REYES & REYES
A B O G A D O S

SEÑOR
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
E. S. D.

REF: **Expediente 12-162-306**

TÍTULO SOLICITADO: **COMPOSICIÓN DE ENCAPSULAMIENTO DE LIBERACIÓN RÁPIDA.**

PUBLICACIÓN: **Gaceta 663 de 01/03/2013, Nº de publicación 89**

PRIORIDAD: **US 61/306,744 de 22/02/2010**

SOLICITANTE: **GELITA AG**

APODERADO: **LUZ CLEMENCIA DE PAEZ.**

TRÁMITE: **SUSTENTACION DE OPOSICIÓN**

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **TECNOQUÍMICAS S.A.**,dentro del trámite de la referencia, en ejercicio de lo dispuesto por el artículo 42 inciso 2º de la Decisión 486 de 2000, por medio del presente escrito, procedo a sustentar y complementar la oposición presentada el 11 de marzo de 2013, en los siguientes términos:

I. RATIFICACIÓN

Comedidamente me permito insistir en los argumentos planteados en la oposición respectiva, los cuales, como se dijo en su momento, demuestran que la solicitud de la referencia incumple los requisitos de patentabilidad establecidos por los artículos 14 y 18 de la Decisión 486 de 2000, y que por ello no merece recibir el beneficio patentario.

- En primera instancia, recordaremos que habíamos objetado ciertas reivindicaciones como la 2, 5 – 8, 12 – 18, 20, 24 – 25, 27 – 31, 35 – 37, 49 – 54, ya que al referirse específicamente a pesos moleculares, proporciones, solubilidades, velocidades de disolución, u otras especificaciones del producto terminado, no tienen por sí mismos naturaleza inventiva ya que corresponden a simples resultados a obtener.

- En segundo lugar, enfocándonos en el análisis de requerimientos de patentabilidad para la solicitud colombiana en trámite, habíamos corroborado que la solicitud no es nueva, pues un único documento seleccionado dentro de la amplia literatura encontrada en el estado del arte, la publicación americana US 4,681,765, revela una composición **encapsulada de liberación rápida**, la cual comprende un agente de liberación rápida insoluble en agua (**carbonato de calcio**) como desintegrante y un componente de **gelatina.** Por esta razón se concluye que la solicitud no es nueva, dado que contiene todas las características técnicas esenciales de la reivindicación 1 de la solicitud colombiana en trámite.

- Por último, se había mencionado un segundo documento, la publicación americana **US 2008/0275140 "Process for making a low molecular weight gelatine hydrolysate and gelatine hydrolysate compositions**", que revela composiciones de gelatina hidrolizada en cápsula y explica como procesar tal componente de gelatina para mejorar las propiedades de disolución.

- Las **cápsulas** de **gelatina** del arte previo, pueden ser elaboradas con **plastificantes tales como sorbitol y glicerol** y adicionalmente pueden contener agua cuyos porcentajes pueden variar de acuerdo a las necesidades.

- Dicha anterioridad había solucionado el problema el problema técnico al enseñar que la gelatina era usada en la industria farmacéutica para la manufactura de composiciones en cápsulas de gelatina tanto duras como blandas.

- Por lo tanto mediante un segundo documento reiteramos que la solicitud carece totalmente de todo indicio de novedad dado que se evidencian

composiciones de liberación rápida con gelatina y un hidrolizado de gelatina, tal como se presenta la reivindicación 2, incluso con los mismos pesos moleculares elegidos por la solicitud en trámite.

De aquí que, según lo previamente enseñado en el estado de la técnica, podemos evidenciar que la reivindicación independiente (1) y sus dependientes no cumplen con los requisitos de patentabilidad, ya que las composiciones sugeridas allí no son nuevas y por lo tanto tampoco son inventivas, más aún, cuando ya se sabía cómo resolver el mismo problema técnico propuesto por la solicitud colombiana CO 12-162-306, con la misma ventaja técnica.

