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**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY**

JANSSEN, L.P.,)
JANSSEN PHARMACEUTICA N.V., and)
ORTHO-MCNEIL NEUROLOGICS, INC.,)
)
Plaintiffs,)
)
v.)
)
KV PHARMACEUTICAL COMPANY,)
)
Defendant.)
_____)

Civ. Action No. _____

**COMPLAINT FOR
PATENT INFRINGEMENT**

Filed Electronically

Plaintiffs Janssen, L.P., Janssen Pharmaceutica N.V., and Ortho-McNeil Neurologics, Inc. (collectively, "Janssen"), by their attorneys, for their complaint against KV Pharmaceutical Company, allege as follows:

The Parties

1. Plaintiff Janssen, L.P., a wholly owned subsidiary of Johnson & Johnson, is a limited partnership organized and existing under the laws of the State of New Jersey and has its principal place of business at 1125 Trenton-Harbourton Road, Titusville, New Jersey 08560.

2. Plaintiff Janssen Pharmaceutica N.V., a wholly owned subsidiary of Johnson & Johnson, is a corporation organized and existing under the laws of Belgium and has its principal place of business at Turnhoutseweg 30, B-2340 Beerse, Belgium.

3. Plaintiff Ortho-McNeil Neurologics, Inc., a wholly owned subsidiary of Johnson & Johnson, is a corporation organized and existing under the laws of the State of New Jersey and has its principal place of business at 1125 Trenton-Harbourton Road, Titusville, New Jersey 08560.

4. Upon information and belief, Defendant KV Pharmaceutical Company (“KV Pharmaceutical”) is a corporation organized and existing under the laws of the State of Delaware and has a principal place of business at 2503 South Hanley Road, St. Louis, Missouri 63144. Upon information and belief, KV Pharmaceutical is registered to do business in New Jersey and does do business in New Jersey. KV Pharmaceutical also maintains a registered agent in New Jersey for the receipt of service of process at Corporation Trust Company, 820 Bear Tavern Road, West Trenton, NJ 08628.

5. Upon information and belief, KV Pharmaceutical is in the business of manufacturing, distributing, and selling generic pharmaceutical products, which are copies of products invented and developed by innovator pharmaceutical companies.

6. KV Pharmaceutical prepared and filed with the FDA, pursuant to 21 U.S.C. 355(j), ANDA No. 79-189 concerning galantamine hydrobromide extended-release capsules (two strengths: Eq. 8 mg base and 16 mg base) and seeks approval of that application from the Food and Drug Administration (“FDA”). KV Pharmaceutical also prepared and filed with the FDA an amendment to ANDA No. 79-189 concerning galantamine hydrobromide extended-release capsules (Eq. 24 mg base) and seeks approval of amended ANDA No. 79-189.

7. Upon information and belief, if amended ANDA No. 79-189 is approved, it is the intention of KV Pharmaceutical to commercially manufacture, use, and sell KV Pharmaceutical’s proposed galantamine hydrobromide extended-release 24 mg capsules in the United States. Upon information and belief, KV Pharmaceutical manufactures, markets, and sells many pharmaceutical products, including numerous generic prescription drug products manufactured and sold pursuant to an approved abbreviated new drug application, that are marketed and sold to customers in the State of New Jersey.

Jurisdiction and Venue

8. This is a civil action for patent infringement arising under the patent laws of the United States, Title 35 of the United States Code, for infringement of United States Patent No. 7,160,559 (“the ’559 patent”). This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338(a).

9. KV Pharmaceutical is subject to personal jurisdiction in this judicial district because it is currently registered in the State of New Jersey to do business and does business in the State of New Jersey and, on information and belief, maintains a

registered agent in New Jersey for the receipt of service of process at Corporation Trust Company, 820 Bear Tavern Road, West Trenton, NJ 08628, and by virtue of, *inter alia*, its having conducted business in the State of New Jersey, having availed itself of the rights and benefits of New Jersey law, and having engaged in substantial and continuing contacts with the State. In addition, upon information and belief, KV Pharmaceutical has availed itself of the benefits of this forum. For example, KV Pharmaceutical has previously submitted to the jurisdiction of this Court by filing suit and by asserting counterclaims in other civil actions initiated in this jurisdiction. Specifically, KV Pharmaceutical consented to jurisdiction and filed a counterclaim in *Warner Chilcott Laboratories Ireland, Ltd., et al. v. Ethex Corporation and KV Pharmaceutical Company*, 03-cv-841 (D.N.J.), *Celgene Corporation, et al. v. KV Pharmaceutical Company*, 07-cv-4819 (D.N.J.), Also in the related case of *Janssen, L.P., et al. v. KV Pharmaceutical Company*, 07-5982 (D.N.J.), KV Pharmaceuticals stated that it would not contest personal jurisdiction in the District of New Jersey for the purposes of that case and filed a counterclaim.

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

Regulatory Requirements for Approval of New and Generic Drugs

11. Any person wishing to market a pioneering drug – that is, a new drug that has not previously been approved by FDA – must first file a New Drug Application (“NDA”) with FDA demonstrating that the drug is safe and effective for its intended use. 21 U.S.C. § 355(b). To secure approval of a NDA, the NDA applicant

must, among other things, collect and submit to FDA extensive animal and human clinical trial data at a substantial cost of time and money.

12. A person wishing to market a generic copy of a pioneering drug that previously has been approved by FDA may follow a truncated approval process by filing an abbreviated new drug application for a generic version of the drug. In the ANDA, the applicant must demonstrate, among other things, bioequivalence of the generic copy of the pioneering drug. 21 U.S.C. § 355(j)(2)(A)(iv). To demonstrate bioequivalence, the ANDA applicant must show that the rate and extent of absorption of the therapeutic ingredient in the generic drug does not significantly differ from that in the pioneering drug, or, if the rate of absorption differs, that such difference is intentional, is reflected in the proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug. 21 U.S.C. § 355(j)(8)(B).

13. However, unlike an NDA applicant, an ANDA applicant is not required to include safety and effectiveness data. The ANDA applicant is not required, for example, to conduct well-controlled clinical trials concerning the safety and effectiveness of the proposed drug. Instead, the ANDA applicant is permitted to piggy-back on the safety and effectiveness data developed and submitted by the approved NDA holder. 21 U.S.C. § 355(j).

14. Nor does an ANDA applicant establish any new conditions of use for the proposed drug product. Instead, an ANDA applicant may seek approval only for conditions of use that previously have been approved in connection with an approved NDA. 21 U.S.C. § 355(j)(2)(A)(i).

15. No person may market in the United States a new drug without an approved NDA or a generic version of a drug without an approved ANDA. 21 U.S.C. § 355(a).

Plaintiffs' Approved Drug Product

16. Janssen is the holder of an approved new drug application, NDA No. 21-615, for galantamine hydrobromide extended release capsules. That NDA was approved by FDA on April 1, 2005 and covers three strengths of capsule – Eq. 8 mg base, 16 mg base, and 24 mg base. The sole indication or condition of use for which galantamine hydrobromide extended release capsules are approved in NDA No. 21-615 is the treatment of mild to moderate dementia of the Alzheimer's type.

17. Pursuant to FDA's approval, Janssen currently markets galantamine hydrobromide extended-release capsules for the treatment of mild to moderate dementia of the Alzheimer's type under the trademark RAZADYNE ER[®]. Until 2005, Janssen marketed its galantamine hydrobromide products under the trademark REMINYL[®].

18. FDA has listed the '559 patent in the Orange Book – formally known as Approved Drug Products With Therapeutic Equivalence Evaluations – in connection with NDA No. 21-615.

