(19) European Patent Office
Office européen des brevets

(11) EP 1 695 699 A1

(12) **EUROPEAN PATENT APPLICATION**
published in accordance with Art. 158(3) EPC

(43) Date of publication:
30.08.2006 Bulletin 2006/35

(21) Application number: **04820201.4**

(22) Date of filing: **07.12.2004**

(51) Int Cl.:
A61K 9/20 *(2006.01)* ***A61K 47/38*** *(2006.01)*
A61K 9/14 *(2006.01)* ***A61K 47/10*** *(2006.01)*
A61K 31/5375 *(2006.01)*

(86) International application number:
PCT/JP2004/018204

(87) International publication number:
WO 2005/055989 (23.06.2005 Gazette 2005/25)

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LI LT LU MC NL PL PT RO SE SI SK TR

(30) Priority: **09.12.2003 JP 2003410961**

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(54) **DRUG-CONTAINING GRAINS AND SOLID PREPARATION CONTAINING THE GRAINS**

(57) The invention provides a medicament-containing particle wherein an unpleasant taste of the medicament is alleviated, which is obtainable by mixing and granulating the following ingredients: (1) the medicament with an unpleasant taste, (2) methylcellulose and (3)mannitol; and a solid preparation including the particle. The invention can make an unpleasant taste of the medicament alleviated and furthermore when the formulation including the particle is administered, the unpleasant taste can be masked and the formulation has a good dissolvability in gastrointestinal tract.

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Description

TECHNICAL FIELD

[0001] The present invention relates to a medicament-containing particle and a solid preparation containing the particle. More particularly, it relates to a medicament-containing particle wherein an unpleasant taste of the medicament having the unpleasant taste is alleviated in buccal cavity, and "a solid preparation containing the particle" which does not substantially induce an unpleasant taste of the medicament and has a good dissolvability in gastrointestinal tract.

BACKGROUND ART

[0002] A lot of medicaments contained in pharmaceutical products induce an unpleasant taste such as bitter taste, astringent taste and pungent taste when the pharmaceutical product is orally administered. In case that a medicament has such an unpleasant taste, it is very difficult for a patient to take a pharmaceutical product containing the medicament. A big problem to be solved for the preparation thereof is how to mask such an unpleasant taste of the medicament in the preparation. In order to solve this problem, i.e. in order to mask the unpleasant taste of the medicament when the medicament is orally administered, a sweater or a flavor has hitherto usually been used as an additive, but sometimes an increased amount of the sweater is required to fully mask a bitter taste. Alternatively, a coating of a medicament or a medicament-containing granule, and so on has been applied with a water-insoluble polymer base such as ethyl cellulose. With respect to this method, however, in order to more effectively depress an unpleasant taste of the medicament, it is necessary to coat it in more coating amount. As a result, the coating may affect a releasing amount of the medicament transferred into gastrointestinal tract and the desired release of the medicament can not be obtained, which is another problem.

[0003] For example, in case of an intrabuccally rapidly disintegrating tablet, it has been desired to produce a tablet having good disintegrability in buccal cavity and good dissolubility in gastrointestinal tract. However, when the intrabuccally rapidly disintegrating tablet contains a medicament having an unpleasant taste, it is difficult to simultaneously satisfy above the two conditions of rapid disintegrability in buccal cavity and alleviation of an unpleasant taste in buccal cavity because these conditions are inconsistent to each other, and it is furthermore difficult to simultaneously satisfy the condition of alleviating an unpleasant taste in buccal cavity and the condition of good dissolubility in gastrointestinal tract, because these conditions are also inconsistent to each other. Furthermore, it is also difficult to simultaneously satisfy all these conditions mentioned above.

[0004] The present inventors have studied for obtaining the desired preparation, and during which they have given in attention to previously granulate the medicament with the other ingredients and further to use a water-soluble polymer in the granulating procedure. It is already known that a particle (or granule) obtained by granulating a medicament is formulated into a drug preparation, for example, WO 2002/002083 discloses "a quick disintegrating tablet in buccal cavity, said quick disintegrating tablet comprising: spray-dried drug-containing particles, wherein each particle comprises a bitter tasting drug and/or a drug of inferior fluidity and a pharmaceutical preparation carrier, wherein each particle has a mean diameter of approximately 50 μm to approximately 250 μm and an apparent specific gravity of approximately 0.5 to approximately 1.2, and a saccharide." The pharmaceutical preparation carrier in this reference includes water-insoluble polymers, gastrosoluble polymers, enterosoluble polymers, wax-like substances and saccharides as an example, in detail, the reference discloses a working example using a water-insoluble polymer. Thus it is disclosed in the patent gazette that such "a particle-form containing a medicament" which includes a water-insoluble polymer such as ethylcellulose may make a bitter thereof masked. In addition, it is disclosed in the patent gazette as "the fluidity of a drug that is not bitter tasting can be improved by the present invention, and in this case, the above-mentioned polymer substances, such as water-insoluble polymer, gastrosoluble polymer, enterosoluble polymer, etc., and wax-like substances, etc., a water soluble polymer, saccharide, etc., can be used as the above-mentioned carrier. Examples of the water-soluble polymers as the carrier are hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyvinyl pyrrolidone, polyvinyl alcohol, etc." Thus, this publication suggests that even if a medicament-containing particle which includes the medicament with a bitter taste and a water-soluble polymer is produced, the bitter taste thereof cannot be masked.