II. COMPLEMENTO DE INFORMACIÓN.

Por si no fuesen suficientes los argumentos planteados en la oposición, nos permitimos someter a consideración del Despacho los siguientes:

- Enfatizamos en el hecho de que al encontrarse todas las características técnicas esenciales en un solo documento, tal como lo es el US, 4,681,765, la solicitud colombiana no cumple con el requisito de patentabilidad de novedad, además, dado que es bien sabido por el experto medianamente versado en la materia que el carbonato de calcio es esencialmente insoluble a rangos de pH de 6 a 8 y se disocia a rangos de pH de 0 a 3 y ya que la composición se degrada igualmente a rangos de pH de 0 a 3 en menos de 15 minutos, necesariamente la composición reivindicada se comportará de la misma manera, pues las propiedades de los compuestos químicos no varían cuando se incluyen en un producto o en otro, es decir, necesariamente se comportarán igual, con mayor razón cuando nos referimos a composiciones que tienen en común los mismos componentes.

- Como si fuera poco, encontramos un tercer documento: la publicación japonesa **JP 02022221 publicada en 1990 titulada "CAPSULE HAVING IMPROVED LUBRICATING PROPERTY DISINTEGRATIN PROPERTY"** que sugiere que las cápsulas de gelatina con carbonato de calcio y gelatina proveen unas propiedades de lubricación excelentes y rápida disolución con

varios rangos de peso, lo cual hace obvia la presente solicitud de patente, por lo cual, uniendo el documento en mención con la publicación americana US 2008/0275140 habría una gran expectativa de éxito ya que ambos enseñan formulaciones de cápsulas en gelatina.

ABSTRACT:

PURPOSE: To obtain capsules having excellent adhesion preventing effects, lubricating properties and disintegrating properties by blending gelatin with a calcium salt or a natural calcium agent consisting essentially of the calcium salt.

CONSTITUTION: **Gelatin** is blended with ≥10wt.%, preferably 40-60wt.% calcium salt such as **calcium carbonate**, calcium hydrogenphosphate, calcium lactate, calcium gluconate or a natural calcium agent such as eggshell, bovine bone powder or shell consisting essentially of the calcium salt to give **capsules** having excellent lubricating properties. When **calcium carbonate** is used as the calcium salt, **calcium carbonate** evolves a carbon dioxide gas under an acidic condition in the stomach and soft **capsules of gelatin** are rapidly and surely destroyed.

Esta anterioridad es un ejemplo más de que la solución al problema técnico propuesto por **la solicitud colombiana en trámite estaba resuelto previamente** en el estado de la técnica, ya que el tipo de composición de encapsulamiento de gelatina y sus componentes eran conocidos y estaba ampliamente establecida su finalidad en la técnica.

- Por si fuera poco en el estado de la técnica se encuentra aún mas literatura en donde se evidencia que utilizan proteínas tales como las gelatinas en composiciones farmacéuticas orales junto con polímeros, la publicación americana **US 2003/017222** del 23 de enero de 2003 y titulada **"BITTERNESS- REDUCE ORAL PHARMACEUTICAL COMPOSITION"** revela:

FIELD OF THE INVENTION

[0001] This invention relates to an oral pharmaceutical composition in which bitterness of a drug having a bitter taste is reduced. Particularly, it relates to a bitterness-reduced oral pharmaceutical composition, which comprises one or more drugs having a bitter taste, one or more solid proteins, and one or more pharmaceutically acceptable water-insoluble polymer bases, wherein the proteins are present in the polymer bases particularly as particles.

