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Fujihara

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(54) **PHARMACEUTICAL COMPOSITION**

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C07D 417/00 (2006.01)
C07D 419/00 (2006.01)

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

USPC **514/254.02**; 544/368

(58) **Field of Classification Search**

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See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,600,579 A * 7/1986 Salpekar et al. 514/629
5,532,372 A 7/1996 Saji et al.
2004/0028741 A1 2/2004 Fujihara

FOREIGN PATENT DOCUMENTS

EP 1327440 A1 7/2003
JP 08-325146 A 10/1990
JP 08-325146 12/1996
JP 8-325146 A 12/1996
JP 2000-26292 A 1/2000
WO WO 01/76557 A1 * 10/2001
WO WO 02/24166 A1 3/2002

WO WO-02/24166 A1 3/2002
WO WO 2004/078173 A1 9/2004
WO WO-2004/078173 A1 9/2004

OTHER PUBLICATIONS

Handbook of Pharmaceutical Excipients, 2nd edition, vol. 491, The Pharmaceutical Press, 1994.
Chueshov, V. I., et al., "Manufacturing Technologies of Drugs," Promyshlennaya Tekhnologiya Lekarstv, vol. 2, pp. 10-11 (1999). Russian Official Action.
Makino, T., et al., "Importance of Gelatinization Degree of Starch Past Binder in Hardness and Disintegration Time of Tablets," Chem. Pharm. Bull., vol. 43, No. 3, pp. 514-116 (1995).
EPO Communication dated Feb. 1, 2012, with enclosed Supplemental Search Report, in EPO Appln. 11181100.6.
Kibbe, Handbook of Pharmaceutical Excipients, Chapter 7, pp. 528-530 (2000).
Request for Invalidation from invalidity proceedings in corresponding Chinese Application No. 200680018223.4 (original Chinese version and English-language translation), Aug. 5, 2012.
Bi Dianzhou, Pharmaceuticals, Edition 4, Beijing: People's Medical Publishing House, Feb. 2003.
"Application and Effect of Pregelatinized Starch in Tablets," Chinese Pharmaceutical Information, vol. 16, Issue 7, 2000, published in 2000.
"Use of Pregelatinized Starch in Tablet Manufacturing," Chinese Pharmaceutical Journal, vol. 29, Issue 4, Apr. 1994, published in Apr. 1994.
"Application of the Pregelatinized Starch in Capsules," Chinese Journal of Modern Applied Pharmacy, vol. 8, Issue 1, Feb. 1991, published in Feb. 1991.
"In Vitro Dissolution and Bioavailability of Acyclovir Capsules Formulated with Pregelatinized Starch," Chinese Journal of Pharmaceuticals, 1998, 29(5), published on May 20, 1998.
Dissolution of Drug Solid Preparation, "Factors Influencing Dissolution Rates," Wu Guangchen, Yue Zhiwei, People's Medical Publishing House, published in Oct. 1994.
Reply Brief from invalidity proceedings in corresponding Chinese Application No. 200680018223.4 (original Chinese version and English-language translation), Oct. 25, 2012.
Examination Decision on the Request for Invalidation in corresponding Chinese Application No. 200680018223.4 (original Chinese version and English-language translation), Apr. 26, 2013.

* cited by examiner

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(57) **ABSTRACT**

A preparation for oral administration comprising: a pregelatinized starch comprising N-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-(2R,3R)-2,3-tetramethylene-butyl]-(1'R,2'S,3'R,4'S)-2,3-bicyclo[2,2,1]-heptanedicarboxyimide hydrochloride (lurasidone) represented by the formula (1) as an active ingredient; a water-soluble excipient; and a water-soluble polymeric binder, the preparation exhibiting an invariant level of elution behavior even when the content of its active ingredient is varied.