[0005] In addition, JP-A-2001-039861 discloses, for example, "a tablet obtained by mixing (1)(a) a granule in which a medicament is included in a water-soluble polymer matrix or a wax matrix and/or (b) a granule prepared by coating a medicament-containing granule with a water-soluble polymer or a water-insoluble polymer film, with (2) an excipient, (3) adding a solvent thereto, kneading the resultant mixture, and (4) placing the kneaded mixture in a mold, and then molding the kneaded mixture to form a tablet." In the reference, hydroxypropyl cellulose, hydroxypropylmethylcellulose, methylcellulose, sodium carboxymethylcellulose, and polyvinylpyrrolidone, polyvinyl alcohol are exemplified as a water-soluble polymer. However, the granule mentioned in patent the gazette has a feature that a medicament can be gradually released in water or in gastrointestinal tract. Accordingly, the problem of the reference is contrary to that of the present invention.

[0006] In addition, WO 2000/024379 discloses a preparation method of drug-containing spherical fine particles that are useful in the production of easily-swallowed, controlled-release preparations. In detail, it discloses that "a preparation method of drug-containing spherical fine particles having a mean particle size of 200 μm or less comprising: adding a binder solution to a mixture containing an excipient powder having the property of retaining a solvent and a drug powder, and granulating by high-speed mixing." In the reference, celluloses such as microcrystalline cellulose, methylcellulose, carmellose sodium, carmellose calcium, and low-substituted hydroxypropyl cellulose, and various starches are exemplified as an excipient having the property of retaining a solvent. However, the patent gazette discloses neither any masking of a bitter taste of a medicament nor any combination of a medicament having an unpleasant taste, methylcellulose and mannitol as in the present invention mentioned hereinafter.

[0007] In addition, JP-A-2000-191518 discloses that "a method for preparing an intrabuccally quickly disintegrating tablet, which comprises dissolving a difficultly soluble pharmaceutical agent together with a surfactant and/or a water-soluble polymer in an organic solvent or an water-containing organic solvent, coating an excipient with the solution or granulating the excipient with the solution to obtain molded products, mixing a saccharide with them, adding an organic solvent, water or an water-containing organic solvent thereto, followed by kneading, and subjecting it to a compression-molding." However, the patent gazette discloses the improvement of dissolubility of a difficultly soluble medicament, but does not disclose a masking of a bitter taste. Additionally, the example section discloses examples only using surfactants, but does not disclose any example using a water-soluble polymer. Furthermore, the patent gazette does not disclose anything about a combination of a medicament with an unpleasant taste, methylcellulose and mannitol as the present invention discloses.

DISCLOSURE OF INVENTION

(Problem to be solved by the invention)

[0008] As mentioned above, with regard to a solid preparation containing a medicament with an unpleasant taste, it had been difficult to mask an unpleasant taste of a medicament and carry out a rapid dissolution in gastrointestinal tract by now.

(Means to solve the problem)

[0009] Under such situation, the present inventors have found that a bitter taste of a medicament in buccal cavity could be alleviated by preparing a medicament-containing particle with methylcellulose which has been used as a conventional base for sustained release or for coating among various water-soluble polymers and a specific sugar alcohol, and furthermore that a rapid dissolution in gastrointestinal tract and a masking of an unpleasant taste could simultaneously be carried out when taking a preparation containing the particle; thereby they have succeeded in resolving the above problem, then have accomplished the present invention. Furthermore, with regard to an intrabuccally rapidly disintegrating preparation, they have found that the present invention make the drug preparation intrabuccally rapidly integrated and also make a bitter taste of the intrabuccal medicament alleviated.

[0010] The present invention provides various embodiments of the invention as mentioned below.

[1] A medicament-containing particle wherein an unpleasant taste of the medicament is alleviated, which is obtainable by mixing and granulating the following ingredients:

(1) the medicament with an unpleasant taste,
(2) methylcellulose, and
(3) mannitol.