Como puede apreciarse, nos encontramos ante un documento adicional que enseña composiciones farmacéuticas orales, utilizadas en este caso para enmascarar el sabor, pero cuyas formulaciones comprenden una o varias proteínas solidas tales como la gelatina, en forma de cápsula y además con polímeros hidroinsolubles tal como la presente solicitud colombiana en trámite, de tal forma que sin perjuicio de la evidente carencia de novedad de la reivindicación independiente comprobada mediante los dos primeros documentos mostrados en la oposición, **US 4,681,765** y **US 2008/0275140**, nos encontramos ante la evidencia de dos (2) documentos más que enseñan cómo llevar a cabo la misma materia reivindicada y la solución al problema técnico, ellos son: **JP 020222** y la presente publicación americana **US 2003/0017222** y que combinados entre sí evidencian también la carencia de nivel inventivo.

[0047] The "solid protein" to be used in the present invention is not particularly limited with the proviso that it is a solid protein which is pharmaceutically acceptable and can attain the object of the invention by employing the constitution of the present invention, and its illustrative examples include bean proteins or processed products thereof, such as soybean protein or a processed soybean protein product and pea protein or a processed pea protein product, milk proteins or processed products thereof, such as casein, casein sodium, processed milk protein products and lactalbumin, egg proteins or processed products thereof, such as egg albumin, and gelatin, of which soybean protein, a processed soybean protein product and gelatin is preferred. These can be easily obtained as commercial products such as CP-GGG (Nitta Gelatin), Ajipron S3 (Ajinomoto), Ajipron SP1 (Ajinomoto) and Q-Lacto No. 5 (Q.P.).

[0058] When the composition of the present invention is made into a pharmaceutical preparation, its dosage form is not particularly limited and various dosage forms generally used as medicaments can be selected. The composition of the present invention can be applied to any bitter drug and exerts particularly useful effects on a drug having a difficulty in preparing a medicament due to its bitterness, particularly on a drug having a markedly low threshold value. For example, it is a preferred embodiment to make the composition of the present invention into oral solid preparations such as granules, or dry syrups, capsules, tablets, troches or chewable tablets in which the granules are contained by a known method. In obtaining the pharmaceutical preparations, known methods generally used in this field can be used optionally, and one and/or two or more of conventionally used additives can be used by optionally combining them. Examples of such additives include binders, disintegrating agents, thickeners, fillers, lubricants, correctives and aromatics.

Por todo lo anterior, ruego se analicen los argumentos expuestos con el rigor y detenimiento habituales y que en consecuencia se decrete, además de la negación de la solicitud en comento, el archivo del expediente que la contiene.

III. ANEXOS

- La publicación japonesa **JP 020222** publicada el 25 de enero de 1990, titulada "Capsule having improved lubricating property disintegrating property" Abstract.
- La publicación americana **US 2003/0017222** publicada el 23 de enero de 2003 y titulada "Bitterness – reduced oral pharmaceutical composition" abstract, pág 1, 3 y 4.

Señor Superintendente,

JOSE LUIS REYES VILLAMIZAR
C.C. 79.152.473 de Usaquén
T.P. 44655 del C. S de la J.

D3 abstract1.jpg

7

PAT-NO: JP402022221A

DOCUMENT-IDENTIFIER: **JP 02022221 A**

TITLE: CAPSULE HAVING IMPROVED LUBRICATING PROPERTY AND DISINTEGRATING PROPERTY

PUBN-DATE: January 25, 1990

INVENTOR-INFORMATION:
NAME
MIURA, TETSUO
WATANABE, TAKAYUKI
SATO, ISAO
KONDO, TAKASHI

ASSIGNEE-INFORMATION:

NAME	COUNTRY
FUJI KAPUSERU KK	N/A

APPL-NO: JP63172056

APPL-DATE: July 11, 1988

INT-CL (IPC): A61K009/48, A61K047/02

ABSTRACT:

PURPOSE: To obtain capsules having excellent adhesion preventing effects, lubricating properties and disintegrating properties by blending gelatin with a calcium salt or a natural calcium agent consisting essentially of the calcium salt.