19. The '559 patent qualifies for listing in the Orange Book in connection with NDA No. 21-615 because it claims an approved use of the drug product that is the subject of that NDA. KV Pharmaceutical has never challenged the listing of the '559 patent in the Orange Book.

KV Pharmaceutical's ANDA

20. KV Pharmaceutical has represented that on or before May 13, 2008, it submitted to FDA an amendment to ANDA (ANDA No. 79-189) and paragraph IV certifications under section 505(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. § 355(j)(2)(A)(vii)(IV), for galantamine hydrobromide extended-release 24 mg capsules purportedly bioequivalent to Janssen's RAZADYNE ER[®] 24 mg product. The purpose of KV Pharmaceutical's amendment to ANDA No. 79-189 and paragraph IV certifications, is to obtain approval under section 505(j) of the FDCA to engage in the commercial manufacture and sale of its proposed galantamine hydrobromide extended-release 24 mg capsules before the expiration of the patents listed in the Orange Book for Janssen's NDA No. 21-615. Hence, KV Pharmaceutical's purpose in submitting the amendment to ANDA No. 79-189 is to market in the United States the galantamine hydrobromide 24 mg capsules described therein before expiration of the '559 patent.

21. On or about May 13, 2008, KV Pharmaceutical sent a letter advising Janssen of KV Pharmaceutical's paragraph IV certification relating to the '559 patent ("KV Pharmaceutical's Notice Letter"). KV Pharmaceutical's Notice Letter reported that KV Pharmaceutical had submitted an amendment to ANDA 79-189 to obtain approval to engage in the commercial manufacture, use, or sale of KV's Galantamine Hydrobromide Extended-release Capsules, 24 mg, before the expiration of the '559 patent. KV Pharmaceutical's Notice Letter included an offer of confidential access that would permit Janssen's outside counsel to review KV Pharmaceutical's amended ANDA.

22. Upon information and belief, the sole condition of use for which KV Pharmaceutical seeks approval in its amended ANDA No. 79-189 for its proposed galantamine hydrobromide extended-release 24 mg capsules is the treatment of mild to moderate dementia of the Alzheimer's type, the same condition of use as that approved in Janssen's NDA No. 21-615.

23. Upon information and belief, the sole indication set forth in the proposed labeling submitted by KV Pharmaceutical in its amended ANDA No. 79-189 for its proposed galantamine hydrobromide extended-release 24 mg capsules is the treatment of mild to moderate dementia of the Alzheimer's type, the same indication as that set forth in the approved labeling for Janssen's RAZADYNE ER[®] capsules.

Count 1: Patent Infringement

24. Janssen realleges paragraphs 1 through 23 above as if fully set forth herein.

25. On January 9, 2007, the United States Patent and Trademark Office duly and legally issued the '559 patent, entitled "Controlled Release Galantamine Formulation." The term of the '559 patent runs through December 20, 2019. A true and correct copy of the '559 patent is attached hereto as Exhibit A.

26. Janssen is the owner of the '559 patent.

27. Janssen currently markets galantamine hydrobromide extended-release capsules in the United States under the trademark RAZADYNE ER[®] and previously marketed its galantamine hydrobromide products in the United States under the trademark REMINYL[®]. The product RAZADYNE ER[®] and the conditions of use for

which RAZADYNE ER[®] is approved fall within one or more of the claims of the '559 patent.

28. KV Pharmaceutical is liable for infringement of the '559 patent under 35 U.S.C. § 271(e)(2)(A) by virtue of its filing an amendment to ANDA No. 79-189 with a paragraph IV certification seeking FDA approval of amended ANDA No. 79-189 prior to expiration of the '559 patent.

29. The 24 mg product for which KV Pharmaceutical seeks approval in its amendment to ANDA No. 79-189 falls within one or more of the claims of the '559 patent. If approved, the manufacture, use, offer for sale, and sale in the United States, and importation into the United States of KV Pharmaceutical's proposed galantamine hydrobromide extended-release 24 mg capsule product would infringe one or more of the claims of the '559 patent.

30. Upon information and belief, if amended ANDA No. 79-189 is approved, KV Pharmaceutical intends to manufacture, use, offer for sale, and sell in the United States, and import into the United States, the galantamine hydrobromide extended-release 24 mg capsule product for which approval is sought in KV Pharmaceutical's amended ANDA No. 79-189.

31. The manufacture, use, offer for sale and sale in the United States, and importation into the United States of KV Pharmaceutical's proposed galantamine hydrobromide extended-release 24 mg capsule product would infringe one or more claims of the '559 patent, and KV Pharmaceutical would be liable for direct infringement under 35 U.S.C. § 271(a).

32. Upon information and belief, the conditions of use for which KV Pharmaceutical seeks approval in its amended ANDA No. 79-189 fall within one or more of the claims of the '559 patent. Upon information and belief, if approved, use of KV Pharmaceutical's proposed galantamine hydrobromide extended-release 24 mg capsule product in accordance with the proposed labeling submitted in amended ANDA No. 79-189 would infringe one or more of the claims of the '559 patent.

33. Upon information and belief, if approved, KV Pharmaceutical's galantamine hydrobromide extended-release 24 mg capsule product for which approval is sought in the amended KV Pharmaceutical ANDA No. 79-189 will be administered to human patients in a therapeutically effective amount for treatment of dementia of the Alzheimer's type, which administration would constitute direct infringement of one or more claims of the '559 patent. Upon information and belief, this infringement will occur at KV Pharmaceutical's behest, with its intent, knowledge, and encouragement, and KV Pharmaceutical will actively induce, encourage, aid, and abet this administration with knowledge that it is in contravention of Janssen's rights under the '559 patent.

34. KV Pharmaceutical's manufacture, use, offer for sale or sale in the United States, or importation into the United States, prior to expiration of the '559 patent, of the galantamine hydrobromide extended-release 24 mg capsule product for which approval is sought in amended ANDA No. 79-189, would actively induce and contribute to infringement of the '559 patent, and KV Pharmaceutical would be liable as an infringer under 35 U.S.C. §§ 271(b) and/or (c).

35. KV Pharmaceutical's infringement of the '559 patent has been, and continues to be, willful.

36. Janssen will be irreparably harmed if KV Pharmaceutical is not enjoined from infringing or actively inducing or contributing to infringement of the '559 patent. Janssen does not have an adequate remedy at law.

Prayer For Relief

WHEREFORE, Plaintiffs seek the following relief:

- A. A judgment that KV Pharmaceutical has infringed the '559 patent under 35 U.S.C. § 271(e)(2)(A), and that such infringement is willful.
- B. A judgment and order pursuant to 35 U.S.C. § 271(e)(4) providing that the effective date of any FDA approval of the amended KV Pharmaceutical ANDA No. 79-189 for galantamine hydrobromide extended-release 24 mg capsules be not earlier than the expiration date of the '559 patent;
- C. A judgment declaring that KV Pharmaceutical's manufacture, use, offer for sale, or sale in the United States, or importation into the United States, of the galantamine hydrobromide extended-release 24 mg capsules for which approval is sought in amended ANDA No. 79-189 would constitute infringement of the '559 patent, or would induce or contribute to such infringement, pursuant to 35 U.S.C. § 271 (a), (b), and/or (c);
- D. A permanent injunction enjoining KV Pharmaceutical and its officers, agents, servants, and employees, and those persons in active concert or participation with any of them, from making, using, selling, or offering to sell in the United States, or importing into the United States, the galantamine hydrobromide extended-release 24 mg capsules for which approval is sought in amended ANDA No. 79-189, or any galantamine

hydrobromide product that infringes or induces or contributes to the infringement of the '559 patent, until expiration of that patent;

- E. A finding that this is an exceptional case, and an award of attorneys' fees in this action pursuant to 35 U.S.C. § 285;
- F. An award of costs and expenses in this action; and
- G. Such further and other relief as this Court determines to be just and proper.

s/Thomas E. Hastings

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DATED: June 17, 2008

CERTIFICATION PURSUANT TO L.CIV.R. 11.2

I hereby certify that to my knowledge the matter in controversy is not the subject of any other action pending in any court, or of any pending arbitration or administrative proceeding, but that in *Janssen, L.P., et al. v. KV Pharmaceutical Company*, Civil Action No. 07-5982 (JAP)(TJB), presently pending in the United States District Court for the District of New Jersey, Janssen has alleged that KV Pharmaceutical Company, by filing its ANDA No. 79-189 (the unamended ANDA at issue here directed to 8 mg and 16 mg capsules), has infringed United States Patent No. 7,160,559 (the same patent at issue here).

