IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ASTELLAS PHARMA INC., ASTELLAS IRELAND CO., LTD. and ASTELLAS PHARMA GLOBAL DEVELOPMENT, INC.,	)	C.A. No. 20-1589-JFB-CJB
Plaintiffs,	)	[redacted]
v.	)	[redacted]
SANDOZ INC. and LEK PHARMACEUTICALS D.D.	)	PUBLIC VERSION FILED: March 15, 2021
Defendants.	)	

FIRST AMENDED COMPLAINT FOR PATENT INFRINGEMENT AGAINST DEFENDANTS SANDOZ AND LEK PHARMACEUTICALS

Plaintiffs Astellas Pharma Inc., Astellas Ireland Co., Ltd., and Astellas Pharma Global Development, Inc. (collectively, "Astellas" or "Plaintiffs"), by their undersigned attorneys, hereby allege as follows:

THE PARTIES

A. Astellas Pharma Inc., Astellas Ireland Co., Ltd., and Astellas Pharma Global Development, Inc.

1. Plaintiff Astellas Pharma Inc. ("API") is a corporation organized and existing under the laws of Japan, having its principal place of business at 2-5-1, Nihonbashi-Honcho, Chuo-Ku, Tokyo 103-8411, Japan. API was formed on April 1, 2005, from the merger of Yamanouchi Pharmaceutical Co., Ltd. and Fujisawa Pharmaceutical Co., Ltd.

2. Plaintiff Astellas Ireland Co., Ltd. ("AICL") is a corporation organized and existing under the laws of Ireland, having its principal place of business at Damastown Road, Damastown Industrial Park, Mulhuddart, Dublin 15, Ireland. AICL is a subsidiary of Plaintiff API.

3. Plaintiff Astellas Pharma Global Development, Inc. ("APGD") is a corporation organized and existing under the laws of the State of Delaware, having its principal place of business at 1 Astellas Way, Northbrook, Illinois 60062. APGD is a subsidiary of Plaintiff API.

B. Sandoz Inc. ("Sandoz") and Lek Pharmaceuticals d.d. ("Lek") (together, "Defendants")

4. On information and belief, Defendant Sandoz is a corporation organized and existing under the laws of Delaware, having a principal place of business at 100 College Road West, Princeton, NJ 08540. On information and belief, Sandoz is in the business of, *inter alia*, developing, manufacturing and/or distributing generic drug products for marketing, sale, and/or use throughout the United States including in this judicial district.

5. On information and belief, Defendant Lek is a corporation organized and existing under the laws of Slovenia, having a principal place of business at Verovškova 57, SI-1526 Ljubljana, Slovenia. On information and belief, Lek is in the business of, *inter alia*, developing, manufacturing and/or distributing generic drug products for marketing, sale, and/or use throughout the United States including in this judicial district.

6. By a letter dated September 9, 2016 ("Sandoz's Notice Letter"), Sandoz notified Plaintiffs that Sandoz had submitted to the United States Food and Drug Administration ("FDA") Abbreviated New Drug Application ("ANDA") No. 209441 for mirabegron extended-release tablets, 25 mg and 50 mg ("Sandoz ANDA"), a drug product that is a generic version of Myrbetriq® extended-release tablets, in the 25 mg and 50 mg strengths ("Sandoz's ANDA Product"). On information and belief, the purpose of Sandoz's submission of the Sandoz ANDA

was to obtain approval under the Federal Food, Drug, and Cosmetic Act ("FDCA") to engage in the commercial manufacture, use, offer for sale, and/or sale of Sandoz's ANDA Product prior to November 4, 2023.

7. In Sandoz's Notice Letter, Sandoz notified Plaintiffs that, as a part of the Sandoz ANDA, Sandoz had filed a certification of the type described in Section 505(j)(2)(A)(vii)(IV) of the FDCA, 21 U.S.C. § 355(j)(2)(A)(vii)(IV), with respect to some of the then-listed patents in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluation ("Orange Book"), asserting that they are invalid, unenforceable, and/or will not be infringed by the commercial manufacture, use, and sale of Sandoz's ANDA Product.

8. On the basis of Sandoz's Notice Letter, Plaintiffs filed suit against Sandoz for infringement of some of the then-listed patents in the Orange Book. *Astellas Pharma Inc. et al. v. Sandoz Inc.*, C.A. No. 16-952 (D. Del.), D.I. 1.

9. In its Answer, Sandoz did not dispute at least subject matter jurisdiction under 35 U.S.C. § 271(e)(2)(A), personal jurisdiction, or venue. *Astellas Pharma Inc. et al. v. Sandoz Inc.*, C.A. No. 16-952 (D. Del.), D.I. 12 at ¶¶ 7-8, 13.

10. Astellas and Sandoz reached a settlement and the case was dismissed. *Astellas Pharma Inc. et al. v. Actavis Elizabeth LLC et al.*, C.A. No. 16-905-JFB-CJB (Cons.) (D. Del.), D.I. 604.

11. On information and belief, Sandoz acted collaboratively with Lek in the development Sandoz's ANDA Product, [redacted]

12. On information and belief, Sandoz acted collaboratively with Lek in the preparation and submission of ANDA No. 209441.

13. On information and belief, and consistent with their past practices, following any FDA approval of ANDA No. 209441, Defendants will work in concert with one another to make, use, offer to sell, and/or sell the generic drug products that are the subject of ANDA No. 209441 throughout the United States, and/or import such generic drug products into the United States, including in this judicial district.

NATURE OF ACTION

14. This is an action for patent infringement of United States Patent No. 10,842,780 ("the '780 Patent"), arising under the United States patent laws, Title 35, United States Code. This action relates to the ANDA submitted by the above-named Defendants under Section 505(j) of the FDCA, 21 U.S.C. § 355(j), seeking FDA approval to market generic pharmaceutical products.

JURISDICTION AND VENUE

15. This Court has jurisdiction over the subject matter of this action under 28 U.S.C. §§ 1331, 1338(a), 2201 and 2202.

16. This Court has personal jurisdiction over Defendants because, among other things, they have committed, or aided, abetted, contributed to, or participated in the commission of, tortious acts of patent infringement in filing the Sandoz ANDA that has led to foreseeable harm and injury to Plaintiffs, and will imminently commit, or aid, abet, contribute to, or participate in the commission of, a tortious act of patent infringement by selling Sandoz's ANDA Product which will lead to foreseeable harm and injury to Plaintiffs.

17. This Court also has personal jurisdiction over Sandoz because of its affiliations with the State of Delaware, including its incorporation in Delaware, are so continuous and systematic as to render it essentially at home in this forum.

18. This Court also has personal jurisdiction over Defendants because each has frequently availed itself of the legal protections of the State of Delaware by, among other things,

admitting jurisdiction and asserting counterclaims in lawsuits filed in the United States District Court for the District of Delaware. *See, e.g., Pharmacyclics LLC v. Sun Pharma Global FZE,* C.A. No. 20-403-CFC (D. Del.).

19. This Court also has personal jurisdiction over Lek pursuant to Fed. R. Civ. P. 4(k)(2) because (a) Astellas's claims arise under federal law; (b) as a foreign Defendant, Lek is not subject to jurisdiction in any state's courts of general jurisdiction; and (c) Lek has sufficient contacts within the United States as a whole, including but not limited to preparing and submitting an ANDA to the FDA and/or manufacturing and/or selling pharmaceutical products distributed throughout the United States, such that this Court's exercise of jurisdiction over Lek satisfies due process.

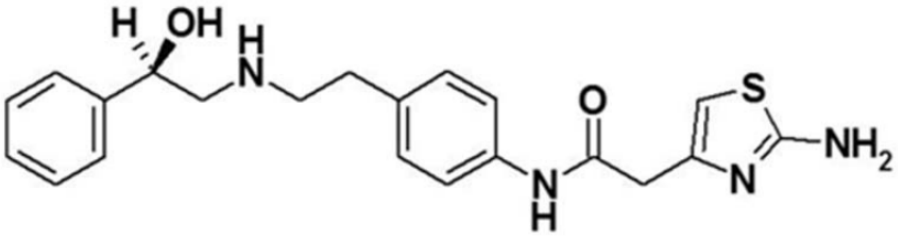
20. For these reasons, and for other reasons that will be presented to the Court if jurisdiction is challenged, the Court has personal jurisdiction over Defendants.

21. Venue is proper in this Court pursuant to 28 U.S.C. §§ 1391 and 1400(b).

MYRBETRIQ® TABLETS

22. APGD holds approved New Drug Application ("NDA") No. 202611 for Myrbetriq® extended-release tablets, 25 mg and 50 mg, which contain the active ingredient, mirabegron. The FDA approved NDA No. 202611 on June 28, 2012 for both the 25 mg and 50 mg extended-release Myrbetriq® tablets.

23. Mirabegron has been referred to chemically as, *inter alia*, (R)-2-(2-aminothiazol-4-yl)-4'-[2-(2-hydroxy-2-phenylethyl)amino]ethyl]acetic acid anilide, (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetanilide, and 2-(2-aminothiazol-4-yl)-N-[4-(2-{[(2R)-2-hydroxy-2-phenylethyl]amino}ethyl)phenyl]acetamide. Mirabegron can be depicted as, *inter alia*, the following formula:



24. Myrbetriq® extended-release tablets, containing 25 mg or 50 mg of mirabegron ("Myrbetriq® Tablets"), are indicated for the treatment of overactive bladder ("OAB") with symptoms of urge urinary incontinence, urgency, and urinary frequency.

25. Myrbetriq® Tablets comprise a sustained release hydrogel-forming formulation containing, *inter alia*, polyethylene oxide and polyethylene glycol as inactive ingredients within the tablet formulation, which function as a means for forming a hydrogel and a means for ensuring penetration of water into the tablets.

26. For quality control purposes in the U.S. market, Myrbetriq® Tablets are subjected to dissolution testing using the United States Pharmacopeia ("USP") Apparatus I. A dissolution test evaluates the rate and extent that a compound forms a solution under carefully controlled conditions. Within the context of regulatory approval, the USP dissolution test helps safeguard against the release of drug products that do not perform acceptably. USP Apparatus I (basket) and II (paddle) provide a platform to evaluate the *in vitro* performance of dosage forms using standardized conditions. These two apparatus, and associated procedures, have become widely used and accepted.

27. When measured in accordance with the United States Pharmacopeia ("USP") dissolution apparatus II, using 900 mL of USP buffer and having a pH of 6.8 at a paddle rotation speed of 200 rpm ("USP II Method"), the Myrbetriq® Tablets release 39% or less of mirabegron after 1.5 hours, and at least 75% mirabegron after 7 hours.

