug glipizide to a patient in clinical need of blood-glucose lowering therapy. The pressing need exists also for an oral dosage form that can deliver glipizide at a controlled rate in a substantially constant dose per unit time for its beneficial therapeutic effects, and remain substantially independent of the changing environment of the gastrointestinal tract It will be appreciated further by those skilled in the dispensing art, that if such a novel and unique dosage form is made available that can administer glipizide in a rate-controlled dose over time, and simultaneously provide blood-glucose lowering therapy, the dosage form would represent an advancement and a valuable contribution to the medical art.

DISCLOSURE OF OBJECTS OF THE INVENTION

Accordingly, in view of the above presentation, it is an immediate object of this invention to provide a dosage form for delivering glipizide in a rate controlled amount, and which dosage form substantially overcomes the deficiencies and omissions associated with the prior art.

Another object of the present invention is to provide a dosage form for orally administering glipizide in a rate-controlled dose for blood-glucose lowering therapy.

Another object of the invention is to provide a pharmaceutical dosage form that makes available controlled and sustained glipizide therapeutic activity to a patient in need of glipizide therapy.

Another object of the invention is to provide a novel dosage form manufactured as an osmotic device that can administer glipizide to a biological receptor site to produce the desired glipizide pharmacological effects.

Another object of the present invention is to provide a dosage form manufactured as an osmotic dosage form that maintains glipizide in the dosage form until released from the dosage form, thereby substantially reducing and/or substantially eliminating the unwanted influences of the gastrointestinal environment of use and still provide controlled administration of glipizide over time

Another object of the present invention is to provide a dosage form that can deliver the substantially aqueous insoluble drug glipizide at a controlled and beneficial known rate over time.

Another object of the present invention is to provide a dosage form adapted for the oral administration of glipizide and which dosage form comprise a first composition and a contacting second composition that operate in combination for the controlled administration of glipizide.

Another object of the present invention is to provide a complete pharmaceutical glipizide regimen comprising a composition comprising glipizide that can be dispensed from a drug delivery dosage form, the use of which requires intervention only for initiation and possibly for termination of the regimen.

Another object of the invention is to provide a method for treating hyperglycemia by orally administering glipizide in a rate-controlled dose per unit time to a warm-blooded animal in need of hyperglycemia therapy.

Another object of the invention is to provide a dosage form comprising the drug N-[2-[4-[[[(cyclohexylamino) carbonyl]-amino]sulfonyl]phenyl]ethyl]-5-methylpyrazinecarboxamide and a pharmaceutically acceptable carrier that forms and provides a dispensable composition when the dosage form is delivering the drug to the patient.

Other objects, features and advantages of this invention will be more apparent to those versed in the dispensing arts from the following detailed specification, taken in conjunction with the drawings and the accompanying claims.

BRIEF DISCLOSURE OF THE DRAWINGS

In the drawings, which are not drawn to scale, but are set forth to illustrate various embodiments of the invention, the drawing figures are as follows:

Drawing FIG. 1 is a view of a dosage form designed and shaped for orally administering glipizide to the gastrointestinal tract of a warm-blooded animal, including humans;

Drawing FIG. 2 is an opened view of the dosage form of drawing FIG. 1 illustrating the structure of the dosage form comprising glipizide;

Drawing FIG. 3 is an opened view of the dosage form of drawing FIG. 1 depicting a different internal structure embodiment provided by the invention;

Drawing FIG. 4 is a graph that depicts the release rate pattern from one embodiment of the dosage form provided by the invention; and,

Drawing FIG. 5 is a graph that depicts the release rate pattern for a different embodiment of the dosage form provided by the invention.

In the drawing figures and in the specification like parts in related drawing figures are identified by like numbers The terms appearing earlier in the specification and in the description of the drawings, as well as embodiments thereof, are further described elsewhere in the disclosure.

DETAILED DISCLOSURE OF THE DRAWING FIGURES

Turning now to the drawing figures in detail, which drawing figures are examples of the dosage forms provided by this invention, and which examples are not to be construed as limiting, one example of the dosage form is illustrated in drawing FIG. 1 and designated by the numeral **10**. In drawing FIG. 1, dosage form **10** comprises a body **11**, which body member **11** comprises a wall **12** that surrounds and encloses an internal compartment, not seen in drawing FIG. 1. Dosage form **10** comprises at least one exit means **13** for connecting the interior of dosage form **10** with the exterior environment of use.

In drawing FIG. 2, dosage form 10 is seen in opened view. In drawing FIG. 2, dosage form **10** comprises a body member **11** comprising wall **12**, which wall surrounds and defines an internal compartment **14**. Wall **12** comprises at least one exit means **13** that connects internal compartment **14** with the exterior of dosage form **10**. Dosage form **10** can comprise more than one exit means **13**. Wall **12** of dosage form **10** comprises in total, or in at least a part, a composition that is permeable to the passage of an exterior fluid present in the environment, and wall **12** is substantially impermeable to the passage of glipizide and other ingredients present in compartment **14**. The composition comprising wall **12** is semipermeable, it is substantially inert, and wall **12** maintains its physical and chemical integrity during the dispensing life of glipizide from dosage form **10**. The phrase, keeps its physical and chemical integrity," means wall **12** does not lose its structure, and it does not change chemically during the glipizide dispensing life of dosage form **10**.

Wall **12**, in a presently preferred embodiment, comprises 80 weight percent (wt %) to 100 weight percent of a composition comprising a cellulose polymer The cellulose polymer comprises a member selected from the group consisting of a cellulose ester, cellulose ether, cellulose ester-ether, cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, and cellulose triacetate. Wall **12**, in another preferred manufacture, comprises from 0 weight percent to 25 weight percent of a member selected from the group consisting of hydroxypropylcellulose and hydroxypropylmethylcellulose, and from 0 to 20 weight percent of polyethylene glycol, with the total amount of all wall-forming components comprising wall **12** equal to 100 weight percent.

Internal compartment **14** comprises an internal glipizide lamina **15**, which glipizide lamina can be defined optionally as a glipizide composition **15**. Internal compartment **14** also comprises an internal displacement lamina **16**, which displacement lamina can be defined optionally as a displacement composition **16**. The glipizide lamina **15** and the displacement lamina **16** initially are in laminar arrangement and they cooperate with each other and with dosage form **10** for the effective delivery of glipizide from dosage form **10**.

The glipizide composition **15**, in a presently preferred embodiment, as seen in FIG. 2, comprises about 1.0 mg to 100 mg of glipizide identified by dots **9**; from 100 mg to 320 mg of a polyethylene oxide comprising 80,000 to 350,000 molecular weight and identified by dashes 17, which performs as a pharmaceutically acceptable carrier for glipizide to provide a dispensable formulation for the substantially aqueous insoluble glipizide from 5 mg to 50 mg of hydroxypropylmethylcellulose comprising a 9,200 to 22,000 molecular weight and identified by vertical lines **18**; and from 0 mg to 7.5 mg of a lubricant such as stearic acid, magnesium stearate, and the like.

The displacement lamina **16**, as seen in drawing FIG. 2, comprises 70 mg to 125 mg of a polyethylene oxide comprising a 4,000,000 to 8,000,000 molecular weight identified as lines **19**; from 20 mg to 50 mg of an osmagent selected from the group consisting of sodium chloride and potassium chloride identified by wavy line 20; and from 5 mg to 15 mg of a hydroxypropylmethylcellulose having a 9,000 to 25,000 molecular weight identified by vertical slashes **21**. Displacement lamina **16** optionally comprises from 0.1 mg to 5 mg of ferric oxide and from 0.01 mg to 5 mg of a lubricant such as magnesium stearate or stearic acid.

Drawing FIG. 3 depicts in opened section another osmotic dosage form **10** provided by the invention. In drawing FIG. 3, dosage form **10** comprises a body **11**, a wall **12**, which wall **12** surrounds an internal compartment **14** with an exit passageway **13** in wall **12**. Internal compartment **14**, in this dosage form, comprises an internal glipizide lamina **15**, which glipizide lamina **15** comprises 2 mg to 25 mg of aqueous insoluble drug glipizide identified by dots **9**; from 100 mg to 150 mg of a hydroxypropylcellulose comprising a 40,000 to 80,000 molecular weight identified by angle **22**; and from 40 mg to 70 mg of a polyvinylpyrrolidone comprising a 30,000 to 70,000 molecular weight and identified by half circle **23**. Internal compartment **14** comprises a displacement lamina **16** comprising 30 mg to 150 mg of sodium carboxymethylcellulose having 200,000 to 1,000,000 molecular weight identified by wavy lines **24**; from 20 mg to 70 mg of an osmagent selected from the group consisting of sodium chloride and potassium chloride identified by circle **25**; and from 0.5 mg to 10 mg of a hydroxypropylmethylcellulose comprising a 9,200 to 22,000 molecular weight identified by squares **26**. Displacement lamina **16** optionally comprises from 0 mg to 5 mg of ferric oxide and optionally 0 mg to 7 mg of a lubricant.

The expression, "exit means **13**," as used herein, comprises means and methods suitable for the controlled metered release of glipizide **9** from compartment **14** of dosage form **10**. The exit means **13** comprises at least one passageway, orifice, or the like, through wall **12** for communication with glipizide **9** in compartment **14**. The expression, "at least one passageway," includes aperture, orifice, bore, pore, or porous element through which glipizide can be released, or hollow fiber, capillary tube, porous overlay, porous insert, and the like. The expression also includes a material that erodes or is fluid-leached from wall **12** in a fluid environment of use

to produce at least one pore-passageway of governed release rate pore-size in wall 12. Representative materials suitable for forming at least one passageway, or a multiplicity of passageways, comprise an erodible polyglycolic acid, or a polylactic acid member in wall 12, a gelatinous filament, polyvinyl alcohol, leachable materials such as a fluid removable pore forming polysaccharide, salt, oxide, polyol, or the like. A passageway or a plurality of passageways can be formed by leaching a material such as sorbitol, lactose, or the like, from wall 12. The passageway can have any shape such as round, triangular, square, elliptical, and the like, for assisting in the metered release of glipizide 9 from dosage form 10. Dosage form 10 can be constructed with one or more passageways in spaced apart relations, or more than one passageway on a single surface of dosage form 10. Passageways and equipment for forming passageways are disclosed in U.S. Pat. Nos. 3,845,770 issued 11/74 to Theeuwes et al; 3,916,899 issued 11/75 to Theeuwes et al; 4,016,880 issued 4/77 to Theeuwes et al; 4,063,064 issued 12/77 to Saunders et al; 4,088,864 issued 5/78 to Theeuwes et al; and, passageways formed by leaching are disclosed in U.S. Pat. Nos. 4,200,098 issued 4/80 to Ayer et al; 4,235,236 issued 11/80 to Theeuwes; and, 4,285,987 issued to Ayer et al.

Dosage form 10 of this invention is manufactured by standard techniques. For example, in one manufacture the drug glipizide is mixed with other composition-forming ingredients and the mix then pressed into a solid lamina possessing dimensions that correspond to the internal dimensions of the compartment space adjacent to the passageway. In another embodiment the beneficial drug glipizide and other composition forming ingredients and a solvent are mixed into a solid, or into a semisolid, by conventional methods such as ballmilling, calendering, stirring, or rollmilling, and then pressed into a preselected lamina forming shape. Next, a lamina composition comprising the osmopolymer and the osmagent are placed in contact with the lamina comprising the beneficial drug glipizide, and the two lamina comprising the laminate are surrounded with a semipermeable wall. The lamination of the glipizide composition and the osmopolymer displacement composition can be accomplished by using a two-layer tablet press technique. The wall can be applied by molding, spraying, or dipping the pressed shapes into wall-forming formulations. Another preferred technique that can be used for applying the wall is the air suspension coating procedure. This procedure consists in suspending and tumbling the two layered laminate in a current of air until the wall forming composition surrounds the laminate. The air suspension procedure is described in U.S. Pat. No. 2,799,241; in *J. Pharm. Assoc., Sci. Ed.*, Vol. 48 pp 451-59 (1959); and *ibid.* Vol. 49, pp 82-84, (1960). Other standard manufacturing procedures are described in *Modern Plastics Encyclopedia* Vol 46, pp 62-70, (1969); and in *Pharmaceutical Sciences*, by Remington, 14th Ed., pp 1626-1978, (1970), published by Mack Publishing Co., Easton, PA.

Exemplary solvents suitable for manufacturing the wall, the laminate, and laminae, comprise inert inorganic and organic solvents that do not adversely affect the final wall and the final laminates. The solvents broadly comprise a member selected from the group consisting of aqueous solvents, alcohols, ketones, esters, ethers, aliphatic hydrocarbons, halogenated solvents, cycloaliphatics, aromatics, heterocyclic solvents, and mixtures thereof. Typical solvents comprise acetone, diacetone, alcohol, methanol, ethanol, isopropyl alcohol, butyl alcohol, methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, methylpropyl ketone, n-hexane, n-heptane, ethylene glycol monoethyl ether, ethylene glycol monoethyl acetate, methylene dichloride, ethylene dichloride, propylene dichloride, acetone and water, acetone and methanol, acetone and ethyl alcohol, methylene dichloride and methanol, ethylene dichloride and methanol, and the like.

DETAILED DISCLOSURE OF EXAMPLES OF THE INVENTION

The following examples are merely illustrative of the present invention, and they should not be considered as limiting the scope of this invention in any way, as these examples and other equivalents thereof will become apparent to those versed in the art in the light of the present disclosure, the drawings and the accompanying claims.

EXAMPLE 1

An oral dosage form, adapted, designed and shaped as an osmotic drug delivery system for admittance into the gastrointestinal tract of a patient in need of glipizide is manufactured as follows: first, 369 g of pharmaceutically acceptable hydroxypropylcellulose comprising a 60,000 average molecular weight is passed through a 20 mesh screen, followed by passing through a 40 mesh screen 162 g of pharmaceutically acceptable polyvinylpyrrolidone comprising a 40,000 average molecular weight. Next, the two screened ingredients are blended with 66 g of glipizide to form a homogeneous blend. The blend is suspended in a fluidized bed and sprayed with an atomized spray comprising an ethanol:water (70:30 vol:vol) solution until granules are formed of the three ingredients. The freshly prepared granules then are passed through a 20 mesh screen. Finally, the screened granulation is mixed with 3 g of magnesium stearate in a rollermill for 5 minutes.