[2] The medicament-containing particle according to the above [1] wherein the amount of the methylcellulose is about 0.05 to about 10 parts by weight per 1 part by weight of the medicament with an unpleasant taste.
[3] The medicament-containing particle according to the above [1] wherein the amount of the methylcellulose is about 0.15 to about 7 parts by weight per 1 part by weight of the medicament with an unpleasant taste.
[4] The medicament-containing particle according to the above [1] wherein the amount of the methylcellulose is about 0.8 to about 5 parts by weight per 1 part by weight of the medicament with an unpleasant taste.
[5] The medicament-containing particle according to any one of the above [1] - [4] wherein the amount of the mannitol is about 0.3 to about 50 parts by weight per 1 part by weight of the methylcellulose.
[6] The medicament-containing particle according to any one of the above [1] - [4] wherein the amount of the mannitol is about 0.5 to about 12 parts by weight per 1 part by weight of the methylcellulose.
[7] The medicament-containing particle according to any one of the above [1] - [4] wherein the amount of the mannitol

is about 0.7 to about 7.5 parts by weight per 1 part by weight of the methylcellulose.

[8] The medicament-containing particle according to any one of the above [1] - [7] wherein the mannitol is D-mannitol.

[9] The medicament-containing particle according to any one of the above [1] - [8] wherein the medicament with an unpleasant taste is 4-amino-5-chloro-2-ethoxy-N-[[4-(4-fluorobenzyl)-2-morpholinyl]methyl]benzamide or a pharmaceutically acceptable salt thereof.

[10] The medicament-containing particle according to the above [1], which is obtainable by mixing and granulating the following ingredients:

(1) (±)-4-amino-5-chloro-2-ethoxy-N-[[4-(4-fluorobenzyl)-2-morpholinyl]methyl]benzamide citrate dihydrate as a medicament,
(2) methylcellulose, and
(3) D-mannitol, wherein the amount of the methylcellulose is about 0.15 to about 7 parts by weight per 1 part by weight of (±)-4-amino-5-chloro-2-ethoxy-N-[[4-(4-fluorobenzyl)-2-morpholinyl]methyl]benzamide citrate, and the amount of the D-mannitol is about 0.5 to about 12 parts by weight per 1 part by weight of the methylcellulose.

[11] A solid preparation comprising the medicament-containing particle set forth in any one of the above [1] - [10] and other ingredients for pharmaceutical preparation.

[12] The solid preparation according to the above [11] which is a tablet-like preparation or a granule-like preparation.

[13] The solid preparation according to the above [12] wherein the tablet-like preparation is in the form of a tablet or a pill.

[14] The solid preparation according to the above [12] wherein the granule-like preparation is in the form of a granule, a fine granule or a powder.

[15] The solid preparation according to any one of the above [11] - [14] which is an intrabuccally rapidly disintegrating preparation.

[16] The solid preparation according to the above [15] wherein the intrabuccally rapidly disintegrating preparation is in the form of a tablet.

[17] The solid preparation according to the above [15] wherein the intrabuccally rapidly disintegrating preparation is a granule-like preparation.

[18] The intrabuccally rapidly disintegrating preparation set forth in any one of the above [15] - [17] which is characterized by the following properties:

(i) disintegrating within 40 seconds on a tongue of a healthy adult with his mouth closed and without chewing,
(ii) dissolving at a substantial dissolution rate of 85% or more after 15 minutes according to the dissolution test described in the Japanese Pharmacopoeia XIV [using Method 2 (50 rpm) for tablets or Method 1 (50 rpm) for granule-like preparation, resolution medium : 900 mL of water], and
(iii) not substantially feeling an unpleasant taste on setting the preparation in buccal cavity.

[19] A composition for preparing the intrabuccally rapidly disintegrating preparation set forth in the above [15], which comprises
a medicament-containing particle wherein an unpleasant taste of the medicament is alleviated, which is obtainable by mixing and granulating the medicament with an unpleasant taste, methylcellulose and mannitol;
an excipient; and
a disintegrator.

[20] A process for preparing a medicament-containing particle wherein an unpleasant taste of the medicament is alleviated, which is obtainable by mixing (1) the medicament with an unpleasant taste, (2) methylcellulose and (3) mannitol, and granulating the mixture with water or a water-containing solvent.

[21] A commercial package which comprises the solid preparation set forth in the above [11] comprising 4-amino-5-chloro-2-ethoxy-N-[[4-(4-fluorobenzyl)-2-morpholinyl]-methyl]benzamide or a pharmaceutically acceptable salt thereof as a medicament with an unpleasant taste; and a written matter as to the solid preparation, including a description on the outside of the package or the written matter inside the package which intends that the solid preparation can/should be used for promoting gastrointestinal motility, improving postgastrectomy condition, or preventing/treating gastroesophageal reflux disease (GERD).