CONSTITUTION: **Gelatin** is blended with ≥10wt.%, preferably 40-60wt.% calcium salt such as **calcium carbonate**, calcium hydrogenphosphate, calcium lactate, calcium gluconate or a natural calcium agent such as eggshell, bovine bone powder or shell consisting essentially of the calcium salt to

give
capsules having excellent lubricating properties. When **calcium carbonate** is
used as the calcium salt, **calcium carbonate** evolves a carbon dioxide gas under
an acidic condition in the stomach and soft **capsules of gelatin** are rapidly and
surely destroyed.

BITTERNESS-REDUCED ORAL PHARMACEUTICAL COMPOSITION

FIELD OF THE INVENTION

[0001] This invention relates to an oral pharmaceutical composition in which bitterness of a drug having a bitter taste is reduced. Particularly, it relates to a bitterness-reduced oral pharmaceutical composition, which comprises one or more drugs having a bitter taste, one or more solid proteins and one or more pharmaceutically acceptable water-insoluble polymer bases, wherein the proteins are present in the polymer bases particularly as particles.

BACKGROUND OF THE INVENTION

[0002] Intrabuccally quick disintegrating tablets can be easily taken even by patients having a difficulty in swallowing. Since a drug having strong bitterness has a low bitterness-feeling concentration, so-called a threshold value, one feels bitterness when the drug is remained in a trace amount in the mouth. Accordingly, when a drug having strong bitterness is applied to intrabuccally quick disintegrating tablets, they cannot be taken easily because the period of time to feel bitterness in the mouth becomes apparently longer than the case of drugs having less bitterness. In addition, intrabuccally quick disintegrating tablets are regarded in most cases as a dosage form in which the taking ability of conventional tablets already on the market is improved. Thus, insurance of bioavailability after made into intrabuccally quick disintegrating tablets is an item naturally required to guarantee their quality. Virtually nothing is known about bitterness-reducing techniques for solving these problems by simultaneously achieving conflicting items, namely the control of excellent drug release in the mouth and the insurance of excellent drug release in the digestive tract, and further enabling application to intrabuccally quick disintegrating tablets.

[0003] It is well known that capsules are prepared by filling gelatin capsules with, e.g., a bitter drug and a filler as a preparation technique for masking bitterness of the bitter drug. However, since capsules are regarded as a dosage form which cannot be taken easily by patients having weak swallowing ability, particularly by old persons and babies, and when the current situation for the improvement of compliance is taken into consideration, selection of a bitterness controlling technique by capsules cannot always be said effective. Concern has been directed toward the development of a technique for controlling bitterness by a preparation designing of a drug itself or a preparation designing of a form containing the drug.

[0004] The current method frequently and generally used as a technique for controlling bitterness by a preparation designing is a method to coat granules or powders containing a bitter drug or a bitter drug itself making use of a pH-independent water-insoluble polymer base such as ethyl cellulose. In this method, it is intended to control release of a drug in the mouth to a minimum drug concentration human can feel its bitterness, namely threshold value or less, so that a drug having lower threshold value (a drug having stronger bitterness) requires larger coating amount to control releasing amount of the drug at a lower level. Thus, in the general coating method which uses a pH-independent water-insoluble polymer base, when taste of a bitter drug, particularly a bitter drug having low threshold value, in the mouth is controlled, namely when the drug release at an early stage is controlled, or when the controlling time is prolonged, it exerts influence also upon releasing amount of the drug when transferred into the digestive tract so that sufficient drug release cannot be obtained.

[0005] In addition, JP-A-2000-327561 (the term "JP-A" as used herein means an published Japanese patent application) discloses an invention regarding a granulating composition which is characterized in that a physiologically active component is dispersed in a gelatin gel. Particularly, its "Detailed Description of the Invention" describes that, when a physiologically active component having an unpleasant taste is dispersed as a powder form in an aqueous solution in which gelatin is dissolved and then the gelatin solution is gelled, e.g., by spraying and cooling the dispersion, powder form of the component is dispersed in the gelatin gel so that it renders possible production of a granulating composition in the form of granules in which the unpleasant taste (e.g., bitterness, sourness or astringency) of the component having unpleasant taste is effectively masked.