Next, a separate hydrogel granulation is prepared as follows: first, 389 g of pharmaceutically acceptable sodium carboxymethylcellulose having 700,000 molecular weight, 174 g of sodium chloride, 30 g of pharmaceutically acceptable hydroxypropylmethylcellulose comprising a 11,200 molecular weight and 6 g of ferric oxide separately are screened through a 40 mesh screen. Then, all the screened ingredients are mixed to produce a homogeneous blend. Next, 300 ml of denatured anhydrous ethanol is added slowly to the blend with continuous mixing for about 5 minutes. The freshly prepared wet granulation is screened through a 20 mesh screen, allowed to dry at room temperature for 16 hours, and again passed through a 20 mesh screen. The screened granulation is mixed with 1.5 g of magnesium stearate in a rollermill for about 5 minutes.

Next, the glipizide granulation, and the hydrogel granulation are compressed into a bilaminate tablet arrangement. First, 200 mg of the glipizide composition is added to a 0.375 inch (9.5 mm) punch and tamped, then, 140 mg of the hydrogel granulation is added to the punch and the two laminae are pressed into a solid, contacting arrangement.

Next, the bilaminate is coated with a semipermeable wall. The semipermeable wall-forming composition comprises 93% cellulose acetate having a 39.8% acetyl content, and 7% polyethylene glycol having a 3350 molecular weight. The wall-forming composition is

dissolved in a cosolvent comprising acetone: water (90:10 wt:wt) to make a 4% solids solution. The wall-forming composition is sprayed onto and around the bilaminate in an Aeromatic® Air Suspension Coater. Then, a 25 mil (0.635 mm) exit orifice is mechanically drilled on the glipizide side of the osmotic dosage form. The residual solvent is removed by drying the osmotic system for 48 hours at 50° C. and 50% humidity. The osmotic systems are dried for 1 hour at 50° C. to remove excess moisture. Attached drawing FIG. 4 shows the in vitro release rate profile for glipizide from the finished osmotic system as released in distilled water. The error bars represent the standard deviation added to and subtracted from the mean of five osmotic delivery system. An osmotic dosage form provided by the invention comprises 11 wt% glipizide, 61.50 wt% hydroxypropyl- cellulose of 60,000 molecular weight, 27.0 wt% polyvinylpyrrolidone of 40,000 molecular weight, 0.5% magnesium stearate in the glipizide composition; 64.8 wt% sodium carboxymethylcellulose of 700,000 molecular weight, 29 wt% sodium chloride, 5 wt% hydroxypropyl-methylcellulose of 11,200 molecular weight and 1.0 wt% ferric oxide, 0.2% magnesium stearate in the hydrogel composition; and, 93.0 wt% cellulose acetate having a 39.8% acetyl content, and 7.0 wt% polyethylene glycol having a 3350 molecular weight in the semipermeable wall formulation.

EXAMPLE 2

A dosage form adapted, designed and shaped as an osmotic drug delivery system is manufactured as follows: first, a glipizide composition is provided by blending together into a homogeneous blend 478 g of pharmaceutically acceptable polyethylene oxide comprising a 200,000 molecular weight, 66 g of glipizide and 54 g of pharmaceutically acceptable hydroxypropylmethylcellulose comprising a 11,200 molecular weight. Then, 425 ml of denatured anhydrous ethanol is added slowly with continuous mixing over 5 minutes. The freshly prepared wet granulation is screened through a 20 mesh screen through a 20 mesh screen, dried at room temperature for 16 hours, and again screened through a 20 mesh screen. Finally, the screened granulation is mixed with 1.5 g of magnesium stearate in a rollermill for 5 minutes.

Next, a hydrogel composition is prepared as follows: first, 412.5 g of pharmaceutically acceptable polyethylene oxide comprising a 7,500,000 molecular weight, 150 g of sodium chloride and 6 g of ferric oxide separately are screened through a 40 mesh screen. Then, all the screened ingredients are mixed with 30 g of hydroxypropylmethylcellulose comprising a 11,200 molecular weight to produce a homogeneous blend. Next, 300 mg of denatured anhydrous alcohol is added slowly to the blend with continuous mixing for 5 minutes. The freshly prepared wet granulation is passed through a 20 mesh screen, allowed to dry at room temperature for 16 hours, and again passed through a 20 mesh screen. The screened granulation is mixed with 1.5 g of magnesium stearate in a rollermill for 5 minutes.

Next, the glipizide composition and the hydrogel composition are compressed into bilaminate tablets. First, 200 mg of the glipizide is added to a 0.375 inch (9.5 mm) punch and tamped, then, 140 mg of the hydrogel composition is added and the laminae are pressed under a pressure head of 2 tons into a contacting laminated arrangement.

Then, the bilaminate arrangements are coated with a semipermeable wall. The wall forming composition comprises 93% cellulose acetate having a 39.8% acetyl content, and 7% polyethylene glycol having a molecular weight of 3350. The wall-forming composition is dissolved in an acetone:water (90:10 wt:wt) cosolvent to make a 4% solids solution. The wall forming composition is sprayed onto and around the bilaminate in an Aeromatic® Air Suspension Coater.

Next, a 25 mil (0.635 mm) exit passageway is mechanically drilled through the semipermeable wall to connect the glipizide drug lamina with the exterior of the dosage system. The residual solvent is removed by drying for 48 hours at 50° C. and 50% humidity. Next, the osmotic systems are dried for 1 hour at 50° C. to remove excess moisture. The dosage form produced by this manufacture provides a glipizide composition comprising 11 wt% glipizide, 79.7 wt% polyethylene oxide of 200,000 molecular weight, 9 wt% hydroxypropylmethylcellulose of 11,200 molecular weight, and 0.3 wt% magnesium stearate; a hydrogel composition comprising 68.8 wt% polyethylene oxide comprising a 7,500,000 molecular weight, 25 wt% sodium chloride, 5 wt% hydroxypropylmethylcellulose, 1.0 wt% ferric oxide and 0.2 wt% magnesium stearate; and a semipermeable wall comprising 93 wt% cellulose acetate comprising a 39.8% acetyl content, and 7.0 wt% polyethylene glycol comprising a 3350 molecular weight.

Accompanying drawing FIG. 5 depicts the in vitro release rate profile of glipizide released from the final dosage form for four dosage forms. The error bars represent the standard deviation added to and subtracted from the mean of the dosage form.

DISCLOSURE OF A METHOD OF USING THE INVENTION

An embodiment of the invention pertains to a method for delivering the beneficial drug glipizide orally at a controlled rate to a warm blooded animal in need of glipizide therapy, which method comprises the steps of: (A) admitting into the warm-blooded animal a dosage from comprising: (1) a wall surrounding a compartment, the wall comprising at least in part a semipermeable polymeric composition permeable to the passage of fluid and substantially impermeable to the passage of glipizide; (2) a pharmaceutically acceptable composition in the compartment comprising about 2.5 mg to 50 mg of hypoglycemic glipizide for performing an antidiabetic program; (3) a hydrogel composition in the compartment comprising a member selected from the group consisting of a polyethylene oxide having a 4,000,000 to 7,500,000 molecular weight and a sodium carboxymethylcellulose having a 200,000 to 1,000,000 molecular weight for imbibing and absorbing fluid for pushing the glipizide composition from the dosage form; and, (4) at least one passageway in the wall for releasing glipizide; (B) imbibing fluid through the semipermeable wall at a rate determined by the permeability of the semipermeable wall and the osmotic pressure gradient across the semipermeable wall causing the hydrogel composition to expand and swell; and (C) delivering the beneficial glipizide from the dosage form through the exit passage to the warm blooded animal over a prolonged period of time to produce the desired hypoglycemic effect.

In summary, it will be appreciated that the present invention contributes to the art an unexpected and unforseen dosage form that possesses the practical utility for administering aqueous insoluble glipizide from an osmotic dosage form at a dose metered release rate per

unit time. While the invention has been described and pointed out in detail with reference to operative embodiments thereof it will be understood that those skilled in the art that various changes, modifications, substitutions and omissions can be made without departing from the spirit of the invention. It is intended, therefore, that the invention embrace those equivalents within the scope of the claims which follow.

We claim:

1. A method for stimulating insulin secretion from the beta cells or pancreatic-islet tissue in a patient in need of insulin secretion, wherein the method comprises:

(a) admitting orally into the patient a dosage form comprising:

(1) a wall comprising a member selected from the group consisting of a cellulose ester, cellulose ether and cellulose ester-ether, which will defines:

(2) a lumen;

(3) a first composition in the compartment comprising 1 mg to 100 mg of the drug N-[2-[4-[[[(cyclohexylamino) carbonyl]amino]sulfonyl]-phenyl]ethyl]-5-methylpyrazinecarboxamide for stimulating insulin secretion and a pharmaceutically acceptable carrier therefore;

(4) a second composition in the compartment comprising a therapeutically acceptable hydrogel;

(5) an exit passageway in the wall for delivering the first composition from the lumen;

(b) imbibing fluid into the dosage form causing the first composition to provide a dispensable aqueous composition and the second composition to expand and push against the first composition, whereby the first composition is delivered from the dosage form; and,

(c) stimulating insulin secretion by delivering the first composition comprising 1 mg to 100 mg of the drug to the patient.

2. An improvement in a dosage form for administering an antidiabetic drug to a patient, wherein the dosage form comprises:

(a) a wall comprising a member selected from the group consisting of a cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate and cellulose triacetate, which wall defines;

(b) a compartment;

(c) a displacement composition in the compartment comprising a therapeutically acceptable hydrogen that absorbs fluid, expands and pushes a drug composition from the compartment;

(d) an exit passageway in the wall for delivering a drug composition from the compartment; and wherein the improvement comprises:

(e) a drug composition in the compartment, said drug composition comprising 1 mg to 100 mg of substantially aqueous insoluble N-[2-[4-[[[(cyclohexylamino) carbonyl]amino]sulfonyl]phenyl]ethyl]-5-methylpyrazinecarboxamide and a pharmaceutically acceptable carrier therefore, which composition when in the presence of an aqueous fluid that enters the dosage form provides a dispensable aqueous composition that delivers 1 mg to 100 mg of the antidiabetic drug to the patient.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,091,190

DATED : February 25, 1992

INVENTOR(S) : Anthony L. Kuczynski, Atul D. Ayer, Patrick S. Wong

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the Title page, item [75]

Inventor's name incorrect " Patrick S. Wong" should read --Patrick S. L. Wong--.

Column 9, Line 17, "will" should read --wall--; Column 10, line 16, "hydrogen" should read --hydrogel--.

Signed and Sealed this

Nineteenth Day of October, 1993

Attest:

BRUCE LEHMAN

Attesting Officer

Commissioner of Patents and Trademarks

United States Patent [19]

Kuczynski et al.

[11] **Patent Number: 5,545,413**

[45] **Date of Patent: * Aug. 13, 1996**

[54] **DOSAGE FORM FOR ADMINISTERING ORAL HYPOGLYCEMIC GLIPIZIDE**

[75] Inventors: **Anthony L. Kuczynski**; **Atul D. Ayer**; **Patrick S. Wong**, all of Palo Alto, Calif.

[73] Assignee: **Alza Corporation**, Palo Alto, Calif.

[*] Notice: The portion of the term of this patent subsequent to Jul. 2, 2008, has been disclaimed.

[21] Appl. No.: **650,822**

[22] Filed: **Jan. 22, 1991**

Related U.S. Application Data

[62] Division of Ser. No. 402,314, Sep. 5, 1989, Pat. No. 5,024,843.

[51] **Int. Cl.**[6] **A61K 9/20**; A61K 47/38; A61K 47/32; A61K 9/16

[52] **U.S. Cl.** **424/473**; 424/499; 424/501; 514/866

[58] **Field of Search** 424/472, 473, 424/499, 501

[56] **References Cited**

U.S. PATENT DOCUMENTS

2,799,241	7/1957	Wurster	118/24
2,909,462	10/1959	Warfield et al.	167/56
3,845,770	11/1974	Theeuwes et al.	128/260
3,916,899	11/1975	Theeuwes et al.	128/260
4,016,880	2/1983	Theeuwes et al.	128/260
4,063,064	12/1977	Saunders et al.	219/121 L
4,088,864	5/1978	Theeuwes et al.	219/121 LM
4,200,098	4/1980	Ayer et al.	128/260
4,285,987	8/1981	Ayer et al.	427/3
4,627,851	12/1986	Wong et al.	424/473
4,673,405	6/1987	Guittard et al.	424/473
4,708,868	11/1987	Brickl et al.	424/80
4,803,076	2/1989	Ranade	424/438
4,851,232	7/1989	Urquhart et al.	424/469
4,902,514	2/1990	Barclay et al.	424/473
5,002,772	3/1991	Curatolo et al.	424/438
5,019,396	5/1991	Ayer et al.	424/473
5,024,843	6/1991	Kuczynski et al.	424/499
5,028,434	7/1991	Barclay et al.	424/473

OTHER PUBLICATIONS

Martindale, *The Extra Pharmacopoeia*, 29th Ed. (1989) p. 390.

AHFS Drug Information, (1989) pp. 1741–1745.

J. Am. Phar. Assoc., Sci. Ed., vol. 48 (1959) pp. 451–459.

J. Am. Phar. Assoc., Sci. Ed., vol. 49 (1960) pp. 82–84.

Remington's *Pharmaceutical Sciences*, 14th Ed., (1970) pp. 1626–1678.

Primary Examiner—Edward J. Webman

Attorney, Agent, or Firm—Paul L. Sabatine; Felissa H. Cagan; Mary Ann Dillahunty

[57] **ABSTRACT**

A dosage form is disclosed comprising the antidiabetic drug glipizide for administering to a patient in need of glipizide therapy.