PRIOR MYRBETRIQ® LITIGATION WITH SANDOZ

28. Within 45 days of receipt of Sandoz's Notice Letter, Astellas initiated a suit for infringement of some of the then-listed patents in the Orange Book for Myrbetriq® Tablets, United States Patent Nos. 7,342,117 ("the '117 Patent"), 7,982,049 ("the '049 Patent"), 8,835,474 ("the '474 Patent") and RE44,872 ("the '872 Patent") against Sandoz. *Astellas Pharma Inc. et al. v. Sandoz Inc.*, C.A. No. 16-952 (D. Del.), D.I. 1. Astellas reached a settlement with Sandoz, and this suit has concluded. *Astellas Pharma Inc. et al. v. Actavis Elizabeth LLC et al.*, C.A. No. 16-905-JFB-CJB (Cons.) (D. Del.), D.I. 604. This suit did not involve the '780 Patent because, *inter alia*, it concluded before the issuance of the '780 Patent.

29. On information and belief, Defendants have made, and continue to make, substantial preparation to engage in the commercial manufacture, use, offer to sell, or sale of Sandoz's ANDA Product prior to the expiration of the '780 Patent, at the latest upon the expiration of the '117, '049, '474 and '872 Patents to the extent Defendants have received final approval of the Sandoz ANDA.

THE PATENT-IN-SUIT

30. The United States Patent & Trademark Office ("PTO") duly and legally issued the '780 Patent, entitled "Pharmaceutical Composition for Modified Release," on November 24, 2020. A true and correct copy of the '780 Patent is attached as **Exhibit A**.

31. The Orange Book lists the '780 Patent in connection with NDA 202611 as covering Myrbetriq®.

32. API is the record owner and assignee of the '780 Patent.

33. The '780 Patent will expire no earlier than September 28, 2029.

34. AICL is the exclusive licensee of the '780 Patent with the rights to develop, import, market, sell, distribute, and promote any and all pharmaceutical formulations in finished package forms which contain mirabegron as the active ingredient in the United States.

35. APGD has contracted with AICL to, *inter alia*, clinically develop mirabegron, prepare and submit NDA No. 202611 for marketing approval of Myrbetriq® Tablets in the United States.

36. AICL has contracted with Astellas Pharma US, Inc., a subsidiary of API to, *inter alia*, market and sell Myrbetriq® Tablets, in the United States on its behalf.

37. Myrbetriq® Tablets are covered by one or more claims of the '780 Patent.

MIRABEGRON ANDA FILERS

38. In June 2013, FDA issued a notice in the Federal Register (78 Fed. Reg. 37230 at 31 (June 20, 2013)) regarding bioequivalence guidance to be published on its website for mirabegron ANDAs. On its website, FDA lists the following dissolution requirements for mirabegron ANDA filers in order to establish bioequivalence with Myrbetriq® Tablets ("Mirabegron Bioequivalence Guidance"):

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)	Date Updated
Mirabegron	Tablet (Extended Release)	I (Basket)	100	Phosphate Buffer, pH 6.8	900	1, 3, 5, 7, 8.5, 10 and 12 hours	05/09/2013

39. On information and belief, each mirabegron ANDA filer will be required to meet this dissolution method, or an equivalent dissolution method, to meet its bioequivalence requirements for its proposed ANDA product using Myrbetriq® Tablets as the reference standard.

On information and belief, a proposed mirabegron ANDA product will have equivalent dissolution properties to Myrbetriq® Tablets as measured by USP Apparatus I and II.

CLAIMS FOR RELIEF

COUNT I: INFRINGEMENT OF THE '780 PATENT BY SANDOZ AND LEK UNDER 35 U.S.C. § 271(e)(2)(A)

40. Plaintiffs incorporate by reference and reallege paragraphs 1 through 39 above as though fully restated herein.

41. Sandoz, by filing ANDA No. 209441, has necessarily represented to the FDA that, upon approval, Sandoz's ANDA Product will have the same active ingredient, method of administration, dosage form, and dosage amount as Myrbetriq® Tablets, and will be bioequivalent to Myrbetriq® Tablets.

42. Sandoz's ANDA Product contains either 25 mg or 50 mg of mirabegron in extended release tablets. Sandoz's ANDA Product will also be bioequivalent to Myrbetriq® Tablets.

43. On information and belief, Sandoz's ANDA Product contains, *inter alia*, [redacted] On information and belief, the excipients in Sandoz's ANDA Product are substantially similar to Astellas's Myrbetriq® tablets.

44. On information and belief, the excipients included in Sandoz's ANDA Product include a means for forming a hydrogel and a means for ensuring penetration of water into the pharmaceutical composition.

45. On information and belief, and as required by the Mirabegron Bioequivalence Guidance, Sandoz uses an equivalent dissolution method to establish Sandoz's ANDA Product is bioequivalent to Myrbetriq® Tablets. On information and belief, Sandoz's ANDA Product has

equivalent dissolution properties as measured by USP Apparatus II at certain conditions, and will have equivalent dissolution properties as measured by USP Apparatus II as claimed by the '780 Patent, to Myrbetriq® Tablets, which contains a substantially similar hydrogel formulation. On information and belief, because of the dissolution requirements contained within the Mirabegron Bioequivalence Guidance, including the use of Myrbetriq® Tablets as the reference standard, Sandoz's ANDA Product uses a hydrogel formulation, the same as or equivalent to the Myrbetriq® Tablets formulation, that is covered by one or more claims of the '780 Patent.

46. Sandoz, via Sandoz's Notice Letter, has indicated its intent to engage in the commercial manufacture, use, offer for sale, sale, marketing, distributing, and/or importation of Sandoz's ANDA Product prior to the expiration of the '780 Patent.

47. On information and belief, Lek was responsible for, [redacted]

48. On information and belief, Defendants intend to engage in the commercial manufacture, use, offer for sale, sale, marketing, distributing, and/or importation of Sandoz's ANDA Product upon final approval of ANDA No. 209441 and no later than the expiration of the '117, '049, '474 and '872 Patents.

49. Sandoz's submission of ANDA No. 209441 seeking approval to engage in the commercial manufacture, use, offer to sell, or sale of Sandoz's ANDA Product, prior to the expiration of the '780 Patent, constitutes infringement of one or more of the claims of the '780 Patent under 35 U.S.C. § 271(e)(2)(A).

50. On information and belief, Lek actively participated, cooperated, and assisted in the preparation and submission of ANDA No. 209441, and Lek stands to benefit directly from ANDA No. 209441 if it is approved. Lek's active participation in the submission of ANDA No. 209441 to the FDA constituted an act of infringement by Lek of the '780 Patent under 35 U.S.C. § 271(e)(2)(A).

51. The commercial manufacture, use, offer for sale, sale, marketing, distributing, and/or importation of Sandoz's ANDA Product would infringe one or more claims of the '780 Patent, or their equivalents, at least under 35 U.S.C. § 271(a).

52. Unless Defendants are enjoined by the Court, Plaintiffs will be substantially and irreparably harmed by Defendants' infringement of the '780 Patent. Plaintiffs do not have an adequate remedy at law.

COUNT II: DECLARATORY JUDGMENT OF CONTRIBUTORY INFRINGEMENT OF THE '780 PATENT BY SANDOZ AND LEK UNDER 35 U.S.C. § 271(c)

53. Plaintiffs incorporate by reference and reallege paragraphs 1 through 52 above as though fully restated herein.

54. On information and belief, if ANDA No. 209441 is approved by the FDA, Lek will manufacture Sandoz's ANDA Product, and will, without authority, induce or cause others to import Sandoz's ANDA Product into the United States.

55. Sandoz's ANDA Product constitutes a material part of the inventions covered by the claims of the '780 Patent and has no substantial non-infringing uses.

56. On information and belief, Lek has had, and continues to have, knowledge that there is no substantial non-infringing use for Sandoz's ANDA Product.

57. Lek's actions will constitute contributory infringement of the '780 Patent pursuant to 35 U.S.C. § 271(c).

58. As a result of the foregoing facts, there is a real, substantial, and continuing justiciable controversy between Plaintiffs and Lek as to the liability of Lek's infringement of the '780 Patent. Lek's actions have created in Plaintiffs a reasonable apprehension of irreparable harm and loss resulting from Lek's threatened imminent actions.

59. Unless Defendants are enjoined by the Court, Plaintiffs will be substantially and irreparably harmed by Defendants' infringement of the '780 Patent. Plaintiffs do not have an adequate remedy at law.

COUNT III: DECLARATORY JUDGMENT OF INDUCED INFRINGEMENT OF THE '780 PATENT BY SANDOZ AND LEK UNDER 35 U.S.C. § 271(b)

60. Plaintiffs incorporate by reference and reallege paragraphs 1 through 59 above as though fully restated herein.

61. On information and belief, if ANDA No. 209441 is approved by the FDA, Lek will manufacture Sandoz's ANDA Product, and will, without authority, induce or cause others to import Sandoz's ANDA Product into the United States.

62. Sandoz's ANDA Product and the use thereof would directly infringe the '780 Patent under 35 U.S.C. § 271(a).

63. On information and belief, Lek has had and continues to have, knowledge of the '780 Patent.

64. On information and belief, Lek has had and continues to have, knowledge that Sandoz's ANDA Product and the use thereof would directly infringe the '780 Patent.

65. Lek's inducement of others to import Sandoz's ANDA Product into the United States will aid and abet the direct infringement of the '780 Patent.

66. On information and belief, Lek specifically intends to induce infringement of the '780 Patent.

67. Lek's actions will constitute inducement of infringement of the '780 Patent pursuant to 35 U.S.C. § 271(b).

68. As a result of the foregoing facts, there is a real, substantial, and continuing justiciable controversy between Plaintiffs and Lek as to the liability of Lek's infringement of the '780 Patent. Lek's actions have created in Plaintiffs a reasonable apprehension of irreparable harm and loss resulting from Lek's threatened imminent actions.