This case is also related to two other cases presently pending in this forum. One of these cases is *Janssen, L.P., et al. v. Barr Laboratories, Inc., et al.*, Civil Action No. 07-1515 (JAP)(TJB), presently pending in the United States District Court for the District of New Jersey. In Civil Action No. 07-1515, Janssen has alleged that Barr Laboratories, by filing its ANDA No. 78-189, has infringed United States Patent No. 7,160,559 (the same patent at issue here). The other case is *Janssen, L.P., et al. v. Sandoz Inc.*, Civil Action No. 08-2892 (JAP)(JJH), presently pending in the United States District Court for the District of New Jersey. In Civil Action No. 08-2892, Janssen has alleged that Sandoz, Inc., by filing its ANDA No. 78-685, has infringed United States Patent No. 7,160,559 (the same patent at issue here).

s/Thomas E. Hastings
Thomas E. Hastings

Dated: June 17, 2008

EXHIBIT A



US007160559B1

(12) **United States Patent**
McGee et al.

(10) **Patent No.:** **US 7,160,559 B1**
(45) **Date of Patent:** **Jan. 9, 2007**

(54) **CONTROLLED RELEASE GALANTAMINE COMPOSITION**

(75) Inventors: **John Paul McGee**, Antwerp (BE); **Paul Marie Victor Gillis**, Beerse (BE); **Marc Maurice Germain De Weer**, Vosselaar (BE); **Valentin Florent Victor de Condé**, Lommel (BE); **Herman Johannes Catherina de Bruijn**, Meer (BE); **Frederic Anne Rodolf Van Dycke**, Antwerp (BE)

(73) Assignee: **Janssen Pharmaceutica N.V.**, Beerse (BE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/868,991**

(22) PCT Filed: **Dec. 20, 1999**

(86) PCT No.: **PCT/EP99/10257**

§ 371 (c)(1),
(2), (4) Date: **Jul. 26, 2001**

(87) PCT Pub. No.: **WO00/38686**

PCT Pub. Date: **Jul. 6, 2000**

(30) **Foreign Application Priority Data**

Dec. 24, 1998 (EP) 98204447

(51) **Int. Cl.**

A61K 9/50 (2006.01)
A61K 9/24 (2006.01)
A61K 9/56 (2006.01)
A61K 9/58 (2006.01)
A61K 9/26 (2006.01)

(52) U.S. Cl. **424/501**; 424/472; 424/459;
424/462; 424/469; 424/471

(58) **Field of Classification Search** 514/215;
424/489, 490, 464, 465, 474, 468, 457, 472,
424/458, 459, 462, 469, 471, 501; 206/528,
206/532, 534, 539

See application file for complete search history.

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Primary Examiner—Michael Hartley

Assistant Examiner—Blessing Fubara

(74) *Attorney, Agent, or Firm*—Mary A. Appollina

(57) **ABSTRACT**

The present invention is concerned with controlled release compositions for oral administration comprising galantamine; and with processes of preparing such controlled release compositions.

15 Claims, No Drawings

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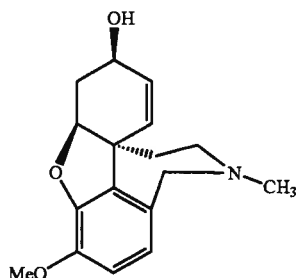
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CONTROLLED RELEASE GALANTAMINE COMPOSITION

This application is a National Stage application under 35 U.S.C. 371 of Application No. PCT/EP99/10257 filed Dec. 20, 1999, which claims priority from EP 98204447.1, filed Dec. 24, 1998, the contents of all of which are hereby incorporated by reference.

The present invention is concerned with controlled release compositions for oral administration comprising galantamine; and with processes of preparing such controlled release compositions.

Galantamine (I), a tertiary alkaloid, has been isolated from the bulbs of the Caucasian snowdrops *Galanthus woronowi* (Proskumina, N. F. and Yakoleva, A. P. 1952, *Alkaloids of Galanthus woronowi*. II. Isolation of a new alkaloid. (In Russian.) *Zh. Obschchei Khim.* (J. Gen. Chem.) 22, 1899–1902). It has also been isolated from the common snowdrop *Galanthus nivalis* (Boit, 1954).



The chemical name of galantamine is [4aS-(4 α , 6 β , 8aR*)]-4a, 5, 9, 10, 11, 12-hexahydro-3-methoxy-11-methyl-6H-benzofuro[3a, 3, 2-ef][2]benzazepin-6-ol; both the base compound and its hydrobromide are laevorotatory. Galantamine is a well-known acetylcholinesterase inhibitor which is active at nicotinic receptor sites but not on muscarinic receptor sites. It is capable of passing the blood-brain barrier in humans, and presents no severe side effects in therapeutically effective dosages.

Galantamine has been used extensively as a curare reversal agent in anaesthetic practice in Eastern bloc countries (cf. review by Paskow, 1986) and also experimentally in the West (cf. Bretagne and Valetta, 1965; Wislicki, 1967; Consanitis, 1971).

Galantamine has been marketed by Waldheim (Sanochemia Gruppe) as Nivalin™ in Germany and Austria since the 1970s for indications such as facial neuralgia.

The use of galantamine or an analogue or a pharmaceutically acceptable acid addition salt thereof for the preparation of a medicament for treating Alzheimer's Dementia (AD) and related dementias has been described in EP-0,236,684 (U.S. Pat. No. 4,663,318). This patent only has a generic disclosure of possible dosage forms of galantamine. CA-1, 326,632 generically discloses slow release formulations of galantamine.

The use of galantamine for treating alcoholism and the administration via a transdermal therapeutic system (TTS) or patch is disclosed in EP-0,449,247 and WO-94/16707. Similarly, the use of galantamine in the treatment of nicotine dependence using administration via a transdermal therapeutic system (TTS) or patch is disclosed in WO-94/16708. Treatment of nerve gas poisoning is disclosed in DE-4,342,174.

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A number of applications by E. Snorrason disclose the use of galantamine, analogues thereof and pharmaceutically acceptable salts thereof for the preparation of medicaments for treating mania (U.S. Pat. No. 5,336,675), chronic fatigue syndrome (CFS) (EP-0,515,302; U.S. Pat. No. 5,312,817), the negative effects of benzodiazepine treatment (EP-0,515,301) and the treatment of schizophrenia (U.S. Pat. No. 5,633,238). In these applications and patents, e.g. in U.S. Pat. No. 5,312,817, a number of immediate release tablet formulations of galantamine hydrobromide are given.