[0006] In general, an advantage of the use of gelatin as a coating base or matrix base in a pharmaceutical preparation is that the thus obtained preparation is quickly dissolved after its administration, but sufficient drug release control cannot be obtained in most cases due to the high solubility of gelatin. In fact, as is evident from the test data of Table 1 of the specification, drug release control by the technique is limited to 3 to 5 minutes, further drug release control in the mouth cannot be expected from the technical idea that gelatin is used and a granulating composition is produced by dispersing a bitter drug in its gel. Particularly, when application to a drug having considerably low threshold value and application to a dosage form such as intrabuccally quick disintegrating tablets in which a drug is retained in the mouth are taken into consideration, it is considered that a release control of 5 to 10 minutes is necessary so that there is room for further improvement.

[0007] Accordingly, the object of the present invention is to provide a bitterness-reduced oral pharmaceutical composition which has excellent drug release-controlling ability in the mouth even 5 to 10 minutes after its administration and excellent drug release ability in the digestive tract and can be applied to intrabuccally quick disintegrating tablets without using capsules.

DISCLOSURE OF THE INVENTION

[0008] In the case of coating which uses, e.g., a polymer base, a method in which coating is carried out by preparing a coating solution by dissolving all components is generally used, and control of the desired drug release is achieved by the coating amount and ratio of the components. For example, it is possible to delay or quicken the release by mixing a water-insoluble polymer base with a water-soluble polymer base and changing their ratio, or to delay or quicken the release by changing the coating amount. However, when drug release is controlled to control bitterness in the mouth, it exerts influence upon releasing amount of the drug when transferred into the digestive tract so that sufficient drug release cannot be obtained.

[0009] Under such circumstances, the present inventors have hit upon an idea on a use mode for effectively bringing

granulated product prepared by using saccharides having low moldability spraying saccharides having high moldability as a binder, thereby effecting at least one of coating and granulating,

[0032] 9. the intrabuccally quick disintegrating tablet according to the item 8, wherein the production process contains humidification and drying steps,

[0033] 10. the intrabuccally quick disintegrating tablet according to the item 9, wherein the saccharides having low moldability are one or more saccharides selected from lactose, mannitol, glucose, sucrose, xylitol and erythritol,

[0034] 11. the intrabuccally quick disintegrating tablet according to the item 9, wherein the saccharides having high moldability are one or more saccharides selected from maltose, maltitol, sorbitol and trehalose,

[0035] 12. the oral pharmaceutical preparation, wherein it is prepared by coating core granules containing one or more drugs having a bitter taste with a coating solution containing one or more solid proteins or thermally denatured products thereof and one or more pharmaceutically acceptable water-insoluble polymer bases, and subsequently drying the granules,

[0036] 13. the oral pharmaceutical composition according to the item 12, wherein the protein is one or more proteins selected from a bean protein or a processed bean protein product, a milk protein or a processed milk protein product, an egg protein or a processed egg protein product and gelatin,

[0037] 14. the oral pharmaceutical composition according to the item 13, wherein the protein is a thermally denatured product,

[0038] 15. the oral pharmaceutical composition according to the item 12, wherein the pharmaceutically acceptable water-insoluble polymer base is pH-independent,

[0039] 16. an intrabuccally quick disintegrating tablet, which comprises the oral pharmaceutical composition described in the item 15,

[0040] 17. an intrabuccally quick disintegrating tablet, which comprises the oral pharmaceutical composition described in the item 16 and saccharides,

[0041] 18. the intrabuccally quick disintegrating tablet according to the item 17, wherein the saccharides are granulated product prepared by using saccharides having low moldability spraying saccharides having high moldability as a binder, thereby effecting at least one of coating and granulating,

[0042] 19. the intrabuccally quick disintegrating tablet according to the item 18, wherein the production process contains humidification and drying steps,

[0043] 20. the intrabuccally quick disintegrating tablet according to the item 19, wherein the saccharides having low moldability are one or more saccharides selected from lactose, mannitol, glucose, sucrose, xylitol and erythritol, and

[0044] 21. the intrabuccally quick disintegrating tablet according to the item 19, wherein the saccharides having high moldability are one or more saccharides selected from maltose, maltitol, sorbitol and trehalose.