69. Unless Defendants are enjoined by the Court, Plaintiffs will be substantially and irreparably harmed by Defendants' infringement of the '780 Patent. Plaintiffs do not have an adequate remedy at law.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs API, AICL, and APGD, pray for a judgment in their favor and against Defendants, and respectfully request the following relief:

A. A judgment that Sandoz's submission and maintenance of the Sandoz ANDA constituted an act of infringement of the '780 Patent;

B. A judgment that Lek's active participation in the submission of ANDA No. 209441 seeking FDA approval for the commercial manufacture, use, offer for sale, sale, and/or importation of Sandoz's ANDA Product before the expiration of the '780 Patent constituted an act of infringement of the '780 Patent;

C. A judgment declaring that Lek's activities will induce and/or contribute to the infringement of the '780 Patent;

D. A judgment (or a declaration) that Defendants' making, using, offering to sell, or selling in the United States or importing into the United States of Sandoz's ANDA Product will infringe the '780 Patent;

E. A permanent injunction restraining and enjoining each Defendant, its affiliates, subsidiaries, and each of their officers, agents, attorneys and employees, and those acting in privity or concert with them, from engaging in the commercial manufacture, use, offer for sale, or sale within the United States, or importation into the United States, of Sandoz's ANDA Product until the expiration of the '780 Patent, including any extensions and/or periods of exclusivity to which Plaintiffs and/or the '780 Patent are or become entitled;

F. An order pursuant to 35 U.S.C. § 271(e)(4)(A) providing that the effective date of any approval of the Sandoz ANDA shall be a date that is not earlier than the expiration date of the '780 Patent, including any extensions and/or periods of exclusivity to which Plaintiffs and/or the '780 Patent are or become entitled;

G. Damages, including monetary and other relief, to Plaintiffs if any Defendant engages in commercial manufacture, use, offers to sell, sale, or importation into the United States of its Proposed ANDA Product, prior to the expiration date of the '780 Patent, including any extensions and/or additional periods of exclusivity to which Plaintiffs are or become entitled;

H. A declaration that this case is "exceptional" within the meaning of 35 U.S.C. § 285 and an award of reasonable attorney fees, costs, expenses, and disbursements of this action; and

I. Such other and further relief as the Court may deem just and proper.

Dated: March 8, 2021

MCCARTER & ENGLISH, LLP

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EXHIBIT A

US010842780B2

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

(10) **Patent No.: US 10,842,780 B2**
(45) **Date of Patent: Nov. 24, 2020**

(54) **PHARMACEUTICAL COMPOSITION FOR MODIFIED RELEASE**

(71) Applicant: **ASTELLAS PHARMA INC.**, Tokyo (JP)

(72) Inventors: **Yuuki Takaishi**, Tokyo (JP); **Yutaka Takahashi**, Tokyo (JP); **Takashi Nishizato**, Tokyo (JP); **Daisuke Murayama**, Tokyo (JP); **Emiko Murayama**, Tokyo (JP); **Soichiro Nakamura**, Tokyo (JP); **Kazuhiro Sako**, Tokyo (JP)

(73) Assignee: **ASTELLAS PHARMA INC.**, Tokyo (JP)

(*) 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.: **15/432,854**

(22) Filed: **Feb. 14, 2017**

(65) **Prior Publication Data**

US 2017/0231965 A1 Aug. 17, 2017

Related U.S. Application Data

(63) Continuation of application No. 12/568,313, filed on Sep. 28, 2009, now abandoned.

(60) Provisional application No. 61/101,338, filed on Sep. 30, 2008.

(51) **Int. Cl.**

A61K 31/426	(2006.01)
A61K 9/20	(2006.01)
A61K 9/28	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 31/426*** (2013.01); ***A61K 9/2009*** (2013.01); ***A61K 9/2013*** (2013.01); ***A61K 9/2031*** (2013.01); ***A61K 9/2054*** (2013.01); ***A61K 9/2095*** (2013.01); ***A61K 9/2853*** (2013.01); ***A61K 9/2866*** (2013.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

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(Continued)

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(57) **ABSTRACT**

A pharmaceutical composition for modified release, comprising (1) (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetic acid anilide, or a pharmaceutically acceptable salt thereof, (2) at least one additive which ensures penetration of water into the pharmaceutical composition and which has a solubility such that the volume of water required for dissolving 1 g of the additive is 10 mL or less, and (3) a hydrogel-forming polymer having an average molecular weight of approximately 100,000 or more, or a viscosity of 12 mPa·s or more at a 5% aqueous solution at 25° C. is disclosed.

25 Claims, 1 Drawing Sheet

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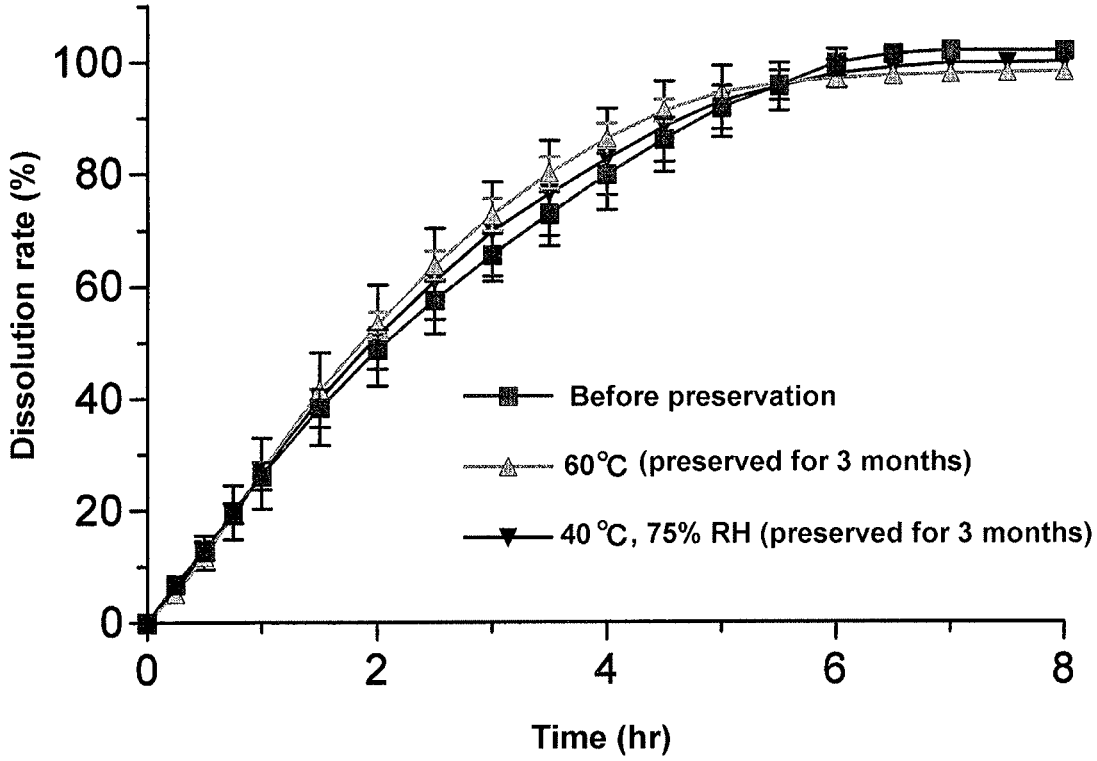

Dissolution rate (%)
100
80
60
40
20
0
0
2
4
6
8
Time (hr)
Before preservation
60℃ (preserved for 3 months)
40 ℃, 75% RH (preserved for 3 months)

PHARMACEUTICAL COMPOSITION FOR MODIFIED RELEASE

CROSS REFERENCE TO RELATED APPLICATIONS

The present application is a continuation of U.S. patent application Ser. No. 12/568,313, filed Sep. 28, 2009, which application claims the benefit of priority to U.S. Patent Application No. 61/101,338, filed Sep. 30, 2008, the teachings of which are hereby incorporated by reference.

TECHNICAL FIELD

The present invention relates to a pharmaceutical composition for modified release capable of reducing food effects, which are observed in conventional tablets, by combining an active ingredient with specific ingredients to control a releasing rate of the active ingredient.

More particularly, the present invention relates to a pharmaceutical composition comprising (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetic acid anilide or a pharmaceutically acceptable salt thereof, an additive which ensures penetration of water into the pharmaceutical composition (hereinafter sometimes referred to as a hydrophilic base), and a polymer which forms a hydrogel, in which the changes in AUC and Cmax caused by the intake of food can be decreased by controlling a releasing rate of the active ingredient.

BACKGROUND ART

(R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetic acid anilide has been created by Astellas Pharma Inc., and it has been reported that this compound has not only both an activity of promoting insulin secretion and an activity of enhancing insulin sensitivity, but also an antiobestic activity and an antihyperlipemic activity based on an activity of selectively stimulating a β3 receptor, and is useful in treating diabetes (see, for example, patent literature 1).

Further, it has been reported that the compound can be used as a therapeutic agent for overactive bladder, such as overactive bladder accompanied by prostatic hyperplasia, or overactive bladder accompanied by urinary urgency, urinary incontinence, and urinary frequency (see, for example, patent literature 2).

A clinical trial of (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetic acid anilide in the form of conventional formulations revealed disadvantages, for example, that pharmacokinetic data unexpectedly varied according to the presence or absence of the intake of food (not published). For example, the rate of decrease of Cmax in a fed state was 67%, and the rate of decrease of AUC in the fed state was 47%, in comparison with those in a fasted state. In this case, Cmax in the fasted state was three times higher than that in the fed state. These problems are considered to be raised by, for example, the changes in pharmacokinetics caused by food, and therefore, the development of a formulation capable of avoiding the effects by food intake is desired.

As a technique of preparing a formulation for modified release, a hydrogel sustained release tablet containing an additive which ensures penetration of water into the tablet, and a hydrogel-forming polymer is disclosed (see, for example, patent literature 3).

However, patent literature 3 does not refer to (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetic acid anilide, and further improvements are needed to produce a pharmaceutical composition.

CITATION LIST

Patent Literature

[patent literature 1] International Publication No. WO 99/20607 (Example 41)
[patent literature 2] International Publication No. WO 2004/041276
[patent literature 3] International Publication No. WO 94/06414

SUMMARY OF INVENTION

Technical Problem

An object of the present invention is to provide a pharmaceutical composition for modified release comprising (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetic acid anilide or a pharmaceutically acceptable salt thereof, in which the pharmaceutical composition has efficacy the same as or higher than those of conventional formulations and has no limitations on food intake, and a process of manufacturing the pharmaceutical composition.

Solution to Problem

The elimination half-life ($T_{1/2}$) of (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetic acid anilide is long (approximately 18 to 24 hours), and thus, a formulation thereof for modified release is not necessarily needed to maintain its blood level. Taking into consideration the results of the clinical trial described above, the present inventors conducted intensive studies to design the formulation by paying attention to the control of a release rate of the drug from a formulation to the extent that the release is not affected by food intake or the like, rather than the addition of release control.

On the basis of blood concentration profiles (in a fasted state/after the intake of food) after administration of a conventional formulation (rapid release formulation), the absorption rate of the drug in a fed state was calculated by a deconvolution method to predict continuous absorption for about 4 hours. The present inventors considered from this result that a formulation capable of continuous drug release for 4 hours or more would be able to reduce the effects by food, because the drug release from the formulation would become the rate-limiting step for absorption.

The present inventors carried out a clinical trial in human using three types of formulations in which the release rate of the drug was controlled (Time when the release percentage of the drug from the unit formulation was 80% (T80%)=4 hr, 6 hr, and 10 hr), and found that all formulations could reduce the effects by food, to complete the present invention.

It is generally known that the retention time in the stomach and the release rate of formulations for modified release vary according to the presence or absence of food intake, and as a result, there is a possibility that blood concentration profiles is changed. However, surprisingly, when using this formulation, the change of the blood concentration profiles was small in the presence or absence of food intake.

The present invention is characterized by providing a pharmaceutical composition for modified release which is not affected by the effects of food intake and exhibits a decreased change in AUC or Cmax.