BRIEF DESCRIPTION OF DRAWINGS

[0011] Fig 1 shows results of the dissolution test using each tablet in Example 1 and Comparative Example 1.

[0012] The "average particle size" used in the present claims and specification, unless otherwise indicated, is denoted as a value measured, for example, by means of a laser diffraction particle size analyzer (HELOS & RODOS) (SYMPATEC Inc.).

[0013] The "per 1 part by weight of the medicament" used in the present claims and specification is based on a form of "pharmaceutically active ingredient" which is generally used in pharmaceutical field. Regarding a medicament as a salt form, it is based on 1 part by weight of the salt thereof. However, when a medicament has crystal water, it is the residual amount by subtracting the amount of crystal water therefrom.

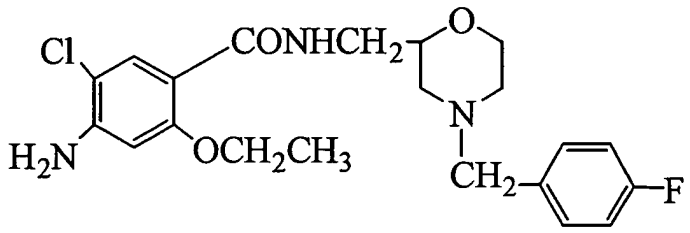
[0014] The medicament-containing particle of the invention is essentially a medicament-containing particle wherein an unpleasant taste of the medicament is alleviated, which is obtainable by mixing and granulating the following ingredients:

(1) the medicament with an unpleasant taste,
(2) methylcellulose, and
(3) mannitol; and each of the ingredients is explained as follows.

(1) A medicament with an unpleasant taste

[0015] There are no special restriction to the "medicament with an unpleasant taste" used in the present invention as long as it is a one that is used for treating or preventing a disease as a pharmaceutically active ingredient, and it is a one with an unpleasant taste such as bitter taste, astringent taste and pungent taste. The medicaments include antipyretic-analgesic-antiinflammatory drugs, quinolone antibacterial agents, antibiotics, antitumor agents, gastrointestinal agents, antidiarrheals, antidepressants, antiepileptics, antihypertensives and so on. The examples of the medicaments include mosapride citrate shown below, quinine sulfate, morphine sulfate, morphine hydrochloride, caffeine, ethenzamide, codeine phosphate, dihydrocodeine phosphate, berberine chloride, acrinol, zonisamide, loperamide hydrochloride, gatifloxacin, sparfloxacin, alacepril, clarithromycin and so on. As mentioned above, the medicament may be in the form of a salt-free or a salt. Additionally it may be in the form of a hydrate.

[0016] Especially, the preferable medicament with an unpleasant taste which is adapted for the present invention is 4-amino-5-chloro-2-ethoxy-N-[[4-(4-fluorobenzyl)-2-morpholinyl]methyl]benzamide or a pharmaceutically acceptable salt thereof, which is shown in the following formula. The compound (or the acid addition salt or the hydrate thereof) is a selective agonist of serotonin 4 receptor, which can exhibit an acceptable effect promoting gastrointestinal motility (US 4,870,074). The compound can be prepared according to, for example, the method described in US 4,870,074 or a modified method thereof. In addition, the compound is also useful as a medicament for treating gastroesophageal reflux disease, postgastrectomy syndrome, or the other gastrointestinal symptom.



[0017] The citrate·dihydrate of the above racemic mixture (hereinafter, occasionally referred to as "mosapride") have already been practically used for improving gastrointestinal symptom accompanied with chronic gastritis, and tablets containing 2.5 mg or 5 mg of mosapride citrate (anhydride) (1.72 mg or 3.44 mg of mosapride) have been marketed under the trade name "Gasmotin" in Japan. These tablets are sold as a film-coating tablet since mosapride is a bitter medicament.

[0018] As another solid preparation containing mosapride; US 4,870,074 discloses a solid preparation containing mosapride citrate, corn starch, lactose, crystalline cellulose, hydroxypropyl cellulose, light anhydrous silicic acid and magnesium stearate in Example 245.

[0019] In addition, WO 2004/066913 discloses a solid preparation (except orally disintegrating tablets) free of film coating, which is substantially free of light anhydrous silicic acid and which comprises mosapride or a salt thereof.

[0020] On the other hand, as an intrabuccally rapidly disintegrating tablet containing mosapride citrate, JP-A-1999-349475 discloses a process for preparing an intrabuccally rapidly disintegrating tablet containing mosapride citrate

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