27 Claims, 3 Drawing Sheets

Figure 1

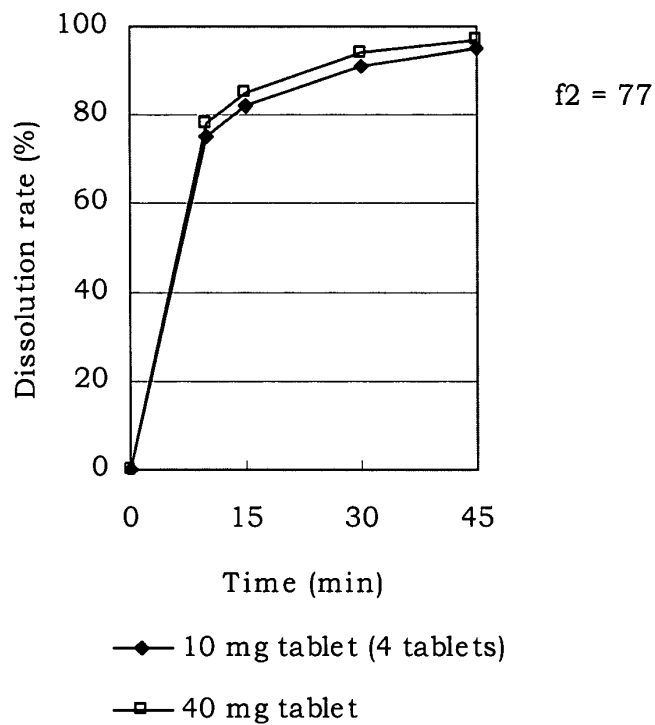


Figure 2

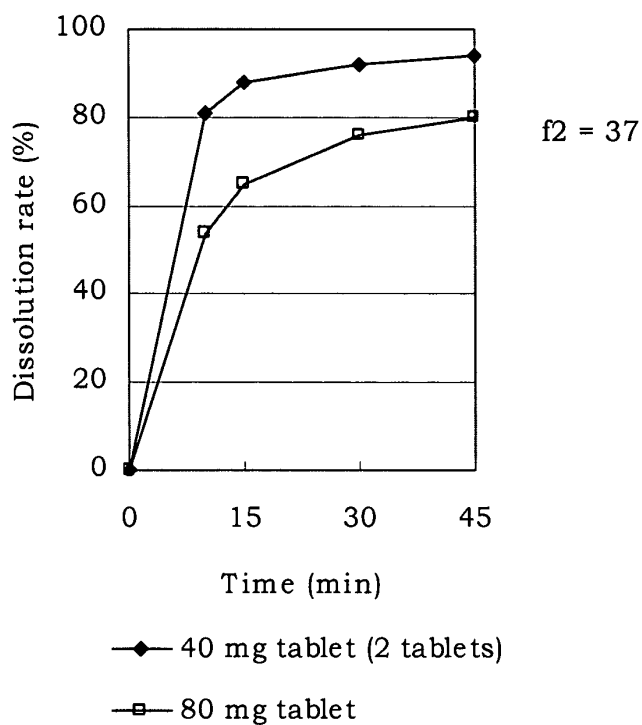
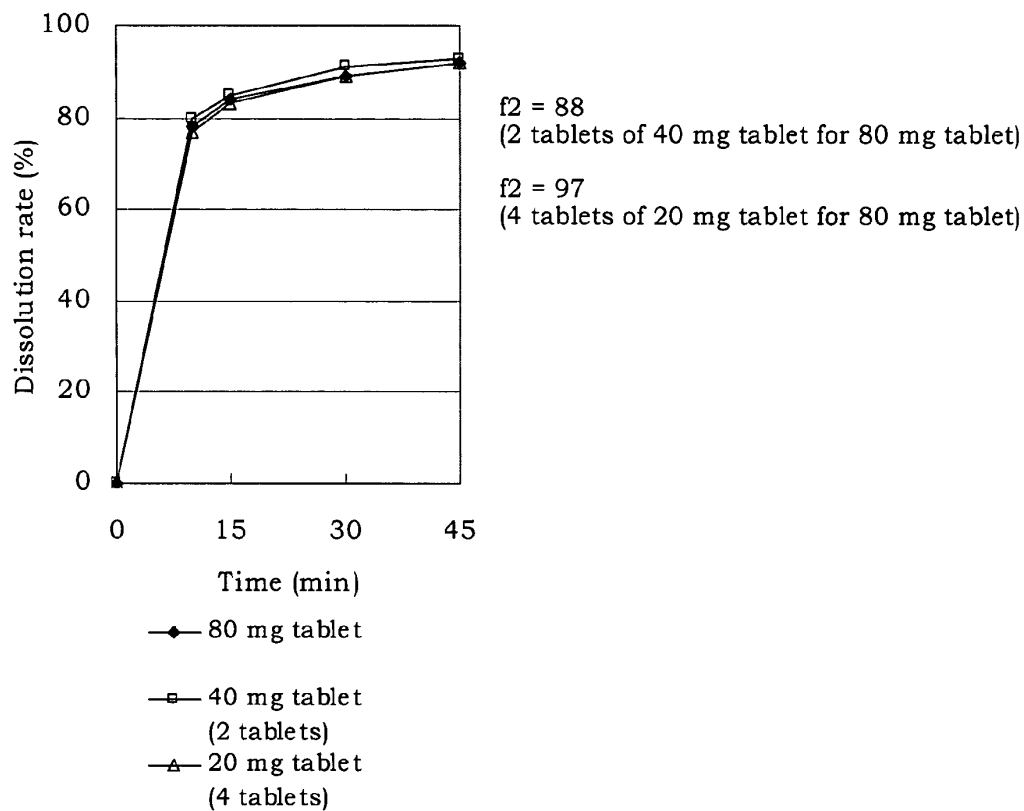


Figure 3



PHARMACEUTICAL COMPOSITION

TECHNICAL FIELD

The present invention relates to an oral preparation with a good disintegration which comprises as an active ingredient N-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperaziny]-(2R,3R)-2,3-tetramethylene-butyl]-(1'R,2'S,3'R,4'S)-2,3-bicyclo[2,2,1]heptanedicarboxyimide hydrochloride (lurasidone). More particularly, the present invention relates to a preparation for oral administration, particularly a tablet, comprising lurasidone as an active ingredient, which has an equivalent dissolution profile of the active ingredient even though contents of the active ingredient therein are varied.