The present invention provides:

[1] a pharmaceutical composition for modified release, comprising (1) (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetic acid anilide, or a pharmaceutically acceptable salt thereof, (2) at least one additive which ensures penetration of water into the pharmaceutical composition and which has a solubility such that the volume of water required for dissolving 1 g of the additive is 10 mL or less, and (3) a hydrogel-forming polymer having an average molecular weight of approximately 100,000 or more, or a viscosity of 12 mPa·s or more at a 5% aqueous solution at 25° C.;

[2] the pharmaceutical composition for modified release of [1], wherein the additive which ensures penetration of water into the pharmaceutical composition is one compound, or two or more compounds selected from the group consisting of polyethylene glycol, polyvinylpyrrolidone, D-mannitol, D-sorbitol, xylitol, lactose, sucrose, anhydrous maltose, D-fructose, dextran, glucose, polyoxyethylene hydrogenated castor oil, polyoxyethylene polyoxypropylene glycol, polyoxyethylene sorbitan higher fatty acid ester, sodium chloride, magnesium chloride, citric acid, tartaric acid, glycine, β-alanine, lysine hydrochloride, and meglumine;

[3] the pharmaceutical composition for modified release of [2], wherein the additive which ensures penetration of water into the pharmaceutical composition is one compound, or two or more compounds selected from the group consisting of polyethylene glycol, polyvinylpyrrolidone, D-mannitol, lactose, sucrose, sodium chloride, and polyoxyethylene polyoxypropylene glycol;

[4] the pharmaceutical composition for modified release of any one of [1] to [3], wherein an amount of the additive which ensures penetration of water into the pharmaceutical composition is 5% by weight to 75% by weight with respect to the total weight of the pharmaceutical composition;

[5] the pharmaceutical composition for modified release of [4], wherein an amount of the additive which ensures penetration of water into the pharmaceutical composition is 5% by weight to 70% by weight with respect to the total weight of the pharmaceutical composition;

[6] the pharmaceutical composition for modified release of any one of [1] to [5], wherein the hydrogel-forming polymer is one compound, or two or more compounds selected from the group consisting of polyethylene oxide, hydoxypropyl methylcellulose, hydroxypropyl cellulose, carboxymethyl cellulose sodium, hydroxyethyl cellulose, and a carboxyvinyl polymer;

[7] the pharmaceutical composition for modified release of [6], wherein the hydrogel-forming polymer is one compound, or two or more compounds selected from the group consisting of polyethylene oxide, hydoxypropyl methylcellulose, and hydroxypropyl cellulose;

[8] the pharmaceutical composition for modified release of any one of [1] to [7], wherein an amount of the hydrogel-forming polymer is 1% by weight to 70% by weight with respect to the total weight of the pharmaceutical composition;

[9] the pharmaceutical composition for modified release of any one of [1] to [8], further comprising an antioxidant;

[10] the pharmaceutical composition for modified release of [9], wherein the antioxidant is one compound, or two or more compounds selected from the group consisting of butyl hydroxytoluene, propyl gallate, and sodium ascorbate;

[11] the pharmaceutical composition for modified release of claim **10**, wherein the antioxidant is butyl hydroxytoluene;

[12] the pharmaceutical composition for modified release of any one of [9] to [11], wherein an amount of the antioxidant is 0.025% by weight to 0.25% by weight;

[13] the pharmaceutical composition for modified release of any one of [1] to [12], further comprising a stabilizer;

[14] the pharmaceutical composition for modified release of [13], wherein the stabilizer is one compound, or two or more compounds selected from the group consisting of yellow ferric oxide, red ferric oxide, and black iron oxide;

[15] the pharmaceutical composition for modified release of [14], wherein the stabilizer is yellow ferric oxide and/or red ferric oxide;

[16] the pharmaceutical composition for modified release of any one of [13] to [15], wherein an amount of the stabilizer is 0.05% by weight to 1% by weight;

[17] a process of manufacturing a pharmaceutical composition for modified release, characterized by comprising mixing (1) (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetic acid anilide, or a pharmaceutically acceptable salt thereof with (2) at least one additive which ensures penetration of water into the pharmaceutical composition and which has a solubility such that the volume of water required for dissolving 1 g of the additive is 10 mL or less and (3) a hydrogel-forming polymer having an average molecular weight of approximately 100,000 or more, or a viscosity of 12 mPa·s or more at a 5% aqueous solution at 25° C., wherein an amount of the additive is 5% by weight to 75% by weight with respect to the total weight of the pharmaceutical composition, and an amount of the hydrogel-forming polymer is 1% by weight to 70% by weight with respect to the total weight of the pharmaceutical composition;

[18] the process of [17], wherein the additive which ensures penetration of water into the pharmaceutical composition is one compound, or two or more compounds selected from the group consisting of polyethylene glycol, polyvinylpyrrolidone, D-mannitol, D-sorbitol, xylitol, lactose, sucrose, anhydrous maltose, D-fructose, dextran, glucose, polyoxyethylene hydrogenated castor oil, polyoxyethylene polyoxypropylene glycol, polyoxyethylene sorbitan higher fatty acid ester, sodium chloride, magnesium chloride, citric acid, tartaric acid, glycine, β-alanine, lysine hydrochloride, and meglumine; and

[19] the process of [17] or [18], wherein the hydrogel-forming polymer is one compound, or two or more compounds selected from the group consisting of polyethylene oxide, hydoxypropyl methylcellulose, hydroxypropyl cellulose, carboxymethyl cellulose sodium, hydroxyethyl cellulose, and a carboxyvinyl polymer.

As formulation techniques for reducing or avoiding the changes in pharmacokinetics such as AUC or Cmax accompanied by food intake, a formulation technique concerning a sustained-release pharmaceutical composition containing tamsulosin hydrochloride is disclosed (see Japanese Unexamined Patent Publication (Kokai) No. 2005-162736 and Japanese Unexamined Patent Publication (Kokai) No. 2005-162737). This formulation technique is limited to tamsulosin, and applied to a formulation containing the drug at a low dose (0.4 mg per unit formulation). This formulation enables to control the release of tamsulosin therefrom by being mainly composed of a sustained-release base. By

contrast, the pharmaceutical composition contains the drug at a high dose (i.e., high content per unit formulation), and it is considered difficult to control the release rate of the drug from a formulation containing the sustained-release base at a low content, and therefore, the present invention is technically quite different from the formulation disclosed in these references.

Effects of Invention

According to the present invention, a pharmaceutical composition for modified release which has no limitations on food intake and is stable (for example, reduction of changes in a sequential dissolution profile) can be provided.

Further, a pharmaceutical composition for modified release in which AUC is not reduced can be provided.

With respect to a conventional formulation, the rate of decrease of Cmax in the fed state was 67% in comparison with that in a fasted state. By contrast, with respect to the pharmaceutical composition for modified release of the present invention, the rate of decrease of Cmax in the fed state was 42% in comparison with that in a fasted state, and this result showed that reduction of Cmax caused by food intake could be significantly alleviated by forming its formulation into the pharmaceutical formulation for modified release.

BRIEF DESCRIPTION OF DRAWINGS

The FIGURE is a graph showing dissolution profiles of the pharmaceutical composition for modified release prepared in Example 11, and the time courses thereof.

DESCRIPTION OF EMBODIMENTS

The pharmaceutical composition for modified release of the present invention will be explained hereinafter.

The term "rapid release formulation (conventional formulation)" as used herein means a formulation in which the dissolution rate of the drug from the formulation is 85% or more after 30 minutes from the beginning a dissolution test, which is carried out in accordance with a dissolution test (paddle method) described in the United States Pharmacopoeia under the conditions that 900 mL of an appropriate test fluid (such as a USP buffer, pH 6.8) is used and the paddle rotation speed is 100 rpm. Alternatively, the term means a formulation in which the dissolution rate of the drug from the formulation is 85% or more after 30 minutes from the beginning a dissolution test, which is carried out in accordance with a dissolution test, method 2 described in the Japanese Pharmacopoeia under the conditions that 900 mL of an appropriate test fluid (such as a Mc. Ilvain buffer, pH 6.8) is used and the paddle rotation speed is 50 rpm.

The term "pharmaceutical composition for modified release" as used herein means a formulation in which the dissolution rate of the drug from the formulation is less than 85% after 30 minutes from the beginning a dissolution test carried out under the above conditions, and the drug release is controlled to the extent that the effects by food are reduced. More particularly, it is a formulation in which an additive (hydrophilic base) which ensures penetration of water into the formulation is combined with a polymer which forms a hydrogel.

The wording "the effects by food are reduced" as used herein means, for example, a 10% reduction, a 20% reduction in another embodiment, and a 30% reduction in still another embodiment, in comparison with Cmax of a conventional formulation. Alternatively, the term means, for example, a 10% reduction with respect to the rates of decrease of Cmax and AUC in administration after food intake, in comparison with Cmax and AUC in administration in the fasted state, a 20% reduction in another embodiment, and a 30% reduction in still another embodiment.

The rates of decrease of Cmax and AUC are calculated by the following equations:

$$Rd(Cmax)=[Cmax(FS)-Cmax(FI)]\times 100/Cmax(FS)$$

$$Rd(AUC)=[AUC(FS)-AUC(FI)]1\times 100/AUC(FS)$$

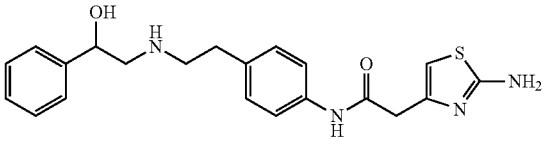
Rd(Cmax): Rate of decrease of Cmax (%)
Cmax(FS): Cmax in administration in the fasted state
Cmax(FI): Cmax in administration after food intake
Rd(AUC): Rate of decrease of AUC (%)
AUC(FS): AUC in administration in the fasted state
AUC(FI): AUC in administration after food intake

The term "formulation in which the effects by food are reduced" as used herein means a formulation in which the dissolution rate of the drug from the formulation is 75% or less after 1.5 hours and 100% or less after 4 hours from the beginning a dissolution test, which is carried out under the above conditions [in accordance with a dissolution test (paddle method) described in the United States Pharmacopoeia under the conditions that 900 mL of an appropriate test fluid (such as a USP buffer, pH 6.8) is used and the paddle rotation speed is 50 to 200 rpm]. In another embodiment, the term means a formulation in which the dissolution rate of the drug from the formulation is 75% or less after 1.5 hours and 75% or more to 100% or less after 7 hours.

The term "stable" as used herein means that it is stable against, for example, heat, temperature, humidity, or light. More particularly, the term means that, for example, when a plastic bottle is filled with a pharmaceutical composition and sealed, and then, the bottle is preserved for three months under the conditions at 40° C. and 75% RH or at 60° C., the change in the dissolution rate at the point showing a dissolution rate of 50% is within ±5% or less. Alternatively, the term means that, for example, when a pharmaceutical composition is exposed to 1.2 million Lux·hr of light, the change in the dissolution rate at the point showing a dissolution rate of 50% is within ±5% or less.

(R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetic acid anilide (hereinafter sometimes referred to as compound A) is represented by the following structural formula.

[Chem. 1]



Compound A may be used in a free form which is not a salt, and may form a salt with an acid in other embodiments. Examples of such a salt include an acid addition salt with a mineral acid such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, phosphoric acid, or the like; and an acid addition salt with an organic acid such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic

acid, malic acid, citric acid, tartaric acid, carbonic acid, picric acid, methanesulfonic acid, ethanesulfonic acid, glutamic acid, or the like.