7 Claims, 2 Drawing Sheets

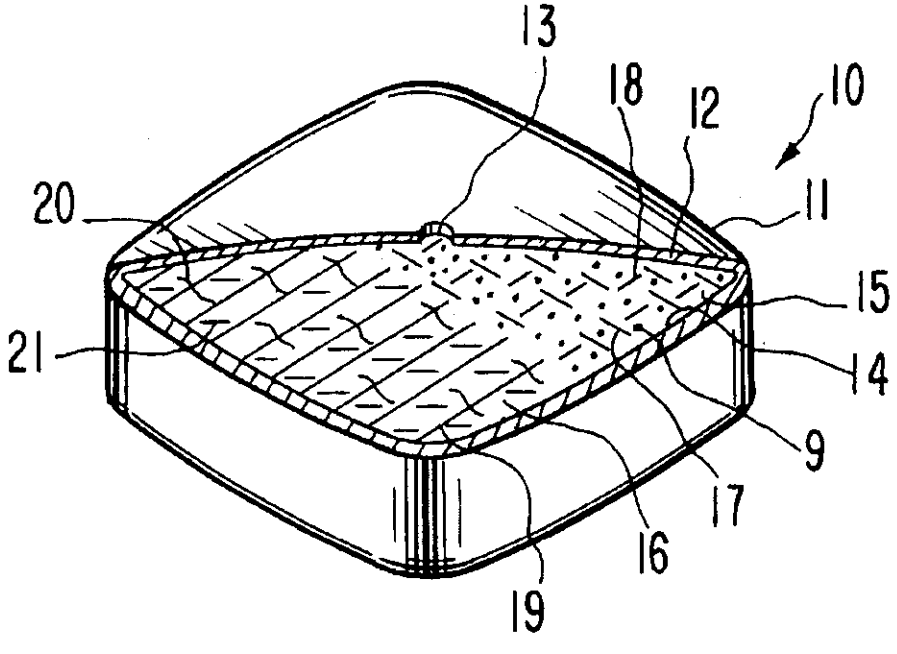


FIG_1

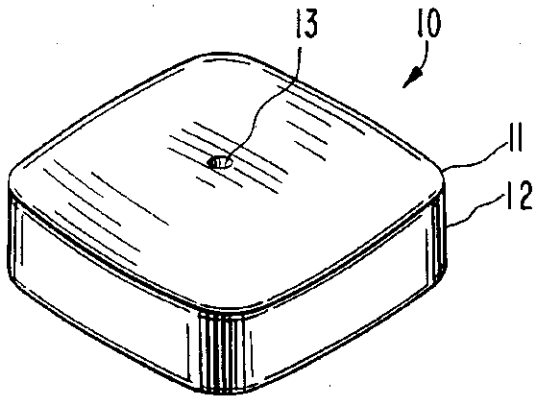


FIG_2

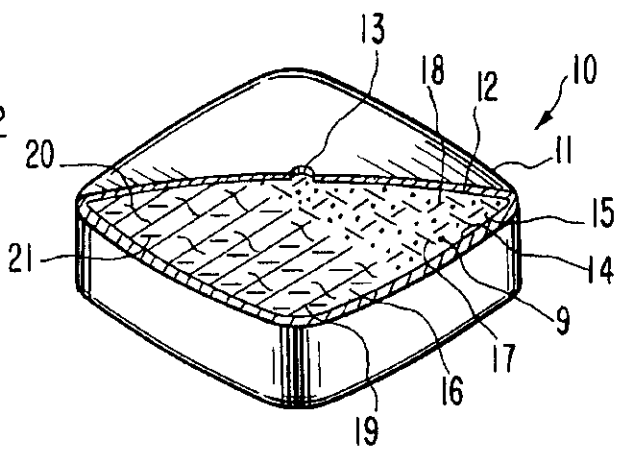


FIG_3

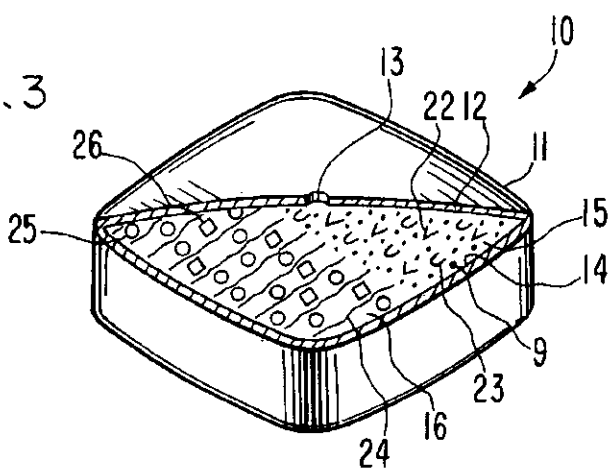


FIG. 4

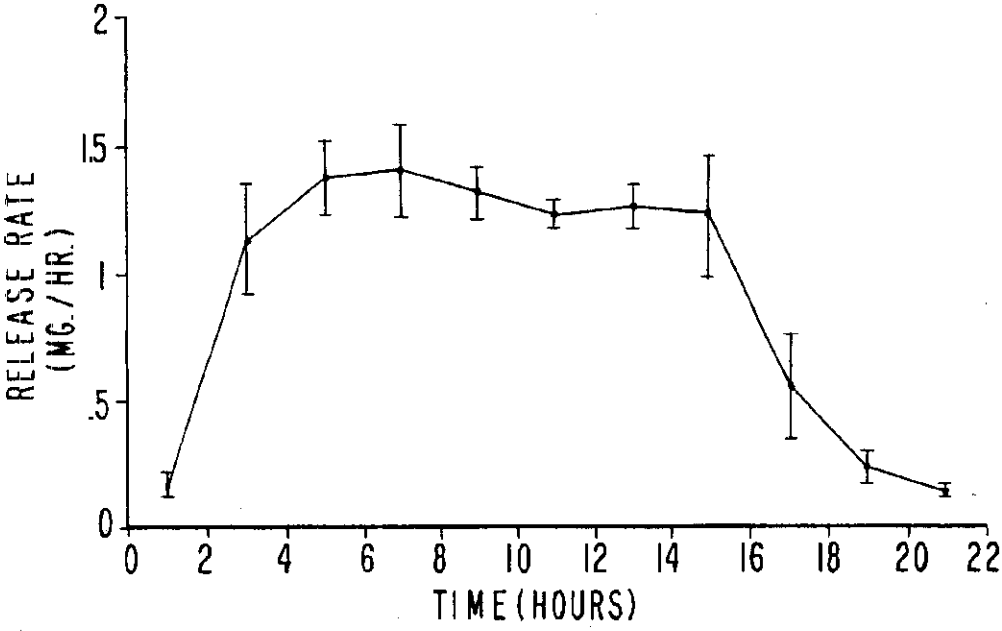
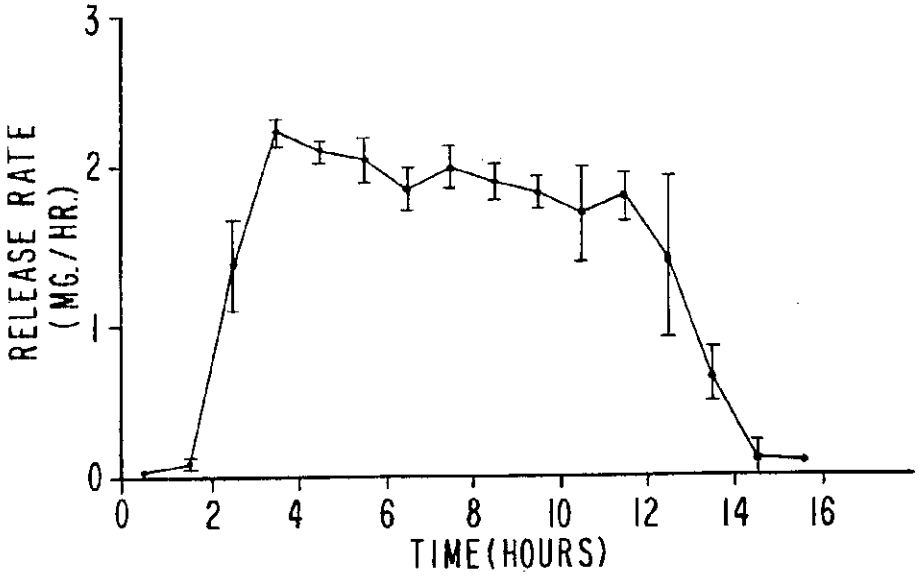

RELEASE RATE (MG./HR.)
2
1.5
1
.5
0
0 2 4 6 8 10 12 14 16 18 20 22
TIME (HOURS)

FIG. 5


RELEASE RATE (MG./HR.)
3
2
1
0
0 2 4 6 8 10 12 14 16
TIME (HOURS)

DOSAGE FORM FOR ADMINISTERING ORAL HYPOGLYCEMIC GLIPIZIDE

CROSS-REFERENCE TO RELATED APPLICATION

This application is a division of U.S. Ser. No. 07/402,314 filed Sep. 5, 1989, now U.S. Pat. No. 5,024,843, issued Jun. 18, 1991.

DISCLOSURE OF TECHNICAL FIELD

This invention pertains to a dosage form comprising the hypoglycemic drug glipizide. The invention concerns also a method for administering glipizide to a recipient in need of glipizide therapy.

DISCLOSURE OF BACKGROUND OF THE INVENTION

A clinical need exists for a dosage form for delivering an oral blood-glucose lowering drug to a patient needing this therapy. Glipizide is an oral blood-glucose lowering drug and it is indicated for the control of hyperglycemia and its associated symptomatology in patients with non-insulin dependent diabetes mellitus. Glipizide is useful therapeutically as an oral hypoglycemic drug because it stimulates insulin secretion from the beta cells of pancreatic-islet tissue, it increases the concentration of insulin in the pancreatic vein, and because it exhibits extrapancreatic action such as the ability to increase the number of insulin receptors.

Glipizide is known chemically as N-[2-[4-[[[(cyclohexylamino) carbonyl]amino]sulfonyl]phenyl]ethyl]-5-methylpyrazinecarboxamide. Glipizide is a white, odorless powder with a pKa of 5.9, and it is insoluble in both water and alcohol. These physical and chemical properties of glipizide do not lend the drug to formulation into a desage form that can administer glipizide at a controlled and known rate per unit time. The properties of glipizide are disclosed in *Martindale The Extra Pharmacopeia,* 29th Ed., p 390, (1989); and, *AHFS Drug Information*, pp 1741–45, (1989).

In the light of the above presentation, it will be appreciated by those versed in the pharmaceutical dispensing art to which this invention pertains, that a pressing need exists for a rate-controlled dosage form that can deliver the valuable drug glipizide to a patient in clinical need of blood-glucose lowering therapy. The pressing need exists also for an oral dosage form that can deliver glipizide at a controlled rate in a substantially constant dose per unit time for its beneficial therapeutic effects, and remain substantially independent of the changing environment of the gastrointestinal tract. It will be appreciated further by those skilled in the dispensing art, that if such a novel and unique dosage form is made available that can administer glipizide in a rate-controlled dose over time, and simultaneously provide blood-glucose lowering therapy, the dosage form would represent an advancement and a valuable contribution to the medical art.

DISCLOSURE OF OBJECTS OF THE INVENTION

Accordingly, in view of the above presentation, it is an immediate object of this invention to provide a dosage form for delivering glipizide in a rate controlled amount, and which dosage form substantially overcomes the deficiencies and omissions associated with the prior art.

Another object of the present invention is to provide a dosage form for orally administering glipizide in a rate-controlled dose for blood-glucose lowering therapy.

Another object of the invention is to provide a pharmaceutical dosage form that makes available controlled and sustained glipizide therapeutic activity to a patient in need of glipizide therapy.

Another object of the invention is to provide a novel dosage form manufactured as an osmotic device that can administer glipizide to a biological receptor site to produce the desired glipizide pharmacological effects.

Another object of the present invention is to provide a dosage form manufactured as an osmotic dosage form that maintains glipizide in the dosage form until released from the dosage form, thereby substantially reducing and/or substantially eliminating the unwanted influences of the gastrointestinal environment in use and still provide controlled administration of glipizide over time.

Another object of the present invention is to provide a dosage form that can deliver the aqueous insoluble drug glipizide at a controlled and beneficial known rate over time.

Another object of the present invention is to provide a dosage form adapted for the oral administration of glipizide and which dosage form comprise a first composition and a contacting second composition that operate in combination for the controlled administration of glipizide.

Another object of the present invention is to provide a complete pharmaceutical glipizide regimen comprising a composition comprising glipizide that can be dispensed from a drug delivery dosage form, the use of which requires intervention only for initiation and possibly for termination of the regimen.

Another object of the invention is to provide a method for treating hyperglycemia by orally administering glipizide in a rate-controlled dose per unit time to a warm-blooded animal in need of hyperglycemia therapy.

Other objects, features and advantages of this invention will be more apparent to those versed in the dispensing arts from the following detailed specification, taken in conjunction with the drawings and the accompanying claims.

BRIEF DISCLOSURE OF THE DRAWINGS

In the drawings, which are not drawn to scale, but are set forth to illustrate various embodiments of the invention, the drawing figures are as follows:

Drawing FIG. 1 is a view of a dosage form designed and shaped for orally administering glipizide to the gastrointestinal tract of a warm-blooded animal, including humans;

Drawing FIG. 2 is an opened view of the dosage form of drawing FIG. 1 illustrating the structure of the dosage form comprising glipizide;

Drawing FIG. 3 is an opened view of the dosage form of drawing FIG. 1 depicting a different internal structure embodiment provided by the invention;

Drawing FIG. 4 is a graph that depicts the release rate pattern from one embodiment of the dosage form provided by the invention; and,

Drawing FIG. 5 is a graph that depicts the release rate pattern for a different embodiment of the dosage form provided by the invention.

In the drawing figures and in the specification like parts in related drawing figures are identified by like numbers. The terms appearing earlier in the specification and in the

description of the drawings, as well as embodiments thereof, are further described elsewhere in the disclosure.

DETAILED DISCLOSURE OF THE DRAWING FIGURES

Turning now to the drawing figures in detail, which drawing figures are examples of the dosage forms provided by this invention, and which examples are not to be construed as limiting, one example of the dosage form is illustrated in drawing FIG. **1** and designated by the numeral **10**. In drawing FIG. **1**, dosage form **10** comprises a body **11**, which body member **11** comprises a wall **12** that surrounds and encloses an internal compartment, not seen in drawing FIG. 1. Dosage form **10** comprises at least one exit means **13** for connecting the interior of dosage form **10** with the exterior environment of use.

In drawing FIG. **2**, dosage form **10** is seen in opened view. In drawing FIG. **2**, dosage form **10** comprises a body member **11** comprising wall **12**, which wall surrounds and defines an internal compartment **14**. Wall **12** comprises at least one exit means **13** that connects internal compartment **14** with the exterior of dosage form **10**. Dosage form **10** can comprise more than one exit means **13**. Wall **12** of dosage form **10** comprises in total, or in at least a part, a composition that is permeable to the passage of an exterior fluid present in the environment, and wall **12** is substantially impermeable to the passage of glipizide and other ingredients present in compartment **14**. The composition comprising wall **12** is semipermeable, it is substantially inert, and wall **12** maintains its physical and chemical integrity during the dispensing life of glipizide from dosage form **10**. The phrase, keeps its physical and chemical integrity," means wall **12** does not lose its structure, and it does not change chemically during the glipizide dispensing life of dosage form **10**.

Wall **12**, in a presently preferred embodiment, comprises 80 weight percent (wt %) to 100 weight percent of a composition comprising a cellulose polymer. The cellulose polymer comprises a member selected from the group consisting of a cellulose ester, cellulose ether, cellulose ester-ether, cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, and cellulose triacetate. Wall **12**, in another preferred manufacture, comprises from 0 weight percent to 25 weight percent of a member selected from the group consisting of hydroxypropylcellulose and hydroxypropylmethylcellulose, and from 0 to 20 weight percent of polyethylene glycol, with the total amount of all wall-forming components comprising wall **12** equal to 100 weight percent.