WO-97/47304 discloses fast-dissolving or immediate release tablets of galantamine prepared by direct compression. These and other art-known immediate release tablets are administered twice (b.i.d.) or thrice (t.i.d.) daily with an interval of 8 hours. The plasma levels of the active ingredient typically raise sharply (early T_{max} and relatively high C_{max}) and decline rapidly (deep trough after about 6 to 8 hours).

Therapy with galantamine can be considered optimal when effective plasma levels are reached when required. In addition, peak values (C_{max}) should be as low and level as possible so as to reduce the incidence and severity of possible side effects. The foregoing requirements not only apply upon single dose administration, but also upon repeated dose administration (until a steady-state condition is reached). In particular, when treating a patient suffering from Alzheimer's Disease, optimum efficacy is expected when effective plasma levels are maintained during daytime; during nighttime galantamine plasma levels probably may be lower. For the treatment of other conditions, for example for treating sleep disordered breathing such as snoring and apnoea (WO-97/22339), one may wish to attain the reverse situation, namely to have effective plasma levels during the night, and lower levels during daytime. For the benefit of the patient and the caretakers, a pharmaceutical dosage form that has to be administered once daily only and yields effective plasma levels for eight hours (nighttime) to 16 hours (daytime) would be highly desirable.

The present invention relates to a controlled release formulation containing galantamine as the active ingredient, characterized in that it comprises particles comprising galantamine or a pharmaceutically acceptable acid addition salt thereof, a water soluble pharmaceutically acceptable excipient and optionally other pharmaceutically acceptable excipients, said particles being coated by a release rate controlling membrane coating. Dosage forms comprising a therapeutically effective amount of said controlled release formulations can be administered orally to a patient once daily. In preferred dosage forms, part of the galantamine is present in an immediate release form, for example, as particles lacking a release rate controlling membrane coating, or as immediate release minitables, or as a topcoat on the controlled release formulation.

Preferably, the formulations according to the present invention comprise galantamine in the form of galantamine hydrobromide (1:1).

The water soluble excipient can conveniently be a film forming polymer. Useful water soluble film forming polymers are polymers that have an apparent viscosity of 1 to 100 mPa.s when dissolved in a 2% aqueous solution at 20° C. solution. For example, the water soluble polymer can be selected from the group comprising

- alkylcelluloses such as methylcellulose,
- hydroxyalkylcelluloses such as hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and hydroxybutylcellulose,

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hydroxyalkyl alkylcelluloses such as hydroxyethyl methylcellulose and hydroxypropyl methylcellulose, carboxyalkylcelluloses such as carboxymethylcellulose, alkali metal salts of carboxyalkylcelluloses such as sodium carboxymethyl-cellulose, carboxyalkyl alkylcelluloses such as carboxymethyl ethylcellulose, carboxyalkylcellulose esters, starches, pectines such as sodium carboxymethylamylopectine, chitine derivates such as chitosan, polysaccharides such as alginic acid, alkali metal and ammonium salts thereof, carrageenans, galactomannans, traganth, agar-agar, gummi arabicum, guar gummi and xanthan gummi, polyarctic acids and the salts thereof, polymethacrylic acids and the salts thereof, methacrylate copolymers, polyvinylalcohol, polyvinylpyrrolidone, copolymers of polyvinylpyrrolidone with vinyl acetate polyalkylene oxides such as polyethylene oxide and polypropylene oxide and copolymers of ethylene oxide and propylene oxide.

Non-enumerated polymers which are pharmaceutically acceptable and have appropriate physico-chemical properties as defined hereinbefore are equally suited for preparing particles according to the present invention.

Preferred water-soluble polymers are for example hydroxypropyl methylcellulose (Methocel®), Pharmacoat®, polymethacrylate (Eudragit E®), hydroxypropylcellulose (Klucel®, or a polyvidone. Especially preferred water-soluble polymers are hydroxypropyl methylcelluloses or HPMC. Said HPMC contains sufficient hydroxypropyl and methoxy groups to render it water-soluble. HPMC having a methoxy degree of substitution from about 0.8 to about 2.5 and a hydroxypropyl molar substitution from about 0.05 to about 3.0 are generally water-soluble. Methoxy degree of substitution refers to the average number of methyl ether groups present per anhydroglucose unit of the cellulose molecule. Hydroxypropyl molar substitution refers to the average number of moles of propylene oxide which have reacted with each anhydroglucose unit of the cellulose molecule. Hydroxypropyl methylcellulose is the United States Adopted Name for hypromellose (see Martindale, The Extra Pharmacopoeia, 29th edition, page 1435). Preferably hydroxypropyl methylcellulose with low viscosity, i.e. about 5 mPa.s, is used, e.g. hydroxypropyl methylcellulose 2910 5 mPa.s. In the four digit number "2910", the first two digits represent the approximate percentage of methoxyl groups and the third and fourth digits the approximate percentage composition of hydroxypropoxyl groups. 5 mPa.s is a value indicative of the apparent viscosity of a 2% aqueous solution at 20° C.

Suitable HPMC include those having a viscosity from about 1 to about 100 mPa.s, in particular from about 3 to about 15 mPa.s, preferably about 5 mPa.s. The most preferred type of HPMC having a viscosity of 5 mPa.s., is the commercially available HPMC 2910 5 mPa.s. An equally preferred type of HPMC is admixed with polyethylene glycol 400, commercially available from Colorcon (UK) as Opadry™ OY-7240 clear.

The weight-by-weight ratio of drug:polymer is in the range of 17:1 to 1:5, preferably 10:1 to 1:3. In the case of (galantamine.HBr):(HPMC 2910 5 mPa.s), said ratio may range from about 10:1 to about 1:3, and optimally is from

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7:1 to 1:2. The weight-by-weight ratio of galantamine.HBr to other water-soluble polymers may be determined by a person skilled in the art by straightforward experimentation. The lower limit is determined by practical considerations.

In particular the present invention is concerned with particles which comprise (a) a central, rounded or spherical core, (b) a layer or a coating film of a water-soluble polymer and galantamine hydrobromide (1:1), (c) optionally a seal-coating polymer layer and (d) a release rate controlling membrane coating. The core has a diameter of about 250 to about 1,180 μm (16–60 mesh), preferably of about 600 to about 1,180 μm (16–30 mesh).

Pellets, beads or cores of the dimensions mentioned herein can be obtained by sieving through nominal standard test sieves as described in the CRC Handbook, 64th ed., page F-114. Nominal standard sieves are characterized by the mesh/hole width (μm), DIN 4188 (mm), ASTM E 11-70 (No), Tyler® (mesh) or BS 410 (mesh) standard values. Throughout this description and the claims, particle sizes are designated by reference to the mesh/hole width in μm and to the corresponding Sieve No in the ASTM E11-70 standard.

Materials suitable for use as cores in the particles according to the present invention are manifold, provided that said materials are pharmaceutically acceptable and have appropriate dimensions (about 16–60 mesh) and firmness. Examples of such materials are polymers e.g. plastic resins; inorganic substances, e.g. silica, glass, hydroxyapatite, salts (sodium or potassium chloride, calcium or magnesium carbonate) and the like; organic substances, e.g. activated carbon, acids (citric, fumaric, tartaric, ascorbic and the like acids), and saccharides and derivatives thereof. Particularly suitable materials are saccharides such as sugars, oligosaccharides, polysaccharides and their derivatives, for example, glucose, rhamnose, galactose, lactose, sucrose, mannitol, sorbitol, dextrin, maltodextrin, cellulose, microcrystalline cellulose, sodium carboxymethyl cellulose, starches (maize, rice, potato, wheat, tapioca) and the like saccharides.