The dose of compound A may be appropriately selected in accordance with symptom, age, sex, and the like of the patient to be treated. The daily dose of compound A for oral administration to an adult is generally 0.01 to 100 mg/kg, which is administered once or divided into two to four doses per day.

The content of compound A per formulation is, for example, 1% by weight to 70% by weight, 5% by weight to 70% by weight in another embodiment, and 5% by weight to 50% by weight in still another embodiment. The content of compound A per formulation is 1 mg to 500 mg, and 10 mg to 200 mg in another embodiment.

It is necessary that the hydrogel-forming polymer used in the present invention can control the release rate of the drug, to the extent that the blood concentration profile of the drug is not affected by the presence or absence of food intake.

The molecular weight of the hydrogel-forming polymer is, for example, 100,000 or more, 100,000 to 8,000,000 in another embodiment, 100,000 to 5,000,000 in still another embodiment, and 100,000 to 2,000,000 in still another embodiment. The viscosity of the hydrogel-forming polymer is, for example, 12 mPa·s or more in a 5% aqueous solution at 25° C.; 12 mPa·s or more in a 5% aqueous solution at 25° C., and 40,000 mPa·s or less in a 1% aqueous solution at 25° C. in another embodiment; 400 mPa·s or more in a 2% aqueous solution at 25° C., and 7,500 mPa·s or less in a 1% aqueous solution at 25° C. in still another embodiment; and 400 mPa·s or more in a 2% aqueous solution at 25° C., and 5,500 mPa·s or less in a 1% aqueous solution at 25° C. in still another embodiment.

In the pharmaceutical composition for modified release of the present invention, the release period of time of the drug from the formulation can be arbitrarily controlled by adjusting the viscosity of the polymer which is used as the hydrogel-forming polymer.

The hydrogel-forming polymer used in the present invention is not particularly limited, so long as the release of the drug can be controlled to the extend that the effects of food on compound A may be reduced. Examples of the hydrogel-forming polymer include polyethylene oxide, hydroxypropyl methylcellulose, hydroxypropyl cellulose, carboxymethyl cellulose sodium, hydroxyethyl cellulose, and carboxyvinyl polymers. Examples of the hydrogel-forming polymer in another embodiment include polyethylene oxide, hydroxypropyl methylcellulose, and hydroxypropyl cellulose.

Examples of polyethylene oxide (hereinafter sometimes referred to as PEO) include product names, Polyox WSR-308 [average molecular weight: 8,000,000, viscosity: 10,000-15,000 mPa·s (1% aqueous solution at 25° C.)], Polyox WSR-303 [average molecular weight: 7,000,000, viscosity: 7,500-10,000 mPa·s (1% aqueous solution at 25° C.)], Polyox WSR Coagulant [average molecular weight: 5,000,000, viscosity: 5,500-7,500 mPa·s (1% aqueous solution at 25° C.)], Polyox WSR-301 [average molecular weight: 4,000,000, viscosity: 1,650-5,500 mPa·s (1% aqueous solution at 25° C.)], Polyox WSR-N-60K [average molecular weight: 2,000,000, viscosity: 2,000-4,000 mPa·s (2% aqueous solution at 25° C.)], Polyox WSR-N-12K [average molecular weight: 1,000,000, viscosity: 400-800 mPa·s (2% aqueous solution at 25° C.)], Polyox WSR-1105 [average molecular weight: 900,000, viscosity: 8,800-17,600 mPa·s (5% aqueous solution at 25° C.)], Polyox WSR-205 [average molecular weight: 600,000, viscosity: 4,500-8,800 mPa·s (5% aqueous solution at 25° C.)], Polyox WSR-N-750 [average molecular weight: 300,000, viscosity: 600-1200 mPa·s (5% aqueous solution at 25° C.)], Polyox WSR-N-80 [average molecular weight: 200,000, viscosity: 55-90 mPa·s (5% aqueous solution at 25° C.)], and Polyox WSR-N-10 [average molecular weight: 100,000, viscosity: 12-50 mPa·s (5% aqueous solution at 25° C.)] (DOW).

Examples of hydoxypropyl methylcellulose (hereinafter sometimes referred to as HPMC) include product name Metolose 90SH50000 [viscosity in a 2% aqueous solution at 20° C.: 2,900-3,900 mPa·s], Metolose SB-4 (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20° C.: approximately 4 mPa·S), TC-5RW (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20° C.: approximately 6 mPa·S), TC-5S (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20° C.: approximately 15 mPa·S), TC-5R (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20° C.: approximately 6 mPa·S), TC-5M (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20° C.: approximately 4.5 mPa·S), TC-5E (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20° C.: approximately 3 mPa·S), Metolose 60SH-50 (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20° C.: approximately 50 mPa·s), Metolose 65SH-50 (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20° C.: approximately 50 mPa·s), Metolose 90SH-100 (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20° C.: approximately 100 mPa·s), Metolose 90SH-100SR (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20° C.: approximately 100 mPa·s), Metolose 65SH-400 (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20° C.: approximately 400 mPa·s), Metolose 90SH-400 (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20° C.: approximately 400 mPa·s), Metolose 65SH-1500 (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20° C.: approximately 1,500 mPa·s), Metolose 60SH-4000 (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20° C.: approximately 4,000 mPa·s), Metolose 65SH-4000 (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20° C.: approximately 4,000 mPa·s), Metolose 90SH-4000 (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20° C.: approximately 4,000 mPa·s), Metolose 90SH-4000SR (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20° C.: approximately 4,000 mPa·s), Metolose 90SH-15000 (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20° C.: approximately 15,000 mPa·s), Metolose 90SH-15000SR (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20° C.: approximately 15,000 mPa·s), and Metolose 90SH-30000 (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20° C.: approximately 30,000 mPa·s).

Examples of hydroxypropyl cellulose (hereinafter sometimes referred to as HPC) include HPC-SSL (product name, Nippon Soda Co., Ltd.) (viscosity in a 2% aqueous solution at 20° C.: 2.0-2.9 mPa·S), HPC-SL (product name, Nippon Soda Co., Ltd.) (viscosity in a 2% aqueous solution at 20° C.: 3.0-5.9 mPa·S), HPC-L (product name, Nippon Soda Co., Ltd.) (viscosity in a 2% aqueous solution at 20° C.: 6.0-10.0 mPa·S), HPC-M (product name, Nippon Soda Co.,

Ltd.) (viscosity in a 2% aqueous solution at 20° C.: 150-400 mPa·S), and HPC-H (product name, Nippon Soda Co., Ltd.) (viscosity in a 2% aqueous solution at 20° C.: 1,000-4,000 mPa·S).

Examples of methylcellulose (hereinafter sometimes referred to as MC) include Metolose SM15 (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20° C.: approximately 15 mPa·S), Metolose SM25 (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20° C.: approximately 25 mPa·S), Metolose SM100 (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20° C.: approximately 100 mPa·S), Metolose SM400 (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20° C.: approximately 400 mPa·S), Metolose SM1500 (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20° C.: approximately 1,500 mPa·S), and Metolose SM4000 (product name, Shin-Etsu Chemical Co., Ltd.) (viscosity in a 2% aqueous solution at 20° C.: approximately 4,000 mPa·S).

Examples of carboxymethyl cellulose sodium (hereinafter sometimes referred to as CMCNa) include product names, Sunrose F-30MC [viscosity: 250-350 mPa·s (1% aqueous solution at 25° C.)], Sunrose F-150MC [average molecular weight: 200,000, viscosity: 1,200-1,800 mPa·s (1% aqueous solution at 25° C.)], Sunrose F-600MC [viscosity: 6,000-8,000 mPa·s (1% aqueous solution at 25° C.)], Sunrose F-1000MC [average molecular weight: 420,000, viscosity: 8,000-12,000 mPa·s (the same)], Sunrose F-1400MC [viscosity: 12,000-15,000 mPa·s (1% aqueous solution at 25° C.)], and Sunrose F-300MC [average molecular weight: 300,000, viscosity: 2,500-3,000 mPa·s (the same)] (Nippon Paper Chemicals Co., Ltd.).

Examples of hydroxyethyl cellulose (hereinafter sometimes referred to as HEC) include product names, HEC DAICEL SE850 [average molecular weight: 1,480,000, viscosity: 2,400-3,000 mPa·s (1% aqueous solution at 25° C.)], and HEC DAICEL SE900 [average molecular weight: 1,560,000, viscosity: 4,000-5,000 mPa·s (1% aqueous solution at 25° C.)](Daicel chemical Industries, Ltd.).

Examples of carboxyvinyl polymers include Carbopol 71G (viscosity: 4,000-11,000 mPa·s), Carbopol 971P (viscosity: 4,000-11,000 mPa·s), Carbopol 981 (viscosity: 4,000-10,000 mPa·s), Carbopol 941 (viscosity: 4,000-10,000 mPa·s), Carbopol 934 (viscosity: 30,500-39,400 mPa·s), and Carbopol 934P (viscosity: 29,400-39,400 mPa·s)(B.F-.Goodrich Chemical).

These hydrogel-forming polymers may be used alone, or as an appropriate combination of two or more thereof. A combination of different lots may be used.

The content of the hydrogel-forming polymer is not particularly limited, so long as it is an amount to the extent that the blood concentration profile of the drug is not affected by the presence or absence of food intake. The content of the hydrogel-forming polymer is, for example, 1% by weight to 70% by weight with respect to the total weight of the formulation, and 3% by weight to 70% by weight in another embodiment. The content of the hydrogel-forming polymer is 5% by weight to 70% by weight with respect to the total weight of the formulation, 10% by weight to 60% by weight in another embodiment, and 10% by weight to 40% by weight in still another embodiment. The content of the hydrogel-forming polymer is 0.1% by weight to 1,000% by weight with respect to the weight of the drug, 1% by weight to 500% by weight in another embodiment, and 5% by weight to 300% by weight in still another embodiment.

A polymer of which the viscosity (before mixing) is beyond the specific range can be used as an appropriate combination with one or more other polymers, in case that the mixture obtained by mixing these plural polymers has a viscosity (as measured before the use) within the specific range.

In the additive which ensures penetration of water into the pharmaceutical composition of the present invention (hydrophilic base), the amount of water necessary to dissolve 1 g of the hydrophilic base at 20±5° C. is 10 mL or less, 6 mL or less in another embodiment, 5 mL or less in still another embodiment, and 4 mL or less in still another embodiment. When the hydrophilic base has a high solubility to water, the effect that allows water to penetrate into the formulation is high.