Internal compartment **14** comprises an internal glipizide lamina **15**, which glipizide lamina can be defined optionally as a glipizide composition **15**. Internal compartment **14** also comprises an internal displacement lamina **16**, which displacement lamina can be defined optionally as a displacement composition **16**. The glipizide lamina **15** and the displacement lamina **16** initially are in laminar arrangement and they cooperate with each other and with dosage form **10** for the effective delivery of glipizide from dosage form **10**.

The glipizide composition **15**, in a presently preferred embodiment, as seen in FIG. **2**, comprises about 2.0 mg to 50 mg of glipizide identified by dots **9**; from 100 mg to 320 mg of a polyethylene oxide comprising 80,000 to 350,000 molecular weight and identified by dashes **17**; from 5 mg to 50 mg of hydroxypropylmethylcellulose comprising a 9,200 to 22,000 molecular weight and identified by vertical lines **18**; and from 0 mg to 7.5 mg of a lubricant such as stearic acid, magnesium stearate, and the like.

The displacement lamina **16**, as seen in drawing FIG. **2**, comprises 70 mg to 125 mg of a polyethylene oxide comprising a 4,000,000 to 8,000,000 molecular weight identified as lines **19**; from 20 mg to 50 mg of an osmagent selected from the group consisting of sodium chloride and potassium chloride identified by wavy line **20**; and from 5 mg to 15 mg of a hydroxypropylmethylcellulose having a 9,000 to 25,000 molecular weight identified by vertical slashes **21**. Displacement lamina **16** optionally comprises from 0.1 mg to 5 mg of ferric oxide and from 0.01 mg to 5 mg of a lubricant such as magnesium stearate or stearic acid.

Drawing FIG. **3** depicts in opened section another osmotic dosage form **10** provided by the invention. In drawing FIG. **3**, dosage form **10** comprises a body **11**, a wall **12**, which wall **12** surrounds an internal compartment **14** with an exit passageway **13** in wall **12**. Internal compartment **14**, in this dosage form, comprises an internal glipizide lamina **15**, which glipizide lamina **15** comprises 2 mg to 25 mg of aqueous insoluble drug glipizide identified by dots **9**; from 100 mg to 150 mg of a hydroxypropylcellulose comprising a 40,000 to 80,000 molecular weight identified by angle **22**; and from 40 mg to 70 mg of a polyvinylpyrrol idone comprising a 30,000 to 70,000 molecular weight and identified by half circle **23**. Internal compartment **14** comprises a displacement lamina **16** comprising 30 mg to 150 mg of sodium carboxymethylcellulose having 200,000 to 1,000,000 molecular weight identified by wavy lines **24**; from 20 mg to 70 mg of an osmagent selected from the group consisting of sodium chloride and potassium chloride identified by circle **25**; and from 0.5 mg to 10 mg of a hydroxypropylmethylcellulose comprising a 9,200 to 22,000 molecular weight identified by squares **26**. Displacement lamina **16** optionally comprises from 0 mg to 5 mg of ferric oxide and optionally 0 mg to 7 mg of a lubricant.

The expression, "exit means **13**," as used herein, comprises means and methods suitable for the controlled metered release of glipizide **9** from compartment **14** of dosage form **10**. The exit means **13** comprises at least one passageway, orifice, or the like, through wall **12** for communication with glipizide **9** in compartment **14**. The expression, "at least one passageway," includes aperture, orifice, bore, pore, or porous element through which glipizide can be released, or hollow fiber, capillary tube, porous overlay, porous insert, and the like. The expression also includes a material that erodes or is fluid-leached from wall **12** in a fluid environment of use to produce at least one pore-passageway of governed release rate pore-size in wall **12**. Representative materials suitable for forming at least one passageway, or a multiplicity of passageways, comprise an erodible polyglycolic acid, or a polylactic acid member in wall **12**, a gelatinous filament, polyvinyl alcohol, leachable materials such as a fluid removable pore forming polysaccharide, salt, oxide, polyol, or the like. A passageway or a plurality of passageways can be formed by leaching a material such as sorbitol, lactose, or the like, from wall **12**. The passageway can have any shape such as round, triangular, square, elliptical, and the like, for assisting in the metered release of glipizide **9** from dosage form **10**. Dosage form **10** can be constructed with one or more passageways in spaced apart relations, or more than one passageway on a single surface of dosage form **10**. Passageways and equipment for forming passageways are disclosed in U.S. Pat. Nos. 3,845,770 issued November 1974 to Theeuwes et al; 3,916,899 issued November 1975 to Theeuwes et al; 4,016,880 issued April 1977 to Theeuwes et al; 4,063,064 issued December 1977 to Saunders et al; 4,088,864 issued May 1978 to Theeuwes et al; and, passageways formed by

leaching are disclosed in U.S. Pat. Nos. 4,200,098 issued April 1980 to Ayer et al; 4,235,236 issued November 1980 to Theeuwes; and, 4,285,987 issued to Ayer et al.

Dosage form **10** of this invention is manufactured by standard techniques. For example, in one manufacture the drug glipizide is mixed with other composition-forming ingredients and the mix then pressed into a solid lamina possessing dimensions that correspond to the internal dimensions of the compartment space adjacent to the passageway. In another embodiment the beneficial drug glipizide and other composition forming ingredients and a solvent are mixed into a solid, or into a semisolid, by conventional methods such as ballmilling, calendering, stirring, or roll-milling, and then pressed into a preselected lamina forming shape. Next, a lamina composition comprising the osmopolymer and the osmagent are placed in contact with the lamina comprising the beneficial drug glipizide, and the two lamina comprising the laminate are surrounded with a semipermeable wall. The lamination of the glipizide composition and the osmopolymer displacement composition can be accomplished by using a two-layer tablet press technique. The wall can be applied by molding, spraying, or dipping the pressed shapes into wall-forming formulations. Another preferred technique that can be used for applying the wall is the air suspension coating procedure. This procedure consists in suspending and tumbling the two layered laminate in a current of air until the wall forming composition surrounds the laminate. The air suspension procedure is described in U.S. Pat. No. 2,799,241; in *J. Pharm. Assoc., Sci. Ed.*, Vol. 48 pp 451–59 (1959); and ibid, Vol. 49, pp 82–84, (1960). Other standard manufacturing procedures are described in *Modern Plastics Encyclopedia*, Vol. 46, pp 62–70, (1969); and in *Pharmaceutical Sciences*, by Remington, 14th Ed., pp 1626–1978, (1970), published by Mack Publishing Co., Easton, Pa.

Exemplary solvents suitable for manufacturing the wall, the laminate, and laminae, comprise inert inorganic and organic solvents that do not adversely affect the final wall and the final laminates. The solvents broadly comprise a member selected from the group consisting of aqueous solvents, alcohols, ketones, esters, ethers, aliphatic hydrocarbons, halogenated solvents, cycloaliphatics, aromatics, heterocyclic solvents, and mixtures thereof. Typical solvents comprise acetone, diacetone, alcohol, methanol, ethanol, isopropyl alcohol, butyl alcohol, methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, methylpropyl ketone, n-hexane, n-heptane, ethylene glycol monoethyl ether, ethylene glycol monoethyl acetate, methylene dichloride, ethylene dichloride, propylene dichloride, acetone and water, acetone and methanol, acetone and ethyl alcohol, methylene dichloride and methanol, ethylene dichloride and methanol, and the like.

DETAILED DISCLOSURE OF EXAMPLES OF THE INVENTION

The following examples are merely illustrative of the present invention, and they should not be considered as limiting the scope of this invention in any way, as these examples and other equivalents thereof will become apparent to those versed in the art in the light of the present disclosure, the drawings and the accompanying claims.

EXAMPLE 1

An oral dosage form, adapted, designed and shaped as an osmotic drug delivery system for admittance into the gastrointestinal tract of a patient in need of glipizide is manufactured as follows: first, 369 g of pharmaceutically acceptable hydroxypropylcellulose comprising a 60,000 average molecular weight is passed through a 20 mesh screen, followed by passing through a 40 mesh screen 162 g of pharmaceutically acceptable polyvinylpyrrolidone comprising a 40,000 average molecular weight. Next, the two screened ingredients are blended with 66 g of glipizide to form a homogeneous blend. The blend is suspended in a fluidized bed and sprayed with an atomized spray comprising an ethanol :water (70:30 vol:vol) solution until granules are formed of the three ingredients. The freshly prepared granules then are passed through a 20 mesh screen. Finally, the screened granulation is mixed with 3 g of magnesium stearate in a rollermill for 5 minutes.

Next, a separate hydrogel granulation is prepared as follows: first, 389 g of pharmaceutically acceptable sodium carboxymethylcellulose having 700,000 molecular weight, 174 g of sodium chloride, 30 g of pharmaceutically acceptable hydroxypropylmethylcellulose comprising a 11,200 molecular weight and 6 g of ferric oxide separately are screened through a 40 mesh screen. Then, all the screened ingredients are mixed to produce a homogeneous blend. Next, 300 ml of denatured anhydrous ethanol is added slowly to the blend with continuous mixing for about 5 minutes. The freshly prepared wet granulation is screened through a 20 mesh screen, allowed to dry at room temperature for 16 hours, and again passed through a 20 mesh screen. The screened granulation is mixed with 1.5 g of magnesium stearate in a rollermill for about 5 minutes.

Next, the glipizide granulation, and the hydrogel granulation are compressed into a bilaminate tablet arrangement. First, 200 mg of the glipizide composition is added to a 0.375 inch (9.5 mm) punch and tamped, then, 140 mg of the hydrogel granulation is added to the punch and the two laminae are pressed into a solid, contacting arrangement.

Next, the bilaminate is coated with a semipermeable wall. The semipermeable wall-forming composition comprises 93% cellulose acetate having a 39.8% acetyl content, and 7% polyethylene glycol having a 3350 molecular weight. The wall-forming composition is dissolved in a cosolvent comprising-acetone: water (90:10 wt:wt) to make a 4% solids solution. The wall-forming composition is sprayed onto and around the bilaminate in an Aeromatic® Air Suspension Coater.

Then, a 25 mil (0.635 mm) exit orifice is mechanically drilled on the glipizide side of the osmotic dosage form. The residual solvent is removed by drying the osmotic system for 48 hours at 50° C. and 50% humidity. The osmotic systems are dried for 1 hour at 50° C. to remove excess moisture. Attached drawing FIG. **4** shows the in vitro release rate profile for glipizide from the finished osmotic system as released in distilled water. The error bars represent the standard deviation added to and subtracted from the mean of five osmotic delivery system. An osmotic dosage form provided by the invention comprises 11 wt % glipizide, 61.50 wt % hydroxypropylcellulose of 60,000 molecular weight, 27.0 wt % polyvinylpyrrolidone of 40,000 molecular weight, 0.5% magnesium stearate in the glipizide composition; 64.8 wt % sodium carboxymethylcellulose of 700,000 molecular weight, 29 wt % sodium chloride, 5 wt % hydroxypropylmethylcellulose of 11,200 molecular weight and 1.0 wt % ferric oxide, 0.2% magnesium stearate in the hydrogel composition; and, 93.0 cellulose acetate having a 39.8% acetyl content, and 7.0 polyethylene glycol having a 3350 molecular weight in the semipermeable wall formulation.

EXAMPLE 2

A dosage form adapted, designed and shaped as an osmotic drug delivery system is manufactured as follows: first, a glipizide composition is provided by blending together into a homogeneous blend 478 g of pharmaceutically acceptable polyethylene oxide comprising a 200,000 molecular weight, 66 g of glipizide and 54 g of pharmaceutically acceptable hydroxypropylmethylcellulose comprising a 11,200 molecular weight. Then, 425 ml of denatured anhydrous ethanol is added slowly with continuous mixing over 5 minutes. The freshly prepared wet granulation is screened through a 20 mesh screen, dried at room temperature for 16 hours, and again screened through a 20 mesh screen. Finally, the screened granulation is mixed with 1.5 g of magnesium stearate in a rollermill for 5 minutes.

Next, a hydrogel composition is prepared as follows: first, 412.5 g of pharmaceutically acceptable polyethylene oxide comprising a 7,500,000 molecular weight, 150 g of sodium chloride and 6 g of ferric oxide separately are screened through a 40 mesh screen. Then, all the screened ingredients are mixed with 30 g of hydroxypropylmethylcellulose comprising a 11,200 molecular weight to produce a homogeneous blend. Next, 300 mg of denatured anhydrous alcohol is added slowly to the blend with continuous mixing for 5 minutes. The freshly prepared wet granulation is passed through a 20 mesh screen, allowed to dry at room temperature for 16 hours, and again passed through a 20 mesh screen. The screened granulation is mixed with 1.5 g of magnesium stearate in a rollermill for 5 minutes.

Next, the glipizide composition and the hydrogel composition are compressed into bilaminate tablets. First, 200 mg of the glipizide is added to a 0.375 inch (9.5 mm) punch and tamped, then, 140 mg of the hydrogel composition is added and the laminae are pressed under a pressure head of 2 tons into a contacting laminated arrangement.

Then, the bilaminate arrangements are coated with a semipermeable wall. The wall forming composition comprises 93% cellulose acetate having a 39.8% acetyl content, and 7% polyethylene glycol having a molecular weight of 3350. The wall-forming composition is dissolved in an acetone:water (90:10 wt:wt) cosolvent to make a 4% solids solution. The wall forming composition is sprayed onto and around the bilaminate in an Aeromatic® Air Suspension Coater.

Next, a 25 mil (0.635 mm) exit passageway is mechanically drilled through the semipermeable wall to connect the glipizide drug lamina with the exterior of the dosage system. The residual solvent is removed by drying for 48 hours at 50° C. and 50% humidity. Next, the osmotic systems are dried for 1 hour at 50° C. to remove excess moisture. The dosage form produced by this manufacture provides a glipizide composition comprising 11 wt % glipizide, 79.7 wt % polyethylene oxide of 200,000 molecular weight, 9 wt % hydroxypropylmethylcellulose of 11,200 molecular weight, and 0.3 wt % magnesium stearate; a hydrogel composition comprising 68.8 wt % polyethylene oxide comprising a 7,500,000 molecular weight, 25 wt % sodium chloride, 5 wt % hydroxypropylmethylcellulose, 1.0 wt % ferric oxide and 0.2 wt % magnesium stearate; and a semipermeable wall comprising 93 wt % cellulose acetate comprising a 39.8% acetyl content, and 7.0 wt % polyethylene glycol comprising a 3350 molecular weight.