BACKGROUND ART

Patent Document 1 discloses that a compound such as lurasidone can be orally administered and an oral preparation can be prepared by blending an active ingredient with a conventional carrier, excipient, binder, stabilizer and the like, but there is no disclosure of an oral preparation which shows a rapid dissolution and has an equivalent dissolution profile of the active ingredient even though contents of the active ingredient therein are varied in the wide range, particularly an oral preparation with increased contents of the active ingredient which has a similar dissolution profile to that of multiple tablets with a lower content of the active ingredient per tablet.

For the purpose of securing the bioequivalence when pharmaceutical preparations with different contents of the active ingredient were administered so as to be the same dose to each other, a guideline has been issued, i.e., "Guideline for Bioequivalence Studies of Oral Solid Dosage Forms with Different Content" (Notification No. 64 of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, promulgated on Feb. 14, 2000) by which it has been required that pharmaceutical preparations with different contents should have an equivalent dissolution profile in each test solution such as buffers of pH 1.2, 3.0 to 5.0 and 6.8 (which correspond to the pH values of stomach, intestine and oral cavity, respectively), water, and saline.

Patent Document 2 discloses an oral preparation comprising lurasidone as an active ingredient, which shows a rapid dissolution and has an equivalent dissolution profile even though contents of the active ingredient therein are varied, particularly an oral preparation with increased contents of the active ingredient which has an equivalent dissolution profile to that of multiple tablets with a lower content of the active ingredient per tablet and can release a slightly water-soluble active ingredient therefrom at a desired concentration.

Patent Document 2 further discloses an oral preparation, particularly a tablet, which shows a rapid dissolution of the active ingredient even though contents of the active ingredient therein are varied in the range of several mg to several tens of mg (e.g. in the range of 5 mg to 20 mg or in the range of 5 mg to 40 mg), and further has an equivalent dissolution profile in the same componential ratio. An oral preparation has been frequently required to be a preparation with higher contents of the active ingredient in order to get higher clinical effects, or a preparation which has an equivalent dissolution profile to that of multiple tablets and can release the active ingredient therefrom at a desired concentration in wider ranges of contents in order to adjust clinical effects depending on conditions of patients. The art disclosed in Patent Document 2 may provide an oral preparation which has an equivalent dissolution profile in the range of 5 mg to 40 mg of lurasidone per tablet, as shown in FIG. 1. However, as shown in FIG. 2, when the content of the active ingredient per tablet was increased to double, i.e., 80 mg tablet, it could not have an equivalent dissolution profile. Hence, it remains in a state of administer-

ing multiple tablets at one time or using a tablet having a big size which is difficult to administer. Therefore, for such a slightly water-soluble active ingredient as lurasidone, it has been difficult to provide an oral preparation having an equivalent dissolution profile even in high content or in wider ranges of contents of the active ingredient.

In Patent Document 2, a water-soluble polymer binder includes starch, but there is no description about a pregelatinized starch therein. The pregelatinized starch is known to remarkably improve a disintegration and a dissolution of a pharmaceutical composition as described, for example, in Patent Document 3, but it is often used, typically, in 10% or less of contents as also described in Non-patent Document 1. Patent Document 1: JP2800953

Patent Document 2: WO2002/024166

Patent Document 3: JP2000-26292

Non-patent Document 1: Handbook of Pharmaceutical Excipients, 2nd edition, 491, 1994, The Pharmaceutical Press

DISCLOSURE OF INVENTION

Problems To Be Resolved By the Invention

The present invention is directed to provide an oral preparation comprising lurasidone as an active ingredient which shows a rapid dissolution and has an equivalent dissolution profile even though contents of the active ingredient therein are varied in the wide range, particularly an oral preparation with increased contents of the active ingredient which has a similar dissolution profile to that of multiple tablets with a lower content of the active ingredient per tablet and can release the active ingredient therefrom at a desired concentration.

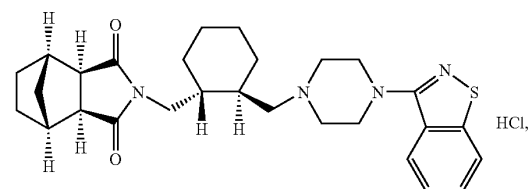
The present invention is directed to provide a preparation for oral administration which comprises as an active ingredient N-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperaziny]-(2R,3R)-2,3-tetramethylene-butyl]-(1'R,2'S,3'R,4'S)-2,3-bicyclo[2,2,1]heptanedicarboxyimide hydrochloride (hereinafter referred to as lurasidone), which has an equivalent dissolution profile of the active ingredient even though contents of the active ingredient therein are varied.

Means of Solving the Problems

The present inventors have intensively studied in order to solve the above problems and found to solve said problems by means of the following methods.

The present invention includes the following embodiments:

- (1) An oral preparation which comprises N-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperaziny]-(2R,3R)-2,3-tetramethylene-butyl]-(1'R,2'S,3'R,4'S)-2,3-bicyclo[2,2,1]heptanedicarboxyimide hydrochloride (lurasidone) of the formula (1):



a pregelatinized starch, a water-soluble excipient and a water-soluble polymer binder.

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