Examples of the hydrophilic base include water-soluble polymers, such as polyethylene glycol [PEG: for example, product names PEG 400, PEG 1500, PEG 4000, PEG 6000, and PEG 20000 (NOF Corporation)], polyvinyl pyrrolidone (PVP: for example, product name PVP K30 (BASF), and the like; sugar alcohols, such as D-mannitol, D-sorbitol, xylitol, and the like; saccharides, such as lactose, sucrose, anhydrous maltose, D-fructose, dextran (for example, Dextran 40), glucose, and the like; surfactants, such as polyoxyethylene hydrogenated castor oil [HCO: for example, Cremophor RH40 (BASF), HCO-40, HCO-60 (Nikko Chemicals)], polyoxyethylene polyoxypropylene glycol [for example, Pluronic F68 (Asahi Denka and the like)], polyoxyethylene sorbitan higher fatty acid esters [Tween: for example, Tween 80 (Kanto Chemical)], and the like; salts, such as sodium chloride, magnesium chloride, and the like; organic acids, such as citric acid, tartaric acid, and the like; amino acids, such as glycine, β-alanine, lysine hydrochloride, and the like; and aminosaccharides, such as meglumine and the like.

As another embodiment, PEG, PVP, D-mannitol, D-sorbitol, xylitol, lactose, sucrose, anhydrous maltose, D-fructose, dextran, glucose, polyoxyethylene polyoxypropylene glycol, sodium chloride, magnesium chloride, citric acid, tartaric acid, glycine, β-alanine, lysine hydrochloride, or meglumine may be used. As still another embodiment, PEG, PVP, D-mannitol, lactose, sucrose, sodium chloride, polyoxyethylene polyoxypropylene glycol, or the like may be used.

These hydrophilic bases may be used alone, or as an appropriate combination of two or more thereof.

The content of the hydrophilic base is not particularly limited, so long as it is an amount capable of controlling the release of the drug to the extent that the release of the drug is not affected by food. The content of the hydrophilic base is, for example, 5% by weight to 75% by weight, 5% by weight to 70% by weight in another embodiment, and 20% by weight to 60% by weight in still another embodiment.

The pharmaceutical composition for modified release of the present invention may be prepared as various dosage forms, which include, for example, formulations for oral administration such as tablets, capsules (including microcapsules), granules, and powder, and formulations for parenteral administration such as suppositories (for example, rectal suppositories or vaginal suppositories). These formulations may be safely administered orally or parenterally. Formulations for oral administration such as tablets, capsules, and granules may be selected in another embodiment.

The pharmaceutical composition for modified release of the present invention may be prepared by mixing the drug, the hydrogel-forming polymers, and the hydrophilic base, and forming the mixture into a predetermined shape. The mixing and forming may be carried out in accordance with

conventional methods widely used in the technical field for formulation. A pharmaceutically acceptable carrier may be used in the mixing and/or forming, if desired.

In the preparation of the pharmaceutical composition for modified release of the present invention, further various pharmaceutical additives may be used, if desired. Such pharmaceutical additives are not particularly limited, so long as they are pharmaceutically acceptable. Examples of the pharmaceutical additives include various organic or inorganic carrier substances which are widely used as formulation materials, such as fillers, lubricants, binders, and disintegrating agents. Other formulation additives such as preservatives, antioxidants, stabilizers, film coating agents, coloring agents, and sweeteners may be used, if desired.

Examples of the fillers include lactose, sucrose, D-mannitol, D-sorbitol, starch, gelatinized starch, dextrin, crystalline cellulose, low substituted hydroxypropyl cellulose, carboxymethyl cellulose sodium, gum arabic, dextrin, pullulan, light anhydrous silicic acid, synthetic aluminum silicate, magnesium aluminate metasilicate, and the like.

Examples of the lubricants include magnesium stearate, calcium stearate, talc, colloidal silica, and the like.

Examples of the binders include gelatinized starch, sucrose, gelatin, gum arabic, methylcellulose, carboxymethyl cellulose, carboxymethyl cellulose sodium, crystalline cellulose, sucrose, D-mannitol, trehalose, dextrin, pullulan, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, and the like.

Examples of the disintegrating agents include lactose, sucrose, starch, carboxymethyl cellulose, carboxymethyl cellulose calcium, croscarmellose sodium, carboxymethyl starch sodium, light anhydrous silicic acid, low substituted hydroxypropylcellulose, and the like.

Examples of the preservatives include p-hydroxybenzoate esters, chlorobutanol, benzyl alcohol, phenethyl alcohol, dehydroacetic acid, sorbic acid, and the like.

The antioxidants are not particularly limited, so long as it can avoid the effects of dissolution behavior. Examples of the antioxidants include butylated hydroxytoluene (BHT), propyl gallate (PG), butylhydroxyanisol (BHA), ascorbic acid, sodium ascorbate, erythorbic acid, sodium nitrite, sodium bisulfite, sodium pyrosulfite, citric acid, and edetate sodium; BHT, PG, and sodium ascorbate in another embodiment; and BHT in still another embodiment.

Examples of the stabilizers include yellow ferric oxide, red ferric oxide, black iron oxide, and the like.

Examples of the film coating agents include pharmaceutically commonly-used bases, such as water-soluble polymers, plasticizers, and inorganic substances, or a combination thereof.

Examples of the coloring agents include water-soluble edible tar pigments (examples: edible pigments such as food red No. 2, food red No. 3, food yellow No. 4, food yellow No. 5, food blue No. 1, and food blue No. 2), water-insoluble lake pigments (examples: aluminum salts of the above water-soluble edible tar pigments), natural pigments (examples: β-carotene, chlorophyll, and colcothar), and the like.

Examples of the sweeteners include saccharin sodium, dipotassium glycyrrhizinate, aspartame, stevia, and the like.

These carriers or formulation additives may be used alone, or as an appropriate combination of two or more thereof.

With respect to the contents thereof, they may be used in appropriate amounts. For example, the content of the antioxidant is 0.025% by weight to 0.25% by weight with respect to the total weight of the formulation, and that of the stabilizer is 0.05% by weight to 1% by weight with respect to the total weight of the formulation.

Hereinafter, the process of manufacturing the pharmaceutical composition for modified release of the present invention will be explained, the present invention is not limited to the following particular embodiments.

The pharmaceutical composition for modified release of the present invention may be prepared by known methods per se, such as dry granulation, wet granulation, fluidized bed granulation, intermittent granulation, agitation granulation, or the like.

As a method of de-lumping or pulverizing the drug, conventional crushing or pulverizing methods may be applied, for example, using an impact mill (Hosokawa Micron Corporation; Fine Impact Mill), a dry & wet mill (Powrex Corporation: Comil), or a cutting mill granulator (Dalton Corporation; Power Mill).

As a method of pulverizing the hydrophilic base, the hydrogel-forming polymer, or the formulation additives, conventional pulverizing methods may be applied, for example, using an impact mill (Hosokawa Micron Corporation; Fine Impact Mill or Sample Mill) or a jet mill (Horkos Corp; Jet Mill).

As a method of granulating the drug, conventional granulation methods may be used. Examples of such methods include a fluidized bed granulation method, an intermittent granulation method, an agitation granulation method, a high-speed agitation granulation method, a tumbling fluidized bed granulation method, an extrusion granulation method, a pulverization granulation method, a dry granulation method, and the like. In another embodiment, examples thereof include a fluidized bed granulation method, an intermittent granulation method, an agitation granulation method, a high-speed agitation granulation method, a tumbling fluidized bed granulation method, and a dry granulation method, and any method capable of granulating the drug may be used. Examples of a granulator include a fluidized bed granulator (for example, Flow Coater; Freund Corporation, or GPCG; Glatt GmbH), a granulation and coating apparatus equipped with a horizontal rotating disc having a flat powder contact portion [for example, a centrifugal fluidizing granulator (for example, CF granulator; Freund Corporation)], a granulation and coating apparatus having a rotating disk with a flat surface placed at the bottom of a fluidized bed and having an aeration portion (for example, Spiralflow, or Flowcoater with a rotor container; Freund Corporation), and a dry granulator in which material powder is directly compressed, molded, crushed, and sieved (for example, Roller Compactor; Freund Corporation).

In the dry granulation, for example, the drug, the hydrogel-forming polymer, the hydrophilic base, and additives such as a filler may be compression-molded using a dry granulator, and then, may be crushed and sieved to obtain granulated products having a desired size.

In the wet granulation, for example, while the drug, the hydrogel-forming polymer, the hydrophilic base, and additives such as a filler is fluidized, an appropriate amount of water or a liquid containing the hydrophilic base and the binder may be sprayed. The liquid containing the hydrophilic base may be prepared by dissolving or dispersing the essential component in a solvent such as water, ethanol, methanol, or the like. These solvents may be used as an appropriate mixture thereof.

The amount of water used in the granulation is not particularly limited, so long as the binder or formulation additives may be uniformly dissolved and/or suspended (dispersed) in the water. When the hydrophilic base is used

in the solid form, the amount of water is not particularly limited, so long as the hydrogel-forming polymer can be granulated.

When the hydrophilic base is used in the liquid form, the amount of water to the hydrogel-forming polymer is generally 10% by weight or less, 8% by weight or less in another embodiment, and 5% by weight or less in still another embodiment. A method of adding water in the granulation is not particularly limited, so long as a nonuniform mixture consisting of untreated powder and aggregates, which are generally powdery, is not generated. Examples thereof include a continuous spray method in which water is continuously added, an intermittent spray method in which a dry step (and a shaking step, if desired) is carried out during the granulation step, and the like.

The addition rate of water in the granulation is not particularly limited, so long as a nonuniform mixture consisting of untreated powder and aggregates, which are generally powdery, is not generated. In the fluidized bed granulation, the addition rate of water to the hydrogel-forming polymer is generally 0.1% by weight/min. to 1% by weight/min., 0.2% by weight/min. to 0.8% by weight/min. in another embodiment, and 0.4% by weight/min. to 0.6% by weight/min. in still another embodiment.

The temperature of the powder in the granulation is not particularly limited, so long as it does not induce thermal denaturation of the hydrogel-forming polymer. The temperature is, for example, 20° C. to the melting point (62° C. to 67° C.) of the hydrogel-forming polymer, 20° C. to 50° C. in another embodiment, 20° C. to 35° C. in still another embodiment, and 25° C. to 30° C. in still another embodiment.

The concentration of the binder liquid as a solid content which may be used in the granulation is, for example, 1% to 20% as a formulation amount. The binder is not particularly limited, so long as it is pharmaceutically acceptable.

The binder may be added in the solid form to a granulator, and then, water may be sprayed as the binder liquid. Alternatively, the binder may be dissolved in water, and then, the resulting binder liquid may be sprayed.

An appropriate spray rate of the binder liquid varies according to a production method to be applied or its production scale. In a 1-kg scale production by the fluidized bed granulation, the spray rate is 2 g/min. to 20 g/min., and 5 g/min. to 15 g/min. in another embodiment.

An appropriate temperature of the product in the granulation is 15° C. to 50° C., and 15° C. to 40° C. in another embodiment.

The resulting granulated products may be, for example, dried or heated.