Accompanying drawing FIG. 5 depicts the in vitro release rate profile of glipizide released from the final dosage form for four dosage forms. The error bars represent the standard deviation added to and subtracted from the mean of the dosage form.

DISCLOSURE OF A METHOD OF USING THE INVENTION

An embodiment of the invention pertains to a method for delivering the beneficial drug glipizide orally at a controlled rate to a warm blooded animal in need of glipizide therapy, which method comprises the steps of: (A) admitting into the warm-blooded animal a dosage form comprising: (1) a wall surrounding a compartment, the wall comprising at least in part a semipermeable polymeric composition permeable to the passage of fluid and substantially impermeable to the passage of glipizide; (2) a pharmaceutically acceptable composition in the compartment comprising about 2.5 mg to 50 mg of hypoglycemic glipizide for performing an antidiabetic program; (3) a hydrogel composition in the compartment comprising a member selected from the group consisting of a polyethylene oxide having a 4,000,000 to 7,500,000 molecular weight and a sodium carboxymethylcellulose having a 200,000 to 1,000,000 molecular weight for imbibing and absorbing fluid for pushing the glipizide composition from the dosage form; and, (4) at least one passageway in the wall for releasing glipizide; (B) imbibing fluid through the semipermeable wall at a rate determined by the permeability of the semipermeable wall and the osmotic pressure gradient across the semipermeable wall causing the hydrogel composition to expand and swell; and (C) delivering the beneficial glipizide from the dosage form through the exit passage to the warm blooded animal over a prolonged period of time to produce the desired hypoglycemic effect.

In summary, it will be appreciated that the present invention contributes to the art an unexpected and unforseen dosage form that possesses the practical utility for administering aqueous insoluble glipizide from an osmotic dosage form at a dose metered release rate per unit time. While the invention has been described and pointed out in detail with reference to operative embodiments thereof it will be understood that those skilled in the art that various changes, modifications, substitutions and omissions can be made without departing from the spirit of the invention. It is intended, therefore, that the invention embrace those equivalents within the scope of the claims which follow.

We claim:

1. A method for controlling hyperglycemia and its associated symptomatology in a patient in need of glipizide therapy for controlling same, wherein the method comprises:

(a) admitting orally into the patient a dosage form comprising:

(1) a wall comprising at least at part a composition permeable to the passage of fluid, which wall surrounds;

(2) a compartment;

(3) a lamina in the compartment comprising about 2.0 mg to 50 mg of glipizide and a polyethylene oxide comprising an 80,000 to 350,000 molecular weight;

(4) a displacement lamina in the compartment comprising a polyethylene oxide comprising a 4,000,000 to 8,000,000 molecular weight, which displacement lamina imbides fluid, expands and displaces the lamina comprising the glipizide from the compartment;

(5) at least one exit means in the wall for delivering glipizide from the dosage form;

(b) imbibing fluid into the dosage form for contacting the displacement lamina comprising the polyethylene oxide causing it to expand and displace the lamina comprising the glipizide; thereby,

(c) delivering a therapeutically effective amount of glipizide to the patient to produce the intended effects.

2. A method for controlling hyperglycemia and its associated symptomatology in a patient in need of glipizide therapy for controlling same, wherein the method comprises:

(a) admitting orally into the patient a dosage form comprising:

(1) a wall comprising at least in part a composition permeable to the passage of fluid, which wall surrounds;

(2) a compartment;

(3) a lamina in the compartment comprising about 2.0 mg to 50 mg of glipizide and a polyethylene oxide comprising an 80,000 to 350,000 molecular weight;

(4) a displacement lamina in the compartment comprising sodium carboxymethylcellulose comprising a 200,000 to 1,000,000 molecular weight, which displacement lamina imbibes fluid, sweils and pushes glipizide from the compartment;

(5) at least one exit means in the wall for delivering glipizide from the dosage form;

(b) imbibing fluid by the sodium carboxymethylcellulose causing it to expand and push the glipizide from the dosage form; thereby,

(c) delivering a therapeutically effective amount of glipizide to the patient to produce the intended effects.

3. A dosage form for administering glipizide to a patient, wherein the dosage form comprises:

(a) a wall permeable at least in part to the passage of an exterior fluid, which wall surrounds;

(b) a compartment;

(c) a lamina in the compartment comprising from 2 mg to 50 mg of glipizide and a polyethylene oxide comprising a 80,000 to 350,000 molecular weight;

(d) a displacement lamina in the compartment comprising a polyethylene oxide comprising a 4,000,000 to 8,000,000 molecular weight; and,

(e) at least one exit passageway in the wall for connecting the exterior with the interior of the dosage form for delivering glipizide to the patient.

4. The dosage form for administering glipizide to the patient according to claim 3, wherein the patient is a diabetic and the wall of the dosage form is permeable in at least a part to the passage of fluid and comprises a member selected from the group consisting of a cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, and cellulose triacetate, and wherein the wall comprises at least one exit for delivering the glipizide from the dosage form.

5. A dosage form for delivering an antidiabetic glipizide for lowering blood glucose in a patient in need of lowering blood glucose therapy, wherein the dosage form comprises:

(a) a pharmaceutically acceptable wall comprising a composition permeable in at least a part to the passage of fluid, which wall surrounds:

(b) a compartment;

(c) a first lamina in the compartment comprising from 2 mg to 50 mg of glipizide, a polyethylene oxide and a hydroxypropylmethylcellulose comprising a 9,000 to 25,000 average molecular weight;

(d) a second displacement lamina in the compartment comprising a polyethylene oxide polymer comprising a 4,000,000 to 8,000,000 molecular weight; and

(e) at least one passageway in the wall for connecting the exterior with the interior of the dosage form for delivering glipizide from the dosage form to the patient.

6. The dosage form for delivering the antidiabetic glipizide to the patient according to claim 5, wherein the passageway is formed by leaching to provide a passageway of controlled porosity.

7. A dosage form for delivering an antidiabetic drug glipizide to a patient in need of hypoglycemic action, wherein the dosage form comprises:

(a) a pharmaceutically acceptable wall permeable to the passage of a fluid present in the patient, which wall surrounds;

(b) a compartment;

(c) a first lamina in the compartment comprising from 2 mg to 50 mg of glipizide, a hydroxypropylcellulose polymer and a polyvinylpyrrolidone polymer;

(d) a second displacement lamina in the compartment, the displacement lamina comprising sodium carboxymethylcellulose, and hydroxypropylmethylcellulose; and

(e) at least one passageway in the wall for connecting the exterior with the interior of the dosage form for delivering the glipizide from the dosage form to the patient.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,545,413
DATED : August 13, 1996
INVENTOR(S) : Anthony L. Kuczynski, Atul D. Ayer, Patrick S. Wong

It is certified that error appears in the above-indentified patent and that said Letters Patent is hereby corrected as shown below:

Col. 8,
Claim 1, line 59, "imbides" should read —imbibes--; Col. 9, claim 2, line 19, "sweils" should read --swells--.

Signed and Sealed this
Fifth Day of November, 1996

Attest:

BRUCE LEHMAN

Attesting Officer

Commissioner of Patents and Trademarks

United States Patent [19]

Kuczynski et al.

[11] **Patent Number: 5,591,454**

[45] **Date of Patent: Jan. 7, 1997**

[54] **METHOD FOR LOWERING BLOOD GLUCOSE**

[75] Inventors: **Anthony L. Kuczynski**, Mountain View; **Atul D. Ayer**; **Patrick S.-L. Wong**, both of Palo Alto, all of Calif.

[73] Assignee: **ALZA Corporation**, Palo Alto, Calif.

[21] Appl. No.: **442,040**

[22] Filed: **May 16, 1995**

Related U.S. Application Data

[60] Division of Ser. No. 180,409, Jan. 11, 1994, which is a continuation-in-part of Ser. No. 650,822, Jan. 22, 1991, Pat. No. 5,545,413, which is a division of Ser. No. 402,314, Sep. 5, 1989, Pat. No. 5,024,843.

[51] **Int. Cl.**[6] **A61K 9/10**; A61K 9/16; A61K 9/24; A61K 47/32

[52] **U.S. Cl.** **424/486**; 424/488; 424/499; 424/501; 424/473; 514/866

[58] **Field of Search** 424/499, 501, 424/486, 488, 473; 514/866

[56] **References Cited**

U.S. PATENT DOCUMENTS

2,799,241	7/1957	Wurster	118/24
2,909,462	10/1959	Warfield et al.	167/56
3,845,770	11/1974	Theeuwes et al.	128/260
3,916,899	11/1975	Theeuwes et al.	128/260
4,016,880	2/1983	Theeuwes et al.	128/260
4,063,064	12/1977	Saunders et al.	219/121 L
4,088,864	5/1978	Theeuwes et al.	219/121 LM
4,200,098	4/1980	Ayer et al.	128/260
4,285,987	8/1981	Ayer et al.	427/3
4,627,851	12/1986	Wong et al.	424/473
4,673,405	6/1987	Guittard et al.	424/473
4,708,868	11/1987	Bricl et al.	424/80
4,792,448	12/1988	Ranade	424/438
4,803,076	2/1989	Ranade	424/438
4,851,232	7/1989	Urquehart et al.	424/469
4,902,514	2/1990	Barclay et al.	424/473
5,002,772	3/1991	Curatolo	424/438
5,019,396	9/1991	Ayer et al.	424/473
5,024,843	6/1991	Kuczynski et al.	424/499
5,028,434	7/1991	Barclay et al.	424/473

OTHER PUBLICATIONS

Martindale, *The Extra Pharmacopoeia*, 29th Ed. (1989) p. 390.

AHFS Drug Information, (1989) pp. 1741–1745.

J. Am. Phar. Assoc., Sci. Ed., vol. 48 (1959) pp. 451–459.

J. Am. Phar. Assoc., Sci. Ed., vol. 49 (1960) pp. 82–84.

Remington's *Pharmaceutical Sciences*, 14th Ed., (1970) pp. 1626–1678.

Primary Examiner—Edward J. Webman

Attorney, Agent, or Firm—Paul L. Sabatine; Mary Ann Dillahunty; Felissa H. Cagan

[57] **ABSTRACT**

The invention disclosed comprises a method for administering the antidiabetic drug glipizide to a patient in need of glipizide in need of antidiabetic therapy.

3 Claims, 3 Drawing Sheets

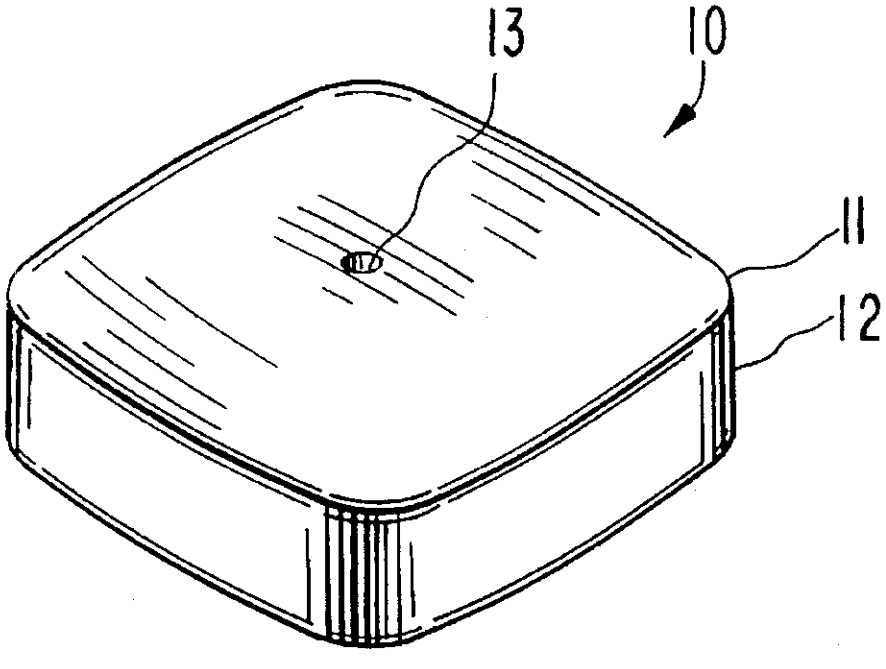


FIG. 1

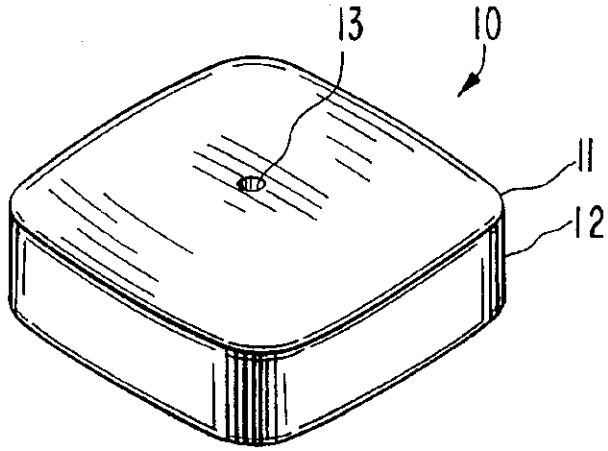


FIG. 2

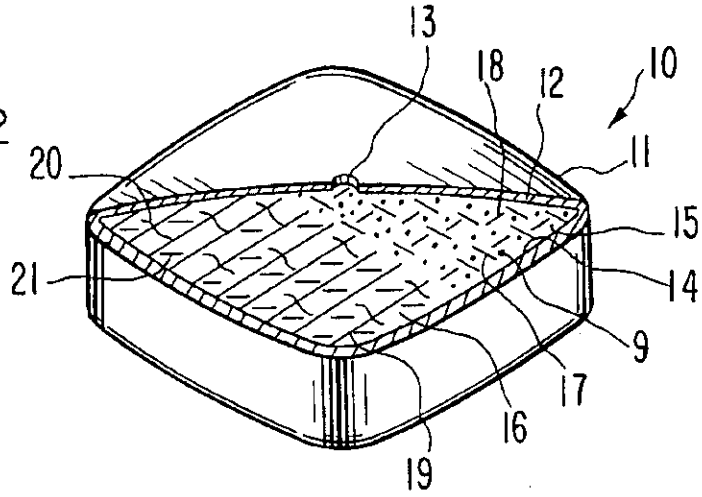
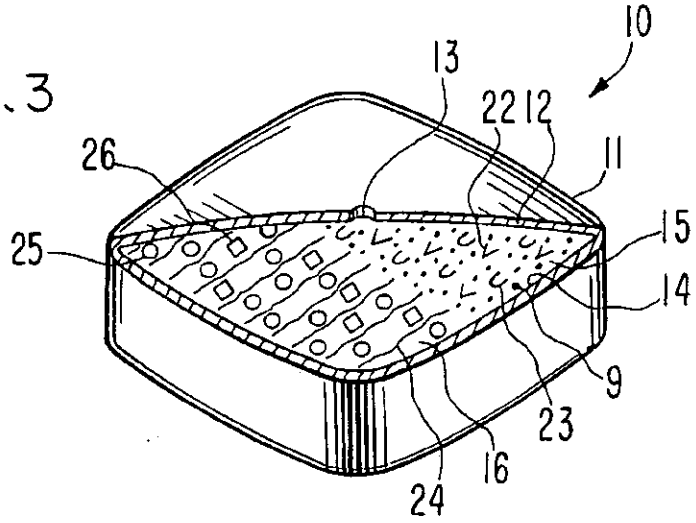