A particularly preferred material suitable for use as cores in the particles according to the present invention is represented by 16–60 mesh sugar spheres (USP 22/NF X VII, p. 1989) which consist of 62.5%–91.5% (w/w) sucrose, the remainder being starch and possibly also dextrines, and which are pharmaceutically inert or neutral. Consequently, these cores are also known in the art as neutral pellets.

Depending on the weight-by-weight ratio of drug:polymer, the water-soluble polymer and galantamine are herein said to form either a layer (ratio >10:1) or a coat or coating film (ratio <10:1).

As an alternative to the drug layered or drug coated inert pellets described thus far, suitable particles comprising galantamine may also be formed by granules or by spheroids (spherical granules) prepared according to art-known methods of granulation and spheronization.

The release rate controlling membrane coating comprises a water insoluble polymer and optionally a plasticizer. Said polymer is ethylcellulose and the plasticizer is selected from the group comprising dibutyl sebacate, diethyl phthalate and triethyl citrate. It is useful to modify the properties of the water-insoluble polymer by the addition of particular amounts of a water-soluble polymer as described hereinbefore, preferably HPMC. The addition of the water-soluble polymer is especially useful to increase the onset of action. For the particles according to the present invention, the ratio ethylcellulose:HPMC can vary from 100:0 to about 70:30, in particular from about 80:20 to about 72.5:27.5, more in particular from about 75:25 to about 72.5:27.5. The release rate controlling membrane coating may be applied to the

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drug coated cores in an aqueous dispersion (Aquacoat™, Surelease™), or as a solution in an organic solvent system. A useful organic system comprises an alcohol, e.g. methanol or ethanol, and optionally a chlorinated hydrocarbon such as for example dichloromethane.

The weight of the release rate controlling membrane coating ranges from 3% to 15% of the uncoated particle, in particular from about 4% to about 12%. The rate of release of the active ingredient from the particles is approximately inversely proportional with the thickness of the release rate controlling membrane coating.

A seal coat lies optionally between the drug core and the release rate controlling membrane coating. The seal coating polymer layer is applied to the drug coated cores to prevent sticking of the particles during the process and to prevent migration of the drug into the the release rate controlling membrane. Preferably, a thin layer of HPMC 2910 5 mPa.s and polyethylene glycol (PEG), in particular polyethylene glycol 400 is used as a seal coating polymer layer.

In addition, the particles according to the present invention may further contain various additives such as thickening agents, lubricants, surfactants, preservatives, complexing and chelating agents, electrolytes or other active ingredients.

The particles can be filled in hard-gelatin capsules such that a therapeutically effective amount of, for example, 8 to 32 mg of the active ingredient is available per dosage form. An advantageous pharmacokinetic profile profile (fast onset, level peak and trough values) is obtained when from 70 to 80% of the galantamine is comprised within the controlled release particles and the remaining 20 to 30% of the galantamine is comprised in an immediate release form, preferably the controlled releases particle amount to 75% of the galantamine and the immediate release form to 25%.

In order to achieve the desired pharmacokinetic, the dosage forms may be filled with particles that release the active ingredient at different rates, at least one kind that releases the active ingredient slowly, and at least one kind that releases the active ingredient more rapidly, in particular one kind that releases the active ingredient immediately, e.g. particles as described that lack the release rate controlling membrane. The different particles may be filled consecutively in the capsules, or they may be premixed and the thus obtained premix may be filled into the capsules (taking into account possible segregation).

Alternatively, the controlled release particles of the present invention may further comprise a top-coat of a water-soluble polymer as described hereinbefore and galantamine which is released practically immediately upon ingestion and thus ensures a rapid onset of action.

Another alternative solution for providing a dosage form with a pharmacokinetic profile as outlined, namely with a fast onset, level peak and trough values, comprises filling a capsule with controlled release particles as described hereinbefore (70 to 80%, preferably 75% of the galantamine dose) together with one or more minitabets which comprise the remaining 20 to 30%, preferably 25% of galantamine. Suitable immediate release tablet formulations of galantamine have been described previously in WO-97/47304.

The present invention also relates to processes of preparing formulations as described hereinbefore comprising admixing galantamine or a pharmaceutically acceptable salt form thereof with a water soluble excipient to form a drug core, optionally applying a seal coat to the drug core, and thereafter applying the release rate controlling membrane coating.

The particles according to the present invention are conveniently prepared in the following manner. A drug coating

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solution is prepared by dissolving into a suitable solvent system appropriate amounts of galantamine.HBr and a water-soluble polymer. A suitable solvent system comprises purified water or an alcohol, preferably ethanol which may be denatured, for example, with butanone. The amounts of solids, i.e. galantamine.HBr and water-soluble polymer, in the drug coating solution may range from 10 to 30% (w/w) and preferably is about 25%. The solution is preferably stirred during the coating process.

The drug coating process (on an industrial scale) is conveniently conducted in a fluidized bed granulator (e.g. Glatt type WSG-30 or GPCG-30) equipped with a Wurster bottom spray insert (e.g. an 18 inch Wurster insert). Laboratory scale process development can be performed on a Glatt type WSG-1 with a 6 inch Wurster bottom insert. Obviously the process parameters depend on the equipment used.

The spraying rate should be regulated carefully. Too low a spraying rate can cause some spray drying of the drug coating solution and result in a loss of product. Too high a spraying rate will cause overwetting with subsequent agglomeration. Agglomeration being the most serious problem, lower spraying rates may be used initially, to be increased as the coating process proceeds and the particles grow larger.

The atomizing air pressure with which the drug coating solution is applied also influences the coating performance. Low atomizing air pressure results in the formation of larger droplets and an increased tendency toward agglomeration. High atomizing air pressure could conceivably carry the risk of spray drying the drug solution, but this was found not to be a problem. Consequently, atomizing air pressure may be set at nearly maximum levels.

Fluidizing air volume can be monitored by operating the exhaust air-valve of the apparatus and should be set in such a manner that optimum pellet circulation is obtained. Too low an air volume will cause insufficient fluidization of the pellets; too high an air volume will interfere with the pellet circulation due to countercurrent air streams developing in the apparatus. In the present process optimum conditions were obtained by opening the exhaust air valve to about 50% of its maximum and gradually increasing the opening thereof to about 60% of the maximum as the coating process proceeded.

The coating process is advantageously conducted by employing an inlet-air temperature ranging from about 50° C. to about 55° C. Higher temperatures may speed up the process but have the disadvantage that solvent evaporation is so rapid that the coating liquid is not spread uniformly on the surface of the pellets resulting in the formation of a drug coating layer with high porosity. As the bulk volume of the coated pellets increases, drug dissolution may decrease significantly to unacceptable levels. Obviously, the optimum process temperature will further depend on the equipment used, the nature of the core, the batch volume, the solvent and the spraying rate.

Parameter settings for optimum coating results are described in more detail in the example hereinafter. Running the coating process under those conditions was found to yield very reproducible results.

In order to decrease residual solvent levels in the pellets following application of the rate controlling membrane from an organic solution, the pellets can conveniently be dried in any suitable drying apparatus. Good results may be obtained using a vacuum tumbler-drier operated at a temperature from about 60° C. to about 90° C., preferably about 80° C., a reduced pressure ranging from about 150-400 mbar

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(15–40 kPa), preferably 200–300 mbar (20–30 kPa), for at least 24 hours, preferably about 36 hours. The vacuum tumbler-drier is conveniently rotated at its minimum speed, e.g. 2 to 3 rpm. After drying, the drug coated cores may be sieved.