In the drying step, an apparatus and a method are not particularly limited, so long as the granulated products can be dried. Examples of an apparatus for drying include a fluidized bed granulator (for example, Flow Coater; Freund Corporation, or GPCG; Glatt GmbH), a granulation and coating apparatus equipped with a horizontal rotating disc having a flat powder contact portion [for example, a centrifugal fluidizing granulator (for example, CF granulator; Freund Corporation)], a granulation and coating apparatus having a rotating disk with a flat surface placed at the bottom of a fluidized bed and having an aeration portion (for example, Spiralflow, or Flowcoater with a rotor container; Freund Corporation), and the like. The conditions for drying are not particularly limited, so long as the granulated products may be generally dried in the fluidized bed. The drying of the granulated products will be almost completed, for example, under the conditions in which the dry inlet air temperature is 50° C. and the drying is carried out until the temperature of the granulated products becomes 40° C. and, in another embodiment, under the conditions in which the dry inlet air temperature is 40° C. and the drying is carried out until the temperature of the granulated products becomes 30° C. As the drying method, forced-air drying or drying under reduced pressure may be used.

After the completion of the granulation, an anti-oxidant may be added.

The granulated products may be sieved.

In the sieving step, an apparatus and a method are not particularly limited, so long as the granulated products can be sieved. Examples of an apparatus for sieving include a screen, a dry & wet mill (Powrex Corporation: Comil), a cutting mill granulator (Dalton Corporation; Power Mill), and the like. The conditions for sieving are not particularly limited, so long as the granulated products may be generally sieved to obtain particles having a desired size.

After the completion of the sieving, an anti-oxidant may be added.

Examples of tabletting include a direct tabletting method in which the drug, the hydrophilic base, and the hydrogel-forming polymer are mixed with an appropriate additive(s), and the mixture is compression-molded to obtain tablets; a method in which a composition obtained by a wet granulation (the granulation is carried out by spraying a mixture of the drug, the hydrophilic base, the hydrogel-forming polymer, and additives with a binder liquid) or a melting granulation (the granulation is carried out by heating a mixture of the drug, the hydrophilic base, the hydrogel-forming polymer, and an appropriate low-melting substance) is formed into tablets; and the like.

A rotary tabletting machine, a single punch tabletting machine, and the like may be used as a tabletting machine. A method as well as an apparatus is not particularly limited, so long as a compression-molded product (preferably tablets) can be pharmaceutically produced.

After the tabletting, the obtained tablets may be dried. The initial water content of the tablet is, for example, 2% by weight/tablet or less, 1.5% by weight/tablet or less in another embodiment, and 0.9% by weight/tablet or less in still another embodiment.

After the tabletting, the obtained tablets may be film coated using a pan coating machine at an amount of 1% by weight to 5% by weight per tablet.

EXAMPLES

The present invention will now be further illustrated by, but is by no means limited to, the following Examples.

Example 1

In a mortar, 10 g of compound A, 2.5 g of polyethylene oxide (Dow chemical; product name: WSR N-60K; The same compound was used in the following Examples, unless otherwise specified.), and 7.5 g of polyethylene glycol (Sanyo Chemical Industries, Ltd.; PEG 6000; The same compound was used in the following Examples.) were mixed well. The mixture was formed into tablets using Autograph (Shimadzu; The same apparatus was used in the following Examples.) to obtain a pharmaceutical composition for modified release of the present invention having a tablet weight of 400 mg.

Example 2

In a mortar, 10 g of compound A, 3.5 g of polyethylene oxide, and 6.5 g of polyethylene glycol were mixed well,

and the mixture was formed into tablets using Autograph to obtain a pharmaceutical composition for modified release of the present invention having a tablet weight of 400 mg.

Example 3

In a mortar, 10 g of compound A, 6.25 g of polyethylene oxide, and 5 g of polyethylene glycol were mixed well, and the mixture was formed into tablets using Autograph to obtain a pharmaceutical composition for modified release of the present invention having a tablet weight of 425 mg.

Example 4

In a mortar, 10 g of compound A, 5 g of hydroxypropyl methylcellulose (Shin-Etsu Chemical Co., Ltd.; HPMC90SH-4000SR), and 5 g of polyethylene glycol were mixed well, and the mixture was formed into tablets using Autograph to obtain a pharmaceutical composition for modified release of the present invention having a tablet weight of 400 mg.

Example 5

In a mortar, 10 g of compound A, 5 g of hydroxypropyl methylcellulose (Shin-Etsu Chemical Co., Ltd.; HPMC90SH-100000SR), and 5 g of polyethylene glycol were mixed well, and the mixture was formed into tablets using Autograph to obtain a pharmaceutical composition for modified release of the present invention having a tablet weight of 400 mg.

Example 6

In a mortar, 10 g of compound A, 7.5 g of hydroxypropyl methylcellulose (Shin-Etsu Chemical Co., Ltd.; HPMC90SH-100SR), and 2.5 g of polyethylene glycol were mixed well, and the mixture was formed into tablets using Autograph to obtain a pharmaceutical composition for modified release of the present invention having a tablet weight of 400 mg.

Example 7

After 400 g of compound A, 140 g of polyethylene oxide, 251.2 g of polyethylene glycol, 0.8 g of finely ground BHT (Merck; The same compound was used in the following Examples.) and 8 g of magnesium stearate were weighed out, these compounds were mixed using a mixer. The mixture was compression-molded using Roller Compactor Mini (Freund Corporation) and sieved to obtain a pharmaceutical composition for modified release (granules) of the present invention. The obtained granules were formed into tablets using a rotary tabletting machine (Hata Iron Works Co., Ltd.; The same apparatus was used in the following Examples.) to obtain a pharmaceutical composition for modified release (tablets) of the present invention having a tablet weight of 400 mg.

Example 8

The tablets obtained in Example 7 were coated with a film coating agent [Colorcon; Opadry (containing yellow ferric oxide as a stabilizer); The same agent was used in the following Examples, unless otherwise specified.] dispersed into water to obtain a pharmaceutical composition for modified release (tablets) of the present invention.

Example 9

Into a fluidized bed granulating apparatus GPCG-5 (Freund Corporation; The same apparatus was used in the following Examples.), 1500 g of de-lumped compound A, 1050 g of polyethylene oxide, and 1764 g of polyethylene glycol were loaded, and granulated with 1350 g of a 10% by weight aqueous solution of hydroxypropyl cellulose (Nippon Soda Co., Ltd.; HPC-SL; The same compound was used in the following Examples.) to obtain a pharmaceutical composition for modified release (granules) of the present invention. The resulting pharmaceutical composition for modified release (granules) of the present invention was sieved and mixed with 4 g of finely ground BHT and 30 g of magnesium stearate, and the mixture was formed into tablets using a rotary tabletting machine to obtain a pharmaceutical composition for modified release (tablets) of the present invention having a tablet weight of 300 mg. The obtained tablets were spray-coated with an aqueous dispersion of the film coating agent using HiCoater to obtain a pharmaceutical composition for modified release (tablets) of the present invention having a tablet weight of 309 mg.

Example 10

Into a fluidized bed granulating apparatus GPCG-5, 1500 g of de-lumped compound A, 1050 g of polyethylene oxide, 1764 g of polyethylene glycol, and 135 g of hydroxypropyl cellulose (HPC-SL) were loaded, and granulated with purified water to obtain a pharmaceutical composition for modified release (granules) of the present invention. The resulting pharmaceutical composition for modified release (granules) of the present invention was sieved and mixed with 4 g of finely ground BHT and 30 g of magnesium stearate, and the mixture was formed into tablets using a rotary tabletting machine to obtain a pharmaceutical composition for modified release (tablets) of the present invention having a tablet weight of 300 mg. The obtained tablets were spray-coated with an aqueous dispersion of the film coating agent using HiCoater to obtain a pharmaceutical composition for modified release (tablets) of the present invention having a tablet weight of 309 mg.

Example 11

After 400 g of compound A, 100 g of polyethylene oxide, 290 g of polyethylene glycol, 2 g of finely ground BHT, and 8 g of magnesium stearate were weighed out, these compounds were mixed using a mixer. The mixture was compression-molded using Roller Compactor Mini and sieved to obtain a pharmaceutical composition for modified release (granules) of the present invention. The obtained granules were formed into tablets using a rotary tabletting machine to obtain a pharmaceutical composition for modified release (tablets) of the present invention having a tablet weight of 400 mg.

Example 12

In a mortar, 10 g of compound A, 2.5 g of polyethylene oxide (Dow chemical; product name: WSR Coagulant), and 12.5 g of polyethylene glycol were mixed well. The mixture was formed into tablets using Autograph to obtain a phar-

maceutical composition for modified release of the present invention having a tablet weight of 400 mg.

Example 13

In a mortar, 10 g of compound A, 0.5 g of polyethylene oxide (Dow chemical; product name: WSR 301), and 5 g of polyethylene glycol were mixed well. The mixture was formed into tablets using Autograph to obtain a pharmaceutical composition for modified release of the present invention having a tablet weight of 310 mg.

Example 14

In a mortar, 5 g of compound A, 15 g of polyethylene oxide, and 5 g of polyethylene glycol were mixed well. The mixture was formed into tablets using Autograph to obtain a pharmaceutical composition for modified release of the present invention having a tablet weight of 250 mg.

Example 15

In a mortar, 10 g of compound A, 10 g of polyethylene oxide (Dow chemical; product name: WSR N-12K), and 5 g of D-mannitol (Towa Chemical Industry Co., Ltd; product name: Mannit P) were mixed well. The mixture was formed into tablets using Autograph to obtain a pharmaceutical composition for modified release of the present invention having a tablet weight of 500 mg.

Example 16

In a mortar, 2 g of compound A, 2 g of polyethylene oxide, and 10 g of polyethylene glycol were mixed well. The mixture was formed into tablets using Autograph to obtain a pharmaceutical composition for modified release of the present invention having a tablet weight of 350 mg.

Example 17

Into a fluidized bed granulating apparatus GPCG-5, 400 g of de-lumped compound A, 1120 g of polyethylene oxide, and 2313.6 g of polyethylene glycol were loaded, and granulated with 1200 g of a 10% by weight aqueous solution of hydroxypropyl cellulose to obtain a pharmaceutical composition for modified release (granules) of the present invention. The resulting pharmaceutical composition for modified release (granules) of the present invention was sieved and mixed with 6.4 g of finely ground BHT and 40 g of magnesium stearate, and the mixture was formed into tablets using a rotary tabletting machine to obtain a pharmaceutical composition for modified release (tablets) of the present invention having a tablet weight of 250 mg. The obtained tablets were spray-coated with an aqueous dispersion of the film coating agent (containing yellow ferric oxide and red ferric oxide as stabilizers) using HiCoater to obtain a pharmaceutical composition for modified release (tablets) of the present invention having a tablet weight of 257.5 mg.

The formulations in Examples 1 to 17 are shown in Tables 1 to 3.