FIG. 3



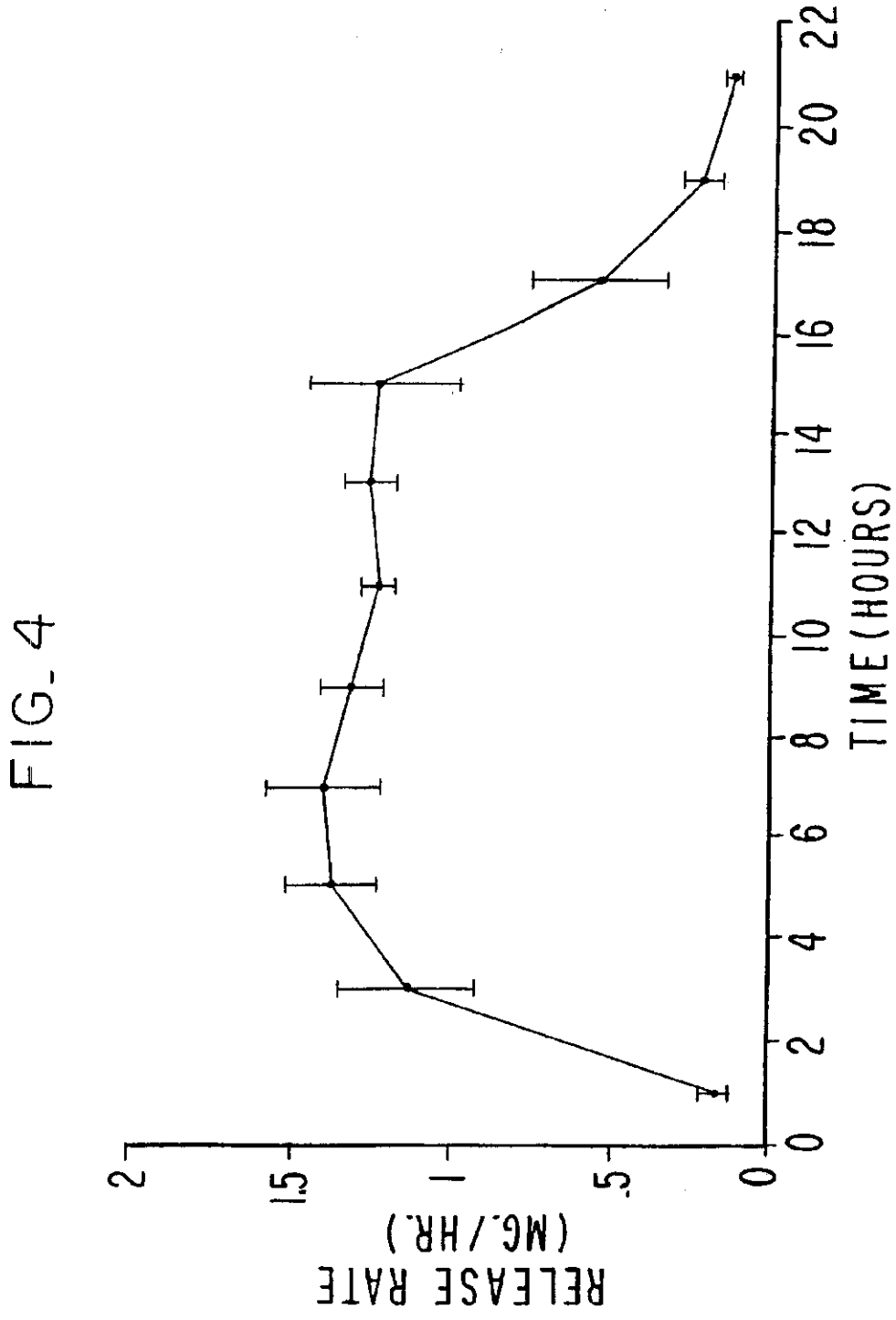
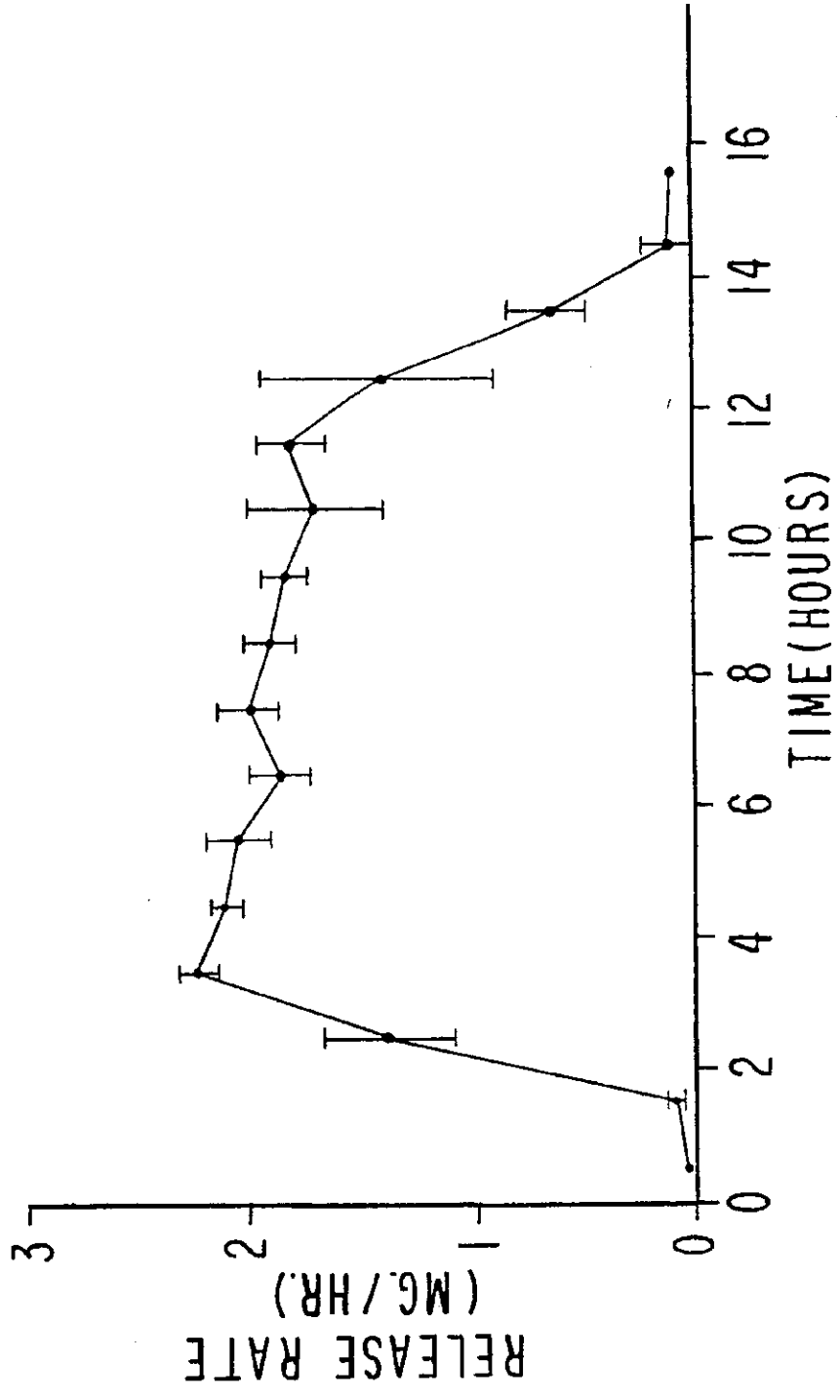


FIG. 4

FIG. 5



METHOD FOR LOWERING BLOOD GLUCOSE

CROSS-REFERENCE TO CO-PENDING APPLICATION

This application is a division of application Ser. No. 08/180,409, filed Jan. 11, 1994, and benefit of the filing date of said earlier filed application is claimed under 35 U.S.C. which is a continuation-in-part of U.S. application Ser. No. 07/650,822 filed Jan. 22, 1991, U.S. Pat. No. 5,545,413 which Ser. No. 07/650,822 is a division of U.S. application Ser. No. 07/402,314, filed Sept. 5, 1989 which Ser. No. 07/402,314 now is U.S. Pat. No. 5,024,843 issued Jun. 18, 1991, and was copending with U.S. Ser. No. 07/652,717 now U.S. Pat. No. 5,091,190 issued Feb. 25, 1992, and benefit of these filing dates is claimed herein.

DISCLOSURE OF TECHNICAL FIELD

This invention pertains to dosage forms comprising the drug glipizide. The invention relates also to compositions comprising glipizide, and the invention concerns additionally a method for administering glipizide to a patient in need of glipizide therapy.

DISCLOSURE OF BACKGROUND OF THE INVENTION

A clinical need exists for a dosage form and for a method for delivering an oral blood-glucose lowering drug to a patient needing this therapy. Glipizide is an oral blood-glucose lowering drug and it is indicated for the control of hyperglycemia and its associated symptomatology in patients with non-insulin dependent diabetes mellitus. Glipizide is useful therapeutically as an oral hypoglycemic drug because it stimulates insulin secretion from the beta cells of pancreatic-islet tissue, it increases the concentration of insulin in the pancreatic vein, and because it exhibits extrapancreatic action such as the ability to increase the number of insulin receptors.

Glipizide is known chemically as N-[2-[4-[[[(cyclohexylamino)carbonyl]amino]sulfonyl]phenyl]ethyl]-5-methylpyrazinecarboxamide. Glipizide is a white, odorless powder with a pKa of 5.9, and it is insoluble in both water and alcohol. These physical and chemical properties of glipizide do not lend the drug to formulation into a dosage form, and these properties do not lead to a method, that in both instances that can administer glipizide at a controlled and known rate per unit time to produce the intended therapy. The properties of glipizide are disclosed in *Martindale The Extra Pharmacopeia*, 29th Ed., p 390, (1989); and, *AHFS Drug Information*, pp 1741–45, (1989).

In the light of the above presentation, it will be appreciated by those versed in the medical and in this pharmaceutical dispensing art to which this invention pertains, that a pressing need exists for dosage forms that can deliver the valuable drug glipizide in a rate-controlled dose to a patient in clinical need of blood-glucose lowering therapy. The pressing need exists also for an oral dosage form and for a method of therapy that can deliver glipizide at a controlled rate in a substantially constant dose per unit time for its beneficial therapeutic effects, and remain substantially independent of the changing environment of the gastrointestinal tract. It will be appreciated further by those skilled in the dispensing art, that if such a novel and unique dosage form and method as made available that can administer glipizide in a rate-controlled dose over time, and simultaneously provide a method of blood-glucose lowering therapy, the dosage form and the accompanying method would represent

an advancement and a valuable contribution to the medical art.

DISCLOSURE OF OBJECTS OF THE INVENTION

Accordingly, in view of the above presentation, it is an immediate object of this invention to provide a dosage form for delivering glipizide in a rate controlled amount, and which dosage form substantially overcomes the deficiencies and omissions associated with the prior art.

Another object of the present invention is to provide a dosage form for orally administering glipizide in a rate-controlled dose for blood-glucose lowering therapy.

Another object of the invention is to provide a pharmaceutical dosage form that makes available controlled and sustained glipizide therapeutic activity to a patient in need of glipizide therapy.

Another object of the invention is to provide a novel dosage form manufactured as an osmotic, diffusional, bioerodible or ion-exchange device that can administer glipizide to a biological receptor site to produce the desired glipizide pharmacological effects.

Another object of the present invention is to provide a dosage form manufactured as an osmotic, diffusional, bioerodible, or ion-exchange dosage form that maintains glipizide in the dosage form until released from the dosage form, thereby substantially reducing and/or substantially eliminating the unwanted influences of the gastrointestinal environment of use and still provide controlled administration of glipizide over time.

Another object of the present invention is to provide a dosage form that can deliver the substantially aqueous insoluble drug glipizide at a controlled and beneficial known rate over time.

Another object of the present invention is to provide a dosage form adapted for the oral administration of glipizide and which dosage form comprise a first composition and a contacting second composition that operate in combination for the controlled administration of glipizide.

Another object of the present invention is to provide a complete pharmaceutical glipizide regimen comprising a composition comprising glipizide that can be dispensed from a drug delivery dosage form, the use of which requires intervention only for initiation and possibly for termination of the regimen.

Another object of the invention is to provide a method for treating hyperglycemia by orally administering glipizide in a rate-controlled dose per unit time to a warm-blooded animal in need of hyperglycemia therapy.

Another object of the invention is to provide a method that engages osmotic, diffusional, bioerodible, or ion-exchange delivery for administering glipizide in a therapeutic dose per unit time or an extended time to a human patient in need of glipizide therapy.

Other objects, features and advantages of this invention will be more apparent to those versed in the dispensing arts from the following detailed specification, taken in conjunction with the drawings and the accompanying claims.

BRIEF DISCLOSURE OF THE DRAWINGS

In the drawings, which are not drawn to scale, but are set forth to illustrate various embodiments of the invention, the drawing figures are as follows:

Drawing FIG. **1** is a view of one dosage form provided by the invention designed and shaped for orally administering glipizide to the gastrointestinal tract of a warm-blooded animal, including humans;

Drawing FIG. **2** is an opened view of a dosage form of drawing FIG. **1** illustrating the structure of the dosage form comprising glipizide;

Drawing FIG. **3** is an opened view of the dosage form of drawing FIG. **1** depicting a different internal structure embodiment provided by the invention;

Drawing FIG. **4** is a graph that depicts the release rate pattern from one embodiment of the dosage form provided by the method of the invention that administers glipizide at a rate-controlled by the dosage form over an extended period of therapy; and,

Drawing FIG. **5** is a graph that depicts the release rate pattern for a different embodiment of the dosage form provided by the invention, wherein the glipizide is administered by a method employing an osmotic, diffusional, bioerodible, or ion-exchange dosage form.

In the drawing figures and in the specification like parts in related drawing figures are identified by like numbers. The terms appearing earlier in the specification and in the description of the drawings, as well as embodiments thereof, are further described elsewhere in the disclosure.