The seal coat layer is applied to the drug coated cores in the fluidized bed granulator with Wurster bottom spray insert or in a powder coater. The seal coating solution can be prepared by dissolving an appropriate amount of a seal coating polymer into a suitable solvent system. Such a system, is, e.g. purified water or an alcohol, preferably ethanol which may be denatured with, for example, butanone. The amount of seal coating polymer in the seal coating spraying solution may range from 5 to 10% (w/w) and preferably is about 6.6%. The seal coating spraying solution is advantageously stirred during the seal coating process. Appropriate conditions are described in more detail in the example hereinafter.

A further drying step may be required after applying the seal coating polymer layer. Excess solvents could easily be removed while operating the apparatus at the parameter settings used for about 5 to 15 minutes after the spraying had been completed.

The release rate controlling membrane coating polymer layer is applied to the drug (or seal) coated cores in a fluidized bed granulator with Wurster bottom spray insert. The release rate controlling membrane coating suspension or solution can be prepared by suspending or dissolving an appropriate amount of a release rate controlling membrane coating polymer into a suitable solvent system. Such a system, is, e.g. purified water or an alcohol, preferably ethanol which may be denatured with, for example, butanone, dichloromethane which may be admixed with an alcohol, preferably methanol or ethanol. The amount of release rate controlling membrane coating polymer in the spraying suspension or solution may range from 5 to 40% (w/w) and preferably is about 30%. The release rate controlling membrane coating spraying suspension or solution is advantageously stirred during the spraying process. The parameter setting for conducting this last step is essentially similar to that used in the previous coating processes. Appropriate conditions are described in more detail in the example hereinafter.

All coating processes are preferably conducted under an inert atmosphere of e.g. nitrogen. The coating equipment should preferably be grounded and provided with an appropriate solvent recovery system containing an efficient condensing system.

The particles may be filled in hard-gelatin capsules using standard automatic capsule filling machines. Suitable earthing and de-ionisation equipment can advantageously prevent development of electrostatic charges.

Capsule filling speed may influence weight distribution and should be monitored. Good results are obtained when operating the equipment at about 75% to 85% of the maximum speed and in many cases when operating at full speed.

Dosage forms according to the present invention having an advantageous pharmacokinetic profile as outlined, namely a fast onset and level peak and trough values, are capable of releasing in 500 ml USP buffer (pH 6.8) at 37° C. in an Apparatus 2 (USP 23, <711> Dissolution, pp 1791–1793, paddle, 50 rpm) from 20 to 40% of the total amount of galantamine.HBr in 1 hour, and more than 80% of the total amount of galantamine.HBr in 10 hours. Said dosage forms provide a mean maximum plasma concentration of galantamine from 10 to 60 ng/ml and a mean

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minimum plasma concentration from 3 to 15 ng/ml after repeated administration every day through steady-state conditions.

The formulation according to the present invention deliver a therapeutically effective amount of galantamine to a patient during the 24 hours following a single once daily administration.

The present invention also concerns pharmaceutical packages suitable for commercial sale comprising a container, a formulation of galantamine as claimed in claim 1, and associated with said package written matter specifying how said formulation should be administered.

Said pharmaceutical packages may be adapted for titrating a patient who is ‘acetylcholine esterase inhibitor’-naïve, i.e. a patient who has not been exposed to an acetylcholine esterase inhibitor before and who should start with small, well-tolerated doses before being exposed to ever higher doses until the optimal dose is reached. Said packages typically comprises 21–35 daily sequential dosage units of (a) a first group of 7 to 14 dosage units comprising from 5 to 10 mg galantamine, (b) a second group of 7 to 14 dosage units comprising from 10 to 20 mg galantamine, (c) a third group of 7 to 14 dosage units comprising from 15 to 30 mg galantamine, and (d) optionally a fourth group of 7 dosage units comprising from 20 to 40 mg galantamine.

Alternatively, the pharmaceutical packages may be adapted for treating a patient who is ‘acetylcholine esterase inhibitor’-tolerant, i.e. a patient who has been exposed to an acetylcholine esterase inhibitor before and who tolerate an optimal dose. Said packages typically comprises daily dosage units comprising from 15 to 30 mg galantamine.

A method of treating Alzheimer’s dementia and related dementias in a human while substantially reducing (avoiding) the concomitant liability of adverse effects associated with acetyl cholinesterase inhibitors, comprising administering to a human in need of such treatment, a therapeutically effective amount of galantamine in a controlled release formulation as claimed in claim 1, said amount being sufficient to alleviate said Alzheimer’s dementia and related dementias, but insufficient to cause said adverse effects.

The related dementia belongs to the group consisting of vascular dementia, Lewy body disease, autism, mental retardation, bipolar disorder psychiatric conditions, disruptive behaviour, attention deficit hyperactivity disorder, substance abuse, extreme aggression, especially conduct disorder, nicotine cessation and withdrawal.

The adverse effects belong to the group comprising nausea, vomiting, sweating, restlessness, and insomnia.

Experimental part
Example 1: 8 mg galantamine CR oral capsule (F1)

Ingredients:

galantamine hydrobromide	10.253 mg (8 mg galantamine base)
sugar spheres (18–20 mesh)	63.283 mg
HPMC 2910 5 mPa · s	1.465 mg
purified water	37.105 µl *
HPMC 2910 5 mPa · s	1.500 mg
polyethylene glycol 400	0.150 mg
purified water	23.350 µl *
ethylcellulose aqueous dispersion	10.220 mg (30%)

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-continued

Experimental part	
Example 1: 8 mg galantamine CR oral capsule (F1)	
Ingredients:	
dibutyl sebacate	0.736 mg
purified water	10.220 µl *
capsule nr. 4	

*: these ingredients do not occur in the end product

Preparation:

a) Drug coat suspension

Galantamine hydrobromide (123 g) was suspended in 297 ml purified water and heated to 70–80° C. HPMC 2910 5 mPa.s (17.58 g) was dissolved in the heated suspension whilst stirring.

b) Seal coat solution

Purified water (93.4 g) was heated to 70–80° C. and HPMC 2910 4 mPa.s (18 g) and polyethylene glycol 400 (1.8 g) were dissolved therein. The solution was then further diluted with purified water (186.8 g).

c) Release rate controlling membrane coat dispersion

To a gently stirred aqueous dispersion of ethylcellulose (122.6 g; 30%) was added dibutyl sebacate (8.832 g). The dispersion was diluted with purified water (122.6 g).

d) Coating process

A fluidized-bed granulator (Glatt, type WSG 1) equipped with a 6 inch Wurster (bottom spray) insert was loaded with 18–20 mesh sugar spheres (759.4 g). The spheres were warmed with dry air of about 50° C. The fluidizing air volume was controlled by opening the exhaust air valve to approximately 45% of its maximum. The drug coat suspension was sprayed on the spheres moving in the apparatus. The suspension was sprayed at a delivery rate of about 5 to 30 g.min⁻¹ at an atomizing air pressure of about 1.6 to 4.0 bar (0.16–0.4 MPa). When the spraying process was completed, the coated spheres were dried by further supplying dry air of 60° C. for about 2 minutes. The coated spheres were then seal coated with the sealcoat solution using the same parameters as used in the drug coating process. After drying for about 2 minutes, the seal coated spheres were allowed to cool to room temperature and filled into a stainless steel drum.