TABLE 1

Examples	1	2	3	4	5	6
compound A (g)	10	10	10	10	10	10
PEO WSR N-60K (g)	2.5	3.5	6.25	—	—	—
HPMC 90SH-4000SR (g)	—	—	—	5	—	—
HPMC 90SH-100000SR (g)	—	—	—	—	5	—
HPMC 90SH-100SR (g)	—	—	—	—	—	7.5
PEG (g)	7.5	6.5	5	5	5	2.5

TABLE 2

Examples	7	8	9	10	11
compound A (g)	400	400	1500	1500	400
PEO WSR N-60K (g)	140	140	1050	1050	100
PEG (g)	251.2	251.2	1764	1764	290
HPC-SL (g)	—	—	135	135	—
magnesium stearate (g)	8	8	30	30	8
BHT (g)	0.8	0.8	4	4	2
film coating agent (g)	—	23.7	134	134	—

TABLE 3

Examples	12	13	14	15	16	17
compound A (g)	10	10	5	10	2	400
PEO WSR N-60K (g)	—	—	15	—	2	1120
PEO WSR coagulant (g)	2.5	—	—	—	—	—
PEO WSR 301 (g)	—	0.5	—	—	—	—
PEO WSR N-12K (g)	—	—	—	10	—	—
PEG (g)	12.5	5	5	—	10	2313.6
D-mannitol	—	—	—	5	—	—
HPC-SL (g)	—	—	—	—	—	120
magnesium stearate (g)	—	—	—	—	—	40
BHT (g)	—	—	—	—	—	6.4
film coating agent (g)	—	—	—	—	—	120

Comparative Example 1

After 400 g of pulverized compound A was mixed with 1200 g of D-mannitol, 320 g of purified water was further added, and the whole was kneaded using an agitation granulator (Powrex Corporation; VG-25). The resulting aggregate was sieved through a screen having an opening of 850 μm, and dried using a fluidized bed granulating apparatus (Freund Corporation; FLO-1). The dried products were sieved through a screen having an opening of 500 μm, and filled into No. 1 capsules at a content of 320 mg per capsule to obtain a pharmaceutical composition for comparison containing 80 mg of compound A.

EXPERIMENTAL EXAMPLES

1. Dissolution test

The pharmaceutical compositions prepared in Examples 2, 8, and 9 were subjected to a dissolution test carried out in accordance with a USP dissolution test (paddle method). As a test fluid, 900 mL of a phosphate buffer (pH 6.8) was used. The pharmaceutical composition prepared in Comparative Example 1 was tested in accordance with a dissolution test, method 2 described in the Japanese Pharmacopoeia. As a test fluid, 900 mL of a Mc. Ilvain buffer (pH 6.8) was used, and the paddle rotation speed was 50 rpm.

The results are shown in Table 4. The dissolution rate after 1.5 hours of the pharmaceutical composition for modified release prepared in each Example was less than 40%. By contrast, the composition prepared in Comparative Example showed a high dissolution rate of 85% or more after 0.5 hour.

TABLE 4

	Example 2	Example 8	Example 9	Comparative Example 1
0.5 hr.	—	—	—	95%
1.5 hr.	35%	39%	32%	—
2.5 hr.	57%	61%	54%	—
4.5 hr.	93%	95%	92%	—

2. Stability Test

Plastic bottles were filled with the pharmaceutical composition for modified release prepared in Example 11, and sealed. These bottles were preserved under the conditions at 40° C. and 75% RH or at 60° C. for 3 months. After the preservation, each pharmaceutical composition was subjected to a dissolution test carried out in accordance with a USP dissolution test (paddle method). As a test fluid, 900 mL of a phosphate buffer (pH 6.8) was used. The results are shown in FIG. **1**. The acceleration of a dissolution rate was not observed after the preservation for 3 months under the conditions at 40° C. and 75% RH or at 60° C., and the results were indicative that the pharmaceutical composition was stable.

The pharmaceutical compositions for modified release prepared in Examples 8 and 9 were packed with alminum/alminum blister, and preserved under the conditions at 40° C. and 75% RH for 6 months. After the preservation, each pharmaceutical composition was subjected to a dissolution test carried out in accordance with a USP dissolution test (paddle method). As a test fluid, 900 mL of a phosphate buffer (pH 6.8) was used. As a result, changes in the dissolution rate at the point showing a dissolution rate of approximately 50% were 2% and 3%, with respect to the pharmaceutical compositions prepared in Examples 8 and 9, respectively, and the results were indicative that the pharmaceutical compositions were stable.

The pharmaceutical composition for modified release prepared in Example 17 was exposed to 1.2 million Lux·hr of light. After the exposure, the pharmaceutical composition was subjected to a dissolution test carried out in accordance with a USP dissolution test (paddle method). As a test fluid, 900 mL of a phosphate buffer (pH 6.8) was used. As a result, the change in the dissolution rate at the point showing a dissolution rate of approximately 50% was less than 1%, and the result was indicative that the pharmaceutical composition was stable.

3. Pharmacokinetics (PK) Test in Human

The pharmaceutical composition for modified release prepared in Example 8, which contained the equivalent corresponding to 200 mg of compound A, was administered to healthy persons in a fasted state or after 30 minutes from the intake of food, and the plasma levels of the drug were measured.

For comparison, 2 capsules of the pharmaceutical composition (conventional formulation) prepared in Comparative Example 1, which contained the equivalent corresponding to 160 mg of compound A, was administered to healthy persons in a fasted state or after 30 minutes from the intake of food, and the plasma levels of the drug were measured.

With respect to the conventional formulation, the rate of decrease of Cmax in the fed state was 67%, in comparison with that in a fasted state, and the rate of decrease of AUC was 47% (Cmax in the fasted state was approximately three times higher than that in the fed state). With respect to the pharmaceutical composition for modified release of the present invention, the rate of decrease of Cmax in free-feeding was 42%, in comparison with that in a fasted state, and the rate of decrease of AUC was 25%. These results indicated that the reductions of Cmax and AUC caused by food intake could be significantly alleviated by the pharmaceutical composition for modified release of the present invention.

INDUSTRIAL APPLICABILITY

According to the present invention, a pharmaceutical composition for modified release in which the changes in AUC and Cmax caused by food intake can be decreased by controlling a releasing rate of the active ingredient can be provided.

As above, the present invention was explained with reference to particular embodiments, but modifications and improvements obvious to those skilled in the art are included in the scope of the present invention.

The invention claimed is:

1. A pharmaceutical composition, comprising 10 mg to 200 mg of (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetic acid anilide, or a pharmaceutically acceptable salt thereof, in a sustained release hydrogel-forming formulation comprising a hydrogel-forming polymer having an average molecular weight of 100,000 to 8,000,000 and an additive having a water solubility of at least 0.1 g/mL at 20±5° C.,

wherein the hydrogel-forming polymer is at least one compound selected from the group consisting of polyethylene oxide, hydroxypropyl methylcellulose, hydroxypropyl cellulose, carboxymethyl cellulose sodium, hydroxyethyl cellulose, and a carboxyvinyl polymer,

wherein the additive is at least one selected from the group consisting of polyethylene glycol, polyvinylpyrrolidone, D-mannitol, D-sorbitol, xylitol, lactose, sucrose, anhydrous maltose, D-fructose, dextran, glucose, polyoxyethylene hydrogenated castor oil, polyoxyethylene polyoxypropylene glycol, polyoxyethylene sorbitan higher fatty acid ester, sodium chloride, magnesium chloride, citric acid, tartaric acid, glycine, (3-alanine, lysine hydrochloride, and meglumine, and

wherein a drug dissolution rate from the pharmaceutical composition is 39% or less after 1.5 hours, and at least 75% after 7 hours, as measured in accordance with United States Pharmacopoeia in 900 mL of a USP buffer having a pH of 6.8 at a paddle rotation speed of 200 rpm.

2. The pharmaceutical composition according to claim **1**, wherein the additive is at least one selected from the group consisting of polyethylene glycol, polyvinylpyrrolidone, D-mannitol, lactose, sucrose, sodium chloride, and polyoxyethylene polyoxypropylene glycol.

3. The pharmaceutical composition according to claim **1**, wherein an amount of the additive is 5% by weight to 75% by weight with respect to a total weight of the pharmaceutical composition.

4. The pharmaceutical composition according to claim **3**, wherein the amount of the additive is 5% by weight to 70% by weight with respect to the total weight of the pharmaceutical composition.

5. The pharmaceutical composition according to claim claim **1**, wherein the hydrogel-forming polymer is at least one compound selected from the group consisting of polyethylene oxide, hydoxypropyl methylcellulose, and hydroxypropyl cellulose.

6. The pharmaceutical composition according to claim **1**, further comprising an antioxidant.

7. The pharmaceutical composition according to claim 6, wherein the antioxidant is at least one compound selected from the group consisting of butyl hydroxytoluene, propyl gallate, and sodium ascorbate.

8. The pharmaceutical composition according to claim 7, wherein the antioxidant is butyl hydroxytoluene.

9. The pharmaceutical composition according to claim 6, wherein an amount of the antioxidant is 0.025% by weight to 0.25% by weight with respect to a total weight of the pharmaceutical composition.

10. The pharmaceutical composition according to claim 1, further comprising a stabilizer.

11. The pharmaceutical composition according to claim 10, wherein the stabilizer is at least one compound selected from the group consisting of yellow ferric oxide, red ferric oxide, and black iron oxide.

12. The pharmaceutical composition according to claim 11, wherein the stabilizer is yellow ferric oxide and/or red ferric oxide.

13. The pharmaceutical composition according to claim 10, wherein an amount of the stabilizer is 0.05% by weight to 1% by weight with respect to a total weight of the pharmaceutical composition.

14. The pharmaceutical composition according to claim 1, wherein the drug dissolution rate from the pharmaceutical composition is at least 92% after 4.5 hours.

15. The pharmaceutical composition according to claim 1, wherein the average molecular weight of the hydrogel-forming polymer is 100,000 to 2,000,000.

16. The pharmaceutical composition according to claim 1, comprising 10 mg to 200 mg of (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetic acid anilide.

17. A tablet, comprising the pharmaceutical composition according to claim 1.

18. A tablet, comprising the pharmaceutical composition according to claim 16.

19. A method for treating overactive bladder comprising administering the tablet according to claim 17 to a subject in need thereof.

20. A method for treating overactive bladder comprising administering the tablet according to claim 18 to a subject in need thereof.

21. The pharmaceutical composition according to claim 1, wherein the average molecular weight of the hydrogel-forming polymer is 100,000 to 5,000,000.

22. A pharmaceutical composition, comprising 10 mg to 200 mg of (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetic acid anilide, or a pharmaceutically acceptable salt thereof, in a sustained release hydrogel-forming formulation comprising a means for forming a hydrogel and a means for ensuring penetration of water into the pharmaceutical composition,

wherein a drug dissolution rate from the pharmaceutical composition is 39% or less after 1.5 hours, and at least 75% after 7 hours, as measured in accordance with United States Pharmacopoeia in 900 mL of a USP buffer having a pH of 6.8 at a paddle rotation speed of 200 rpm.

23. The pharmaceutical composition according to claim 22, comprising 10 mg to 200 mg of (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl]acetic acid anilide.

24. A tablet, comprising the pharmaceutical composition according to claim 22.

25. A tablet, comprising the pharmaceutical composition according to claim 23.

* * * * *

CERTIFICATE OF SERVICE

The undersigned counsel hereby certifies that true and correct copies of the foregoing document were caused to be served on March 8, 2021 on the following counsel in the manner indicated:

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