DETAILED DISCLOSURE OF THE DRAWING FIGURES

Turning now to the drawing figures in detail, which drawing figures are examples of the dosage forms provided by this invention, and which examples are not to be construed as limiting, one example of the dosage form is illustrated in drawing FIG. **1** and designated by the numeral **10**. In drawing FIG. **1**, dosage form **10** comprises a body **11**, which body member **11** comprises a wall **12** that surrounds and encloses an internal compartment, not seen in drawing FIG. **1**. Dosage form **10** comprises at least one exit means **13** for connecting the interior of dosage form **10** with the exterior environment of use.

In drawing FIG. **2**, dosage form **10** is seen in opened view. In drawing FIG. **2**, dosage form **10** comprises a body member **11** comprising wall **12**, which wall surrounds and defines an internal compartment **14**. Wall **12** comprises at least one exit means **13** that connects internal compartment **14** with the exterior of dosage form **10**. Dosage form **10** can comprise more than one exit means **13**. Wall **12** of dosage form **10** comprises in total, or in at least a part, a composition that is permeable to the passage of an exterior fluid present in the environment, and wall **12** is substantially impermeable to the passage of glipizide and other ingredients present in compartment **14**. The composition comprising wall **12** is semipermeable, it is substantially inert, and wall **12** maintains its physical and chemical integrity during the dispensing life of glipizide from dosage form **10**. The phrase, "keeps its physical and chemical integrity," means wall **12** does not lose its structure, and it does not change chemically during the glipizide dispensing life of dosage form **10**.

Wall **12**, in a present embodiment, comprises 60 weight percent (wt %) to 100 weight percent of a composition comprising a cellulose polymer. The cellulose polymer comprises a member selected from the group consisting of a cellulose ester, cellulose ether, cellulose ester-ether, cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, and cellulose triacetate. Wall **12**, in another manufacture, comprises from 0 weight percent to 25 weight percent of a member selected from the group consisting of hydroalkylcellulose, hydroxypropylalkylcellulose, hydroxypropylcellulose, and hydroxypropylmethylcellulose, and from 0 to 20 weight percent of polyethylene glycol, with the total amount of all wall-forming components comprising wall **12** equal to 100 weight percent.

Internal compartment **14** in one dosage form comprises an internal glipizide lamina **15**, which glipizide lamina can be defined as glipizide composition **15**. Internal compartment **14** also comprises an internal displacement lamina **16**, which displacement lamina can be defined as displacement composition **16**. The glipizide lamina **15** and the displacement lamina **16** initially are in laminar arrangement and they cooperate with each other and with dosage form **10** for the effective delivery of glipizide from dosage form **10**.

The glipizide composition **15**, in a present embodiment, as seen in FIG. **2**, comprises about 2.0 mg to 750 mg of glipizide identified by dots **9**; from 100 mg to 320 mg of a polyethylene oxide comprising 80,000 to 350,000 molecular weight identified by dashes **17**; from 5 mg to 50 mg of hydroxypropylmethylcellulose comprising a 9,200 to 22,000 molecular weight identified by vertical lines **18**; and from 0 mg to 7.5 mg of a lubricant such as stearic acid, magnesium stearate, and the like.

The displacement lamina **16**, as seen in drawing FIG. **2**, comprises 70 mg to 125 mg of a polyethylene oxide comprising a 4,000,000 to **8,000,000** molecular weight identified as lines **19**; from 20 mg to 50 mg of an osmagent selected from the group consisting of sodium chloride and potassium chloride identified by wavy line **20**; and from 5 mg to 15 mg of a hydroxypropylmethylcellulose having a 9,000 to 25,000 molecular weight identified by vertical slashes **21**. Displacement lamina **16** optionally comprises from 0.1 mg to 5 mg of ferric oxide and from 0.01 mg to 5 mg of a lubricant such as magnesium stearate or stearic acid.

Dosage form **10**, in another manufacture the internal compartment **14** comprises a homogenous composition comprising 2.0 mg to 750 mg of glipizide and an osmagent that exhibits an osmotic pressure gradient across semipermeable wall **12** against an external aqueous or biological fluid. The osmagents are known also as osmotically effective solute and as osmotically effective compound. The amount of osmagent is 1 mg to 350 mg for providing the composition comprising glipizide. The osmagent operable for the purpose of this dosage form comprises a member selected from the group consisting of water-soluble inorganic salts, water soluble sugars, organic osmagents and organic salts. Representative osmagents include sodium chloride, potassium chloride, potassium acid phosphate, tartaric acid, citric acid, raffinose, magnesium sulfate, magnesium chloride, urea, inositol, sucrose, glucose, and sorbitol. Osmagents are known in U.S. Pat. No. 4,783,332.

Drawing FIG. **3** depicts in opened section another dosage form **10** provided by the invention. In drawing FIG. **3**, dosage form **10** comprises a body **11**, a wall **12**, which wall **12** surrounds an internal compartment **14** with an exit passageway **13** in wall **12**. Internal compartment **14**, in this dosage form, comprises an internal glipizide lamina **15**, which glipizide lamina **15** comprises 2 mg to 225 mg of aqueous insoluble drug glipizide identified by dots **9**; from 100 mg to 250 mg of a hydroxypropylcellulose comprising a 40,000 to 80,000 molecular weight identified by angle **22**; and from 40 mg to 70 mg of a polyvinylpyrrolidone comprising a 30,000 to 70,000 molecular weight and identified by half circle **23**. Internal compartment **14** comprises a

displacement lamina **16** comprising 30 mg to 150 mg of sodium carboxymethylcellulose having 200,000 to 1,000,000 molecular weight identified by wavy lines **24**; from 20 mg to 70 mg of an osmagent selected from the group consisting of osmogent sodium chloride, and potassium chloride identified by circle **25**; and from 0.5 mg to 10 mg of a hydroxypropylmethylcellulose comprising a 9,200 to 22,000 molecular weight identified by squares **26**. Displacement lamina **16** optionally comprises from 0 mg to 5 mg of ferric oxide and optionally 0 mg to 7 mg of a lubricant.

The expression, "exit means **13**," as used herein, comprises means and methods suitable for the controlled metered release of glipizide **9** from compartment **14** of dosage form **10**. The exit means **13** comprises at least one passageway, orifice, or the like, through wall **12** for communication with glipizide **9** in compartment **14**. The expression, "at least one passageway," includes aperture, orifice, bore, pore, or porous element through which glipizide can be released, or hollow fiber, capillary tube, porous overlay, porous insert, and the like. The expression also includes a material that erodes or is fluid-leached from wall **12** in a fluid environment of use to produce at least one pore-passageway of governed release rate pore-size in wall **12**. Representative materials suitable for forming at least one passageway, or a multiplicity of passageways, comprise an erodible polyglycolic acid, or a polylactic acid member in wall **12**, a gelatinous filament, polyvinyl alcohol, leachable materials such as a fluid removable pore forming polysaccharide, salt, oxide, polyol, or the like. A passageway or a plurality of passageways can be formed by leaching a material such as sorbitol, lactose, or the like, from wall **12**. The passageway can have any shape such as round, triangular, square, elliptical, and the like, for assisting in the metered release of glipizide **9** from dosage form **10**. Dosage form **10** can be constructed with one or more passageways in spaced apart relations, or more than one passageway on a single surface of dosage form **10**. Passageways and equipment for forming passageways are disclosed in U.S. Pat. Nos. 3,845,770 issued Nov. 1974 to Theeuwes et al; 3,916,899 issued Nov. 1975 to Theeuwes et al; 4,016,880 issued Apr. 1977 to Theeuwes et al; 4,063,064 issued Dec. 1977 to Saunders et al; 4,088,864 issued May 1978 to Theeuwes et al; and, passageways formed by leaching are disclosed in U.S. Pat. Nos. 4,200,098 issued Apr. 1980 to Ayer et al; 4,235,236 issued Nov. 1980 to Theeuwes; and, 4,285,987 issued to Ayer et al.

Dosage form **10** used for the purpose of the invention includes also dosage forms **10** that mediate the efficiency of glipizide by imparting enhanced therapy from administering glipizide by the method of the invention. Dosage forms **10** contemplated by the invention also comprise dosage form selected from the group consisting of a bioerodiable-mediated dosage form, diffusion-mediated dosage form and ion-exchange mediated dosage form.

The bioerable-mediated dosage form **10** comprises a bioerodable polymer matrix containing glipizide. Dosage form **10** provides a mediated-release rate of glipizide delivered to a glipizide-drug receptor as the polymer matrix bioerodes at a release-rate controlled by the biocroding matrix over time. Bioerodable polymers for forming the dosage form containing glipizide include a member selected from the group consisting of poly(ester) poly(amine), poly (lactide), poly(glycolide), poly(lactide-co-glycolide), poly-(caprolactone), poly(hydroxybutyrei acid), poly(orthoester), poly(orthocarbonate), poly(acetal), poly(carbohydrate), poly(peptide), and poly(dehydropyran). The bioerodable-mediated dosage form comprises 2.0 mg to 750 mg of glipizide compounded with the bioerodable polymer.

The diffusion-mediated dosage form **10** comprises a membrane-controlled diffusion that permits diffusion of glipizide through a polymer membrane or diffusion of glipizide through a porous polymer membrane. The diffusion mediated dosage form **10** structurally includes a polymer matrix with glipizide thereon that is released by the process of diffusion, and a reservoir or depot polymer dosage form with glipizide in the reservoir that is released therefrom by a process of diffusion through a contacting polymer rate-governing membrane. Representative of polymers for providing a diffusional dosage form comprise a member selected from the group consisting of poly (olefin), poly(vinyl), poly (carbohydrate), poly(peptides), poly (condensation), poly(rubber), and poly(silicon). Representative of specific polymers are a member selected from the group consisting of poly(ethylene), poly(propylene), copoly(ethylenevinylacetate), poly(isobutylethylene), poly(vinylacetate), cross-linked poly(vinyl-alcohol), poly(methyacrylate), poly(amide), poly(ester), poly(ether), and poly(silicone).

The ion-exchange mediated dosage form comprises water-insoluble-crosslinked polymers with glipizide bound to the resin. The glipizide is released at a rate controlled by the glipizide-resin complex by the ionic environment within the gastrointestinal tract. The ion-exchanged mediated dosage form comprises cation-exchange resins containing electronegative charges and anion-exchange resins containing electropositive charges. The cation-exchange resins include strong-acid weak-acid resins as with sulfonic acid, carboxylic acid, and phosphonic acid, and the anion-exchange resins include strong-base and weak-base resins as with quaternary ammonium, secondary amine, tertiary amine aromatic, and tertiary amine aliphatic resins. Specific examples of ion-exchange resins mention is made of acidic ion-exchange resins mention is made of acidic ion-exchange resins such as Amberlite IR-120, basic ion-exchange resins such as Amberlite IRA-400, and weak basic ion-exchange resins such as Amberlite IR-45.

PROCEDURES FOR MANUFACTURING THE DOSAGE FORM

Dosage form **10** of this invention is manufactured by standard techniques. For example, in one manufacture the drug glipizide is mixed with other composition-forming ingredients and the mix then pressed into a solid lamina possessing dimensions that correspond to the internal dimensions of the compartment space adjacent to the passageway. In another embodiment the beneficial drug glipizide and other composition forming ingredients and a solvent are mixed into a solid, or into a semisolid, by conventional methods such as ballmilling, calendering, stirring, or roll-milling, and then pressed into a preselected lamina forming shape. Next, a lamina composition comprising the osmopolymer and the osmagent are placed in contact with the lamina comprising the beneficial drug glipizide, and the two lamina comprising the laminate are surrounded with a semipermeable wall. The lamination of the glipizide composition and the osmopolymer displacement composition can be accomplished by using a two-layer tablet press technique. The wall can be applied by molding, spraying, or dipping the pressed shapes into wall-forming formulations. Another preferred technique that can be used for applying the wall is the air suspension coating procedure. This procedure consists in suspending and tumbling the two layered laminate in a current of air until the wall forming composition surrounds the laminate. The air suspension

procedure is described in U.S. Pat. No. 2,799,241; in *J. Pharm. Assoc., Sci. Ed.*, Vol. 48 pp 451–59 (1959); and ibid, Vol. 49, pp 82–84, (1960). Other standard manufacturing procedures are described in *Modern Plastics Encyclopidia*, Vol. 46, pp 62–70, (1969); and in *Pharmaceutical Sciences*, by Remington, 14th Ed., pp 1626–1978, (1970), published by Mack Publishing Co., Easton, Pa.

The bioerodable-mediated dosage form is provided by dispensing or mixing the drug into the bioerodible polymer by blending by spatula, in a v-shaped blender, or on a three-roll mill. The blend is heated until pliable to thoroughly mix the polymer and drug to yield the loaded polymer. After the blend cools to room temperature, the blend can be molded into a preselected design and shaped and sized for therapeutic use.

A diffusion-mediated dosage form is fabricated by mixing the drug in particulate form with a polymer, which can be in solid, semi-solid or liquid form, and distributed therethrough by ballmilling, calendering, stirring, or shaking. Monomers or prepolymers can be used to form the reservoir, or a matrix formed in situ. A reservoir, or matrix comprising drug distributed therethrough can be formed into a solid shape by molding, casting, pressing, extruding or drawing. A polymeric membrane is applied to a reservoir by wrapping, laminating or heat shrinking, or the polymer membrane can be formed by drawing or stamping the polymer thereto. A preformed shape of the polymer, such as tube can be filled with drug and seal to form a closed diffusional form. A polymer membrane, or matrix can be converted to a solid by curing to yield the desired dosage form.

An ion-exchanged mediated dosage form where the absorption of the drug onto the ion-exchange resin to form a drug resin complex, is provided by mixing the drug with an aqueous suspension of the resin and the complex is then dried. Absorption of the drug onto the resin is detected by a change in the pH of the reaction medium. The ion-exchange resin drug complex can be solvated by the use of solvating agents such as polyethylene glycol to enable this complex to release the drug at a controlled-rate over an extended period of drug therapy.

Exemplary solvents suitable for manufacturing the wall, laminate, compositions, comprise inert inorganic and organic solvents that do not adversely affect the final wall and the final laminates. The solvents broadly comprise a member selected from the group consisting of aqueous solvents, alcohols, ketones, esters, ethers, aliphatic hydrocarbons, halogenated solvents, cycloaliphatics, aromatics, heterocyclic solvents, and mixtures thereof. Typical solvents comprise acetone, diacetone, alcohol, methanol, ethanol, isopropyl alcohol, butyl alcohol, methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate methyl isobutyl ketone, methylpropyl ketone, n-hexane, n-heptane, ethylene glycol monethyl ether, ethylene glycol monethyl acetate, methylene dichloride, ethylene dichloride, propylene dichloride, acetone and water, acetone and methanol, acetone and ethyl alcohol, methylene dichloride and methanol, ethylene dichloride and methanol, and the like.