The fluidized-bed granulator (Glatt, type WSG 1) equipped with a 6 inch Wurster (bottom spray) insert was reloaded with the seal coated spheres. The spheres were warmed with dry air of about 50° C. The fluidizing air volume was controlled by opening the exhaust air valve to approximately 45% of its maximum. The release rate controlling membrane coat suspension was sprayed on the spheres moving in the apparatus. The suspension was sprayed at a delivery rate of about 5 to 30 g.min⁻¹ at an atomizing air pressure of about 1.6 to 4.0 bar (0.16–0.4 MPa). After drying for about 2 minutes, the controlled release membrane coated spheres were allowed to cool to room temperature and filled into a stainless steel drum.

e) Drying and curing process

In order to remove agglomerates, the coated spheres were sieved using a sieve having a mesh width of 1.2 mm. The particles were placed in a drying oven at 60° C. during 2 hours so as to cure the release rate controlling membrane.

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f) Capsule filling

The particles were filled into hard-gelatin capsules (size 4) using standard automatic capsule filling machines (e.g. Model GFK-1500, Höfflinger and Karg, Germany). In order to obtain capsules with good weight distribution, capsule filling speed was reduced to about 75–85% of the maximum speed. Each capsule received approximately 87.6 mg particles, equivalent to about 8 mg galantamine.

Example 2: 8 mg galantamine CR oral capsule (F2)

Ingredients:	
galantamine hydrobromide	10.253 mg (8 mg galantamine base)
sugar spheres (18–20 mesh)	63.283 mg
HPMC 2910 5 mPa · s	1.465 mg
purified water	37.105 µl *
HPMC 2910 5 mPa · s	1.500 mg
polyethylene glycol 400	0.150 mg
purified water	23.350 µl *
ethylcellulose aqueous dispersion	25.550 mg (30%)
dibutyl sebacate	1.840 mg
purified water	25.550 µl *
capsule nr. 4	

*: these ingredients do not occur in the end product

The preparation was identical to that described in Example 1 except for the preparation of the release rate controlling membrane dispersion.

c) Release rate controlling membrane coat dispersion

To a gently stirred aqueous dispersion of ethylcellulose (306.6 g; 30%) was added dibutyl sebacate (22.08 g). The dispersion was diluted with purified water (306.6 g).

Example 3: Bioavailability

The bioavailability of a single oral administration of the two controlled release formulations of examples 1 and 2 was compared with that of an immediate release tablet (F3) [WO-97/47304] comprising 4 mg galantamine which was administered twice daily with an interval of 8 hours. Galantamine plasma levels in healthy volunteers (12) were determined by HPLC and the mean values calculated from the individual measurements are reported in the following table.

time (h)	F1	F2	F3
0	nd	nd	nd
0.5	1.6	nd	16.4
1	7.3	nd	24.1
1.5	11.5	nd	20.3
2	16.3	1.8	18.3
3	23.8	3.7	16.9
4	26.7	6.3	14.5
6	25.2	9.5	11.3
8	22.5	10.5	9.3
8.5			18
9			24.5
9.5			25.5
10	18.6	11.1	23.7
11			22.7
12	15.1	12.0	19.3
14	13.4	12.4	15.2
16	10.8	11.7	12.7
24	6.0	8.8	6.6
30	3.5	6.1	3.5
36	2.0	4.3	2.0
48	nd	1.6	nd

nd: not detectable (<1 ng/ml)

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Example 4: oral capsule (F4) comprising 8 mg galantamine
(75% CR pellets and 25% IR tablet)

Ingredients:

sugar spheres (18–20 mesh)	63.482 mg
galantamine hydrobromide	7.69 mg (6 mg galantamine base)
HPMC 2910 5 mPa · s	0.641 mg
purified water	42.932 µl *
HPMC 2910 5 mPa · s	1.436 mg
polyethylene glycol 400	0.145 mg
methylene chloride	12.385 µl *
ethanol 96% (v/v)	10.858 mg *
HPMC 2910 5 mPa · s	1.101 mg
ethylcellulose 20 mPa · s	3.308 mg
diethyl phthalate	0.881 mg
methylene chloride	31.077 µl *
ethanol 96% (v/v)	27.244 mg *
galantamine hydrobromide	2.563 mg (2 mg galantamine base)
spray-dried mixture of lactose monohydrate and microcrystalline cellulose (75:25)	49.302 mg
colloidal anhydrous silica	0.11 mg
croscopolyvidone	2.750 mg
magnesium stearate	0.275 mg

*: these ingredients do not occur in the end product

Preparation:

a) Drug layer suspension

Galantamine hydrobromide was suspended in purified water and heated to 70–80° C. HPMC 2910 5 mPa.s was dissolved in the heated suspension whilst stirring.

b) Seal coat solution

Methylene chloride and ethanol were mixed together and polyethylene glycol and HPMC 2910 5 mPa.s were dissolved therein.

c) Release rate controlling membrane coat solution

Methylene chloride and ethanol were mixed and ethylcellulose 20 mPa.s, HPMC 2910 5 mPa.s and diethyl phthalate were added while stirring the solution.

d) Layering and coating process

A fluidized-bed granulator (Glatt) equipped with a Wurster (bottom spray) insert was loaded with 18–20 mesh sugar spheres. The spheres were warmed with dry air of about 50° C. The fluidizing air volume was controlled by opening the exhaust air valve to approximately 45% of its maximum. The drug layer suspension was sprayed on the spheres moving in the apparatus. When the spraying process was completed, the layered spheres were dried by further supplying dry air of 60° C. for about 2 minutes. The layered spheres were then seal coated with the seal coat solution using the same parameters as used in the drug coating process. After drying for about 2 minutes, the seal coated spheres were allowed to cool to room temperature and filled into a stainless steel drum.

The fluidized-bed granulator (Glatt) equipped with a Wurster (bottom spray) insert was reloaded with the seal coated spheres. The spheres were warmed with dry air of about 50° C. The fluidizing air volume was controlled by opening the exhaust air valve to approximately 45% of its maximum. The release rate controlling membrane coat suspension was sprayed on the spheres moving in the apparatus. After drying for about 2 minutes, the controlled release membrane coated spheres were allowed to cool to room temperature, sieved and filled into a stainless steel drum.

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e) Immediate release minitab

Galantamine hydrobromide, spray-dried mixture of lactose monohydrate and microcrystalline cellulose (75:25), colloidal anhydrous silica, croscopolyvidone and magnesium stearate were mixed in a planetary mixer and compressed in a tableting machine, thus preparing minitabets of 55 mg weight.

f) Capsule filling

The coated spheres and the immediate release minitab were filled into hard-gelatin capsules (size 0) using standard automatic capsule filling machines (e.g. Model GFK-1500, Höfliger and Karg, Germany).

Example 5: galantamine oral capsules (F5, F6, F7, F8)
(75% CR pellets and 25% IR topcoat)

Ingredients:

sugar spheres (18–20 mesh)	63.624 mg
galantamine hydrobromide	7.69 mg (6 mg galantamine base)
HPMC 2910 5 mPa · s and PEG 400	12.687 mg (Opadry™ OY-7240 Clear, Colorcon)
purified water	267.693 µl *
HPMC 29105 mPa · s	1.260 mg
ethylcellulose 20 mPa · s	3.780 mg
diethyl phthalate	1.008 mg
methylene chloride	46.772 µl *
ethanol 96% (v/v)	31.184 mg *
galantamine hydrobromide	2.563 mg (2 mg galantamine base)
HPMC 2910 5 mPa · s and PEG 400	4.229 mg (Opadry OY-7240 Clear)
purified water	89.321 µl *
capsules size nr. 4, 2, 1 and 0.	