DETAILED DISCLOSURE OF EXAMPLES OF THE INVENTION

The following examples are merely illustrative of the present invention, and they should not be considered as limiting the scope of this invention in any way, as these examples and other equivalents thereof will become apparent to those versed in the art in the light of the present disclosure, the drawings and the accompanying claims.

EXAMPLE 1

An oral dosage form, adapted, designed and shaped as drug delivery system for admittance into the gastrointestinal tract of a patient in need of glipizide is manufactured as follows: first, 369 g of pharmaceutically acceptable hydroxypropylcellulose comprising a 60,000 average molecular weight is passed through a 20 mesh screen, followed by passing through a 40 mesh screen 162 g of pharmaceutically acceptable polyvinylpyrrolidone comprising a 40,000 average molecular weight. Next, the two screened ingredients are blended with 66 g of glipizide to form a homogeneous blend. The blend is suspended in a fluidized bed and sprayed with an atomized spray comprising an ethanol:water (70:30 vol:vol) solution until granules are formed of the three ingredients. The freshly prepared granules then are passed through a 20 mesh screen. Finally, the screened granulation is mixed with 3 g of magnesium stearate in a rollermill for 5 minutes.

Next, a separate hydrogel granulation is prepared as follows: first, 389 g of pharmaceutically acceptable sodium carboxymethylcellulose having 700,000 molecular weight, 174 g of sodium chloride, 30 g of pharmaceutically acceptable hydroxypropylmethylcellulose comprising a 11,200 molecular weight and 6 g of ferric oxide separately are screened through a 40 mesh screen. Then, all the screened ingredients are mixed to produce a homogeneous blend. Next, 300 ml of denatured anhydrous ethanol is added slowly to the blend with continuous mixing for about 5 minutes. The freshly prepared wet granulation is screened through a 20 mesh screen, allowed to dry at room temperature for 16 hours, and again passed through a 20 mesh screen. The screened granulation is mixed with 1.5 g of magnesium stearate in a rollermill for about 5 minutes.

Next, the glipizide granulation, and the hydrogel granulation are compressed into a bilaminate tablet arrangement. First, 200 mg of the glipizide composition is added to a 0.375 inch (9.5 mm) punch and tamped, then, 140 mg of the hydrogel granulation is added to the punch and the two laminae are pressed into a solid, contacting arrangement.

Next, the bilaminate is coated with a semipermeable wall. The semipermeable wall-forming composition comprises 93% cellulose acetate having a 39.8% acetyl content, and 7% polyethylene glycol having a 3350 molecular weight. The wall-forming composition is dissolved in a cosolvent comprising acetone: water (90:10 wt:wt) to make a 4% solids solution. The wall-forming composition is sprayed onto and around the bilaminate in an Acromatic® Air Suspension Coater.

Then, a 25 mil (0.635 mm) exit orifice is mechanically drilled on the glipizide side of the osmotic dosage form. The residual solvent is removed by drying the osmotic system for 48 hours at 50° C. and 50% humidity. The osmotic systems are dried for 1 hour at 50 ° C. to remove excess moisture. Attached drawing FIG. 4 shows the in vitro release rate profile for glipizide from the finished osmotic system as released in distilled water. The error bars represent the standard deviation added to and subtracted from the mean of five osmotic delivery system. An osmotic dosage form provided by the invention comprises 11 wt % glipizide, 61.50 wt % hydroxypropyl- cellulose of 60,000 molecular weight, 27.0 wt % polyvinylpyrrolidone of 40,000 molecular weight, 0.5% magnesium stearate in the glipizide composition; 64.8 wt % sodium carboxymethylcellulose of 700,000 molecular weight, 29 wt % sodium chloride, 5 wt % hydroxypropylmethylcellulose of 11,200 molecular weight and 1.0 wt % ferric oxide, 0.2% magnesium stearate in the hydrogel composition; and, 93.0 wt % cellulose acetate having a 39.8% acetyl content, and 7.0 wt % polyethylene glycol having a 3350 molecular weight in the, semipermeable wall formulation.

EXAMPLE 2

A dosage form adapted, designed and shaped as an osmotic delivery system is manufactured as follows: first, a glipizide composition is provided by blending together into a homogeneous blend 478 g of pharmaceutically acceptable polyethylene oxide comprising a 200,000 molecular weight, 66 g of glipizide and 54 g of pharmaceutically acceptable hydroxypropylmethylcellulose comprising a 11,200 molecular weight. Then, 425 ml of denatured anhydrous ethanol is added slowly with continuous mixing over 5 minutes. The freshly prepared wet granulation is screened through a 20 mesh screen through a 20 mesh screen, dried at room temperature for 16 hours, and again screened through a 20 mesh screen. Finally, the screened granulation is mixed with 1.5 g of magnesium stearate in a rollermill for 5 minutes.

Next, a hydrogel composition is prepared as follows: first, 412.5 g of pharmaceutically acceptable polyethylene oxide comprising a 7,500,000 molecular weight, 150 g of sodium chloride and 6 g of ferric oxide separately are screened through a 40 mesh screen. Then, all the screened ingredients are mixed with 30 g of hydroxypropylmethylcellulose comprising a 11,200 molecular weight to produce a homogeneous blend. Next, 300 mg of denatured anhydrous alcohol is added slowly to the blend with continuous mixing for 5 minutes. The freshly prepared wet granulation is passed through a 20 mesh screen, allowed to dry at room temperature for 16 hours, and again passed through a 20 mesh screen. The screened granulation is mixed with 1.5 g of magnesium stearate in a rollermill for 5 minutes.

Next, the glipizide composition and the hydrogel composition are compressed into bilaminate tablets. First, 200 mg of the glipizide is added to a 0.375 inch (9.5 mm) punch and tamped, then, 140 mg of the hydrogel composition is added and the laminae are pressed under a pressure head of 2 tons into a contacting laminated arrangement.

Then, the bilaminate arrangements are coated with a semipermeable wall. The wall forming composition comprises 93% cellulose acetate having a 39.8% acetyl content, and 7% polyethylene glycol having a molecular weight of 3350. The wall-forming composition is dissolved in an acetone:water (90:10 wt:wt) cosolvent to make a 4% solids solution. The wall forming composition is sprayed onto and around the bilaminate in an Aeromatic® Air Suspension Coater.

Next, a 25 mil (0.635 mm) exit passageway is mechanically drilled through the semipermeable wall to connect the glipizide drug lamina with the exterior of the dosage system. The residual solvent is removed by drying for 48 hours at 50° C. and 50% humidity. Next, the osmotic systems are dried for 1 hour at 50° C. to remove excess moisture. The dosage form produced by this manufacture provides a glipizide composition comprising 11 wt % glipizide, 79.7 wt % polyethylene oxide of 200,000 molecular weight, 9 wt % hydroxypropylmethylcellulose of 11,200 molecular weight, and 0.3 wt % magnesium stearate; a hydrogel composition comprising 68.8 wt % polyethylene oxide comprising a 7,500,000 molecular weight, 25 wt % sodium chloride, 5 wt % hydroxypropylmethylcellulose, 1.0 wt % ferric oxide and 0.2 wt % magnesium stearate; and a semipermeable wall comprising 93 wt % cellulose acetate comprising a 39.8% acetyl content, and 7.0 wt % polyethylene glycol comprising a 3350 molecular weight.

Accompanying drawing FIG. 5 depicts the in vitro release rate profile of glipizide released from the final dosage form for four dosage forms. The error bars represent the standard deviation added to and subtracted from the mean of the dosage form.

EXAMPLE 3

A therapeutic dosage form for administering glipizide is made as follows: first, 125 mg of glipizide is sieved through a No. 40 mesh sieve and dry mixed with 125 mg of sorbitol, 100 mg of hydroxypropylmethylcellulose, 25 mg of microcrystalline and 5 mg of sodium chloride. Then, the mixture is blended with ethanol into a uniform, doughy mass. The resulting dough is passed through a No. 20 mesh sieve to form damp granules. The granules are air dried overnight, then re-passed through a No. 20 mesh sieve. Next, the sieve composition is compressed into a 15 mm oval tablet tooling at 2 tons pressure. The resulting compressed cores comprising the homogenous glipizide formulation is coated with about 50 mg of a 50/50 wt % mixture of cellulose acetate and polyethylene glycol deposited from a 95/5 wt % acetone and water solution. Then, the coated dosage form is air dried overnight, and an exit port drilled through the semipermeable wall connecting the exterior of the dosage form with the glipizide.

EXAMPLE 4

A diffusion-mediated dosage form is prepared as follows: first 75 mg of glipizide is mixed with 50 parts of poly(dimethylsiloxane) and 1 part of silicone oil, and to this well-stirred mixture is added 0.15 parts by weight of stannous actoate curing catalyst, and the mixture injected into a poly(ethylene) tube and cured for 30 minutes. Then, the cured reservoir is removed from the poly(ethylene) tube and placed inside a rate-controlling copoly(ethylene-vinyl acetate) tube and sealed with poly(tetrafluoroethylene) plugs and cyanoacrylate adhesive. The dosage form releases glipizide over 24 hours.

EXAMPLE 5

A bioerodible delivery system is prepared by heating poly(2.2-dioxo- trans- 1, 4-cyclohexane dimethylane tetrahydrofuran) to 120° C. and blending therein glipizide and dispersed with mixing for 5 minutes into the hot melt of the polymer. After cooling to room temperature, the glipizide-bioerodable polymer formulation is pressed into a film under 10,000 psi for 5 minutes and placed inside a capsule, and on oral administration the dosage form releases glipizide at a rate controlled over time.

DISCLOSURE OF A METHOD OF USING THE INVENTION

The invention pertains further to a method for delivering the beneficial drug glipizide orally at a controlled rate to a warm blooded animal in need of glipizide therapy by a method selected from the group consisting of osmotic, diffusion, bioerosion and ion-exchange. One method provided by the invention comprises the steps of: (A) admitting into the warm-blooded animal a dosage form comprising: (1) a wall surrounding a compartment, the wall comprising at least in part a semipermeable polymeric composition permeable to the passage of fluid and substantially impermeable to the passage of glipizide; (2) a pharmaceutically acceptable composition in the compartment comprising about 2.0 mg to 750 mg of hypoglycemic glipizide for performing an antidiabetic program; (3) a hydrogel composition in the compartment comprising a poly(ethylene) oxide having a 4,000 to 7,500,000 molecular weight for imbibing

and absorbing fluid for pushing the glipizide composition from the dosage form; and, (4) at least one passageway in the wall for releasing glipizide; (B) imbibing fluid through the semipermeable wall at a rate determined by the permeability of the semipermeable wall and the osmotic pressure gradient across the semipermeable wall causing the hydrogel composition to expand and swell; and (C) delivering the beneficial glipizide from the dosage form through the exit passage to the warm blooded animal over a prolonged period of time to produce the desired hypoglycemic effect.

Another dosage form administered according to the method of the invention comprises the steps of: (A) admitting into a patient in need of glipizide therapy a dosage form comprising: (1) a wall surrounding a compartment, the wall comprising a semipermeable composition permeable to the passage of fluid and substantially impermeable to the passage of glipizide; (2) a glipizide pharmaceutically acceptable composition in the compartment comprising 2.0 mg to 750 mg of hypoglycemic glipizide for performing an antidiabetic program; an expandable, push composition in the compartment comprising a carboxymethylcellulose having a 200,000 to 1,000,000 molecular weight for imbibing and absorbing fluid for pushing the glipizide composition from the dosage form; and, (4) at least one passageway in the semipermeable causing the expandable composition to expand and push the glipizide composition from the dosage form; and (C) delivering the glipizide at a rate of 10 ng to 25 mg per hour over a period of 2 to 24 hours from the dosage form through the exit port to produce the desired hypoglycemic effect.

The glipizide can be administered by administering a dosage form comprising a semipermeable wall that surrounds a compartment housing a composition comprising glipizide and an osmotic effective solute that imbibes fluid through the semipermeable wall into the compartment thereby causing the glipizide to be pumped through the exit port at a rate controlled by the dosage form at 10 ng to 25 mg per hour over an extended period up to 24 hours.

The method comprises further administering glipizide from a dosage form comprising a diffusion-releasing polymer that release glipizide from a polymer glipizide matrix or through a polymer from a glipizide reservoir at a diffusion controlled-rate of administration over an extended time. The method comprises also administering glipizide at a bioerodable controlled-rate and at an ion-exchange controlled-rate over an extended period of time.

In summary, it will be appreciated that the present invention contributes to the art an unexpected and unforseen dosage form that possesses the practical utility for administering aqueous insoluble glipizide from a dosage form at a dose metered release rate per unit time. While the invention has been described and pointed out in detail with reference to operative embodiments thereof it will be understood that those skilled in the art that various changes, modifications, substitutions and omissions can be made without departing from the spirit of the invention. It is intended, therefore, that the invention embrace those equivalents within the scope of the claims which follow.

We claim:

1. A method for treating hyperglycemia in a patient, wherein the method comprises administering to the patient a dosage form comprising 2 mg to 750 mg glipizide that is administered at a therapeutically effective dose of 10 ng to 25 mg over 24 hours from the dosage form comprising 1 mg to 300 osmagent and a hydrogel selected from the group consisting of poly(ethylene oxide) having a 4,000,000 to 8,000,000 molecular weight and a carboxymethylcellulose having a 200,000 to 1,000,000 molecular weight to the patient to produce the intended effect in the patient.

2. A method for treating hyperglycemia in a patient, wherein the method comprises administering to the patient a dosage form comprising a composition that comprises 2.0 mg to 750 mg of a glipizide that is administered at a dose of 10 ng to 25 mg per hour over an extended period of 24 hours, from the composition that comprises 100 mg to 320 mg of a poly(ethylene oxide) having a 80,000 to 350,000 molecular weight and 5 mg to 50 mg of a hydroxypropylmethylcellulose having a 9,200 to 22,000 molecular weight to produce the intended therapy.

3. A method for lowering blood sugar in the treatment of a diabetic patient, which method comprises orally administering to the patient an effective blood sugar lowering dose of a composition comprising glipizide and a pharmaceutically acceptable carrier, which carrier comprises 100 mg to 250 mg of a hydroxypropylmethylcellulose of 40,000 to 80,000 molecular weight and 40 mg to 70 mg of polyvinylpyrrolidone of 30,000 to 70,000 molecular weight, which blood sugar lowering composition is administered over time to produce the intended lowering of the blood sugar in the patient.

* * * * *