*: these ingredients do not occur in the end product

Preparation:

a) Drug coat solution

Galantamine hydrobromide and Opadry OY-7240 Clear were dissolved in purified water at room temperature.

b) Release rate controlling membrane coat solution

Methylene chloride and ethanol were mixed and ethylcellulose 20 mPa.s, PHMC 2910 5 mPa.s and diethyl phthalate were added while stirring the solution.

c) Drug topcoat solution

Galantamine hydrobromide and Opadry™ OY-7240 Clear were dissolved in purified water at room temperature.

d) Coating process

A fluidized-bed granulator (Glatt) equipped with a Wurster (bottom spray) insert was loaded with 18–20 mesh sugar spheres. The spheres were warmed with dry air of about 50° C. The fluidizing air volume was controlled by opening the exhaust air valve to approximately 45% of its maximum. The drug coat solution was sprayed on the spheres moving in the apparatus. When the spraying process was completed, the coated spheres were dried by further supplying dry air of 60° C. for about 2 minutes. The release rate controlling membrane coat solution was sprayed on the spheres moving in the apparatus. After drying for about 2 minutes, the controlled release membrane coated spheres were sprayed with the drug topcoat solution. After drying for about 2 minutes, the topcoated spheres were allowed to cool to room temperature, sieved and were filled into a stainless steel drum.

e) Capsule filling

The topcoated spheres (96.841 mg; 193.683 mg; 290.524; 387.365 mg) were filled into hard-gelatin capsules (size numbers 4, 2, 1, 0) using standard automatic capsule filling

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machines (e.g. Model GFK-1500, Höfliger and Karg, Germany) yielding oral capsules containing respectively 8 mg, 16 mg, 24 mg and 32 mg galantamine base.

Example 6: Galantamine oral capsules (F9) (75% CR pellets and 25% IR topcoat)

Spheres having slightly faster release were made by lowering the ratio of ethylcellulose 20 mPa.s to HPMC 2910 5 mPa.s to 72.5:27.5 (as compared to the ratio 75:25 in the previous example.

Example 7: In vitro dissolution of the topcoated spheres

Comparative in-vitro dissolutions studies were performed on the topcoated spheres formulations F5 to F8 and F9. The medium was 500 ml of USP buffer pH 6.8 at 37° C. in Apparatus 2 (USP 23, <711> Dissolution, pp. 1791–1793) (paddle, 50 rpm). The following results were obtained:

Calculated concentration (% w/w) of the active dose							
Time (min)	sample 1	sample 2	sample 3	sample 4	sample 5	sample 6	average
F5 to F8							
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
60	32.20	30.44	37.47	30.44	30.44	38.05	33.17
120	42.54	41.37	48.39	41.37	42.54	42.54	43.13
240	58.93	60.10	65.96	61.27	61.27	61.27	61.47
480	85.47	80.20	84.30	81.96	81.37	80.79	82.35
720	91.52	90.35	97.37	99.13	92.11	87.42	92.98
1080	96.59	97.18	102.45	102.45	99.52	98.94	99.52
1410	96.40	97.57	103.42	103.42	100.5	101.08	100.40
F9							
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
60	38.9	36.0	36.5	39.5	33.4	37.2	32.86
120	60.3	55.7	56.9	60.4	60.9	55.1	58.2
240	89.5	81.8	86.2	86.7	91.2	84.0	86.6
480	103.4	103.6	95.9	101.7	100.8	105.8	101.9
720	107.0	99.0	104.0	103.1	109.1	100.8	103.8

The invention claimed is:

1. A controlled release formulation containing galantamine as the active ingredient, characterized in that it comprises particles comprising galantamine hydrobromide (1:1), and a water soluble film forming polymer wherein the galantamine hydrobromide (1:1) and the water soluble film forming polymer are layered or coated on inert spheres, said particles being coated by a release rate controlling membrane coating wherein the release rate controlling membrane coating comprises a water insoluble polymer and optionally a plasticizer, and wherein the formulation further comprises a topcoat comprising galantamine and water-soluble polymer and wherein the formulation is capable of releasing in USP buffer pH 6.8 at 37° C. in a paddle apparatus operating at 50 rpm, from 20 to 40% of the total amount of galantamine.HBr in 1 hour, and more than 80% of the total amount of galantamine.HBr in 10 hours.

2. A formulation according to claim 1 wherein the water insoluble polymer is ethylcellulose and the plasticizer is selected from the group consisting of dibutyl sebacate, diethyl phthalate and triethyl citrate.

3. A formulation according to claim 2 wherein the weight of the release rate controlling membrane coating ranges from 3% to 15% of the uncoated particle.

4. A formulation according to claim 1 wherein a seal coat lies between the drug core and the release rate controlling membrane coating.

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5. A formulation according to claim 1 wherein the water soluble film forming polymer is a polymer that has an apparent viscosity of 1 to 100 mPa.s when dissolved in a 2% aqueous solution at 20° C. solution.

6. A formulation according to claim 5 wherein the water soluble polymer is selected from the group consisting of alkylcelluloses such as methylcellulose, hydroxyalkylcelluloses such as hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose and hydroxybutylcellulose, hydroxyalkyl alkylcelluloses such as hydroxyethyl methylcellulose and hydroxypropyl methylcellulose, carboxyalkylcelluloses such as carboxymethylcellulose, alkali metal salts of carboxyalkylcelluloses such as sodium carboxymethylcellulose, carboxyalkylalkylcelluloses such as carboxymethylethylcellulose,

carboxyalkylcellulose esters,

starches,

pectines such as sodium carboxymethylamylopectine,

chitine derivatives such as chitosan,

polysaccharides such as alginic acid, alkali metal and ammonium salts thereof, carrageenans, galactomannans, traganth, agar-agar, gummi arabicum, guar gummi and xanthan gummi,

polyacrylic acids and the salts thereof,

polymethacrylic acids and the salts thereof, methacrylate copolymers,

polyvinylalcohol,

polyvinylpyrrolidone, copolymers of polyvinylpyrrolidone with vinyl acetate

polyalkylene oxides such as polyethylene oxide and polypropylene oxide and copolymers of ethylene oxide and propylene oxide.

7. A formulation according to claim 6 wherein the water soluble polymer is hydroxypropyl methylcellulose HPMC 2910 with an apparent viscosity of 5 mPa.s when dissolved in a 2% aqueous solution at 20° C.

8. A formulation according to claim 7 wherein the weight-by-weight ratio of said hydroxypropyl methylcellulose to galantamine is in the range of 17:1 to 1:5.

9. A formulation according to claim 1 wherein the inert spheres are 16–60 mesh (1,180–250 µm) sugar spheres.

10. A formulation according to any of claim 5, 6, 7, 8, 9 or 4 which delivers a therapeutically effective amount of galantamine to a patient during the 24 hours following a single once daily administration.

11. A formulation according to claim 1 providing a mean maximum plasma concentration of galantamine from 10 to 60 ng/ml and a mean minimum plasma concentration from 3 to 15 ng/ml after repeated administration every day through steady-state conditions.

12. A process of preparing a formulation according to claim 1 comprising admixing galantamine hydrobromide (1:1) with a water soluble film forming polymer and coating onto inert spheres to form a drug core, optionally applying a seal coat to the drug core, applying the release rate controlling membrane coating, and thereafter applying a topcoat comprising galantamine and a water-soluble polymer.

13. A method of treating Alzheimer's dementia in a human while substantially reducing or avoiding the concomitant liability of adverse effects associated with acetyl

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cholinesterase inhibitors, comprising administering to a human in need of such treatment, a therapeutically effective amount of galantamine in a controlled release formulation as claimed in claim 1, said amount being sufficient to alleviate said Alzheimer's dementia, but insufficient to cause said adverse effects.

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14. A method according to claim 13 wherein the adverse effects belong to the group comprising nausea, vomiting, sweating, restlessness, and insomnia.

15. A formulation according to claim 1, wherein the particles are filled in a hard-gelatin capsule.

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