[0045] Other objects and advantages of the invention will become evident as the description progresses.

[0046] The bitterness-reduced oral pharmaceutical composition of the present invention is described further in detail.

[0047] The "solid protein" to be used in the present invention is not particularly limited with the proviso that it is a solid protein which is pharmaceutically acceptable and can attain the object of the invention by employing the constitution of the present invention, and its illustrative examples include bean proteins or processed products thereof, such as soybean protein or a processed soybean protein product and pea protein or a processed pea protein product, milk proteins or processed products thereof, such as casein, casein sodium, processed milk protein products and lactalbumin, egg proteins or processed products thereof, such as egg albumin, and gelatin, of which soybean protein, a processed soybean protein product and gelatin is preferred. These can be easily obtained as commercial products such as CP-GGG (Nitta Gelatin), Ajipron S3 (Ajinomoto), Ajipron SP1 (Ajinomoto) and Q-Lacto No. 5 (Q.P.).

[0048] The term "the protein is present as particles" as used herein means a condition that the protein is observed as particles in appearance when cross section of a film is observed using an electron microscope (SEM). The particle size which can be observed actually as particles cannot be defined clearly, but it is roughly from 500 nm to 100 μm when deduced from a result of SEM observation. In this connection, the particle size shown herein does not always coincide with the range of preferred particle size of the proteins shown in the embodiment of the present invention.

[0049] In order to facilitate the handling to include these proteins in a polymer base, it is desirable to use proteins in the form of powder.

[0050] When particle size distribution of the protein is not uniform or when small particles are desirable from the viewpoint of coating operation, it is possible to refine to a desired particle size using a pulverization apparatus such as jet mill pulverizer or sample mill pulverizer. Alternatively, it is possible to make particle size uniform by dispersing or dissolving the protein in an appropriate solvent (preferably water) and treating it by a known spray drying method, preferably by spray drying with a spray dryer. Particle size of the protein to be used in the present invention is not particularly limited but smaller particles are desirable in order to facilitate insurance of the drug release controlling ability in the buccal-imitated test solution the drug releasing ability in the digestive organ-imitated test solution.

[0051] Illustratively, it is from 1 to 50 μm, preferably from 1 to 30 μm, more preferably from 1 to 10 μm. The description as 1 μm is about the minimum value of particle size actually obtained by tests but is not a substantial lower limit value, because there is a possibility that the same effect of the present invention is confirmed when more smaller particle size is obtained, e.g., by a novel spray dryer.

[0052] In addition, the protein can be subjected to the present invention by treating it with heat. The heat treatment means a technique to denature the protein carried out using an apparatus such as an oven or a dryer, and its conditions can be optionally changed depending on each protein. Illustratively, a treating temperature of from 60 to 170° C., preferably from 90 to 160° C., more preferably from 100 to 140° C., can be employed. The treating time can also be optionally changed, and it is from 1 to 15 hours, preferably from 3 to 12 hours. Since the denaturation of protein intends to effect irreversible condensation accompanied by dehydration, longer time and higher temperature tend to decrease solubility of the protein or permeability of a drug and to reduce its solubility in the digestive tract-imitated test solution. Also, this step is not essential and can be optionally selected by examining releasing ability of the drug.

[0053] The "solid protein" can be used alone or by mixing two or more of them. Mixing amount of the protein varies depending, e.g., on the size of preparation particles so that cannot absolutely be defined, but is from 0.2 to 50% by weight, preferably from 1 to 40% by weight, more preferably from 5 to 30% by weight, based on the whole preparation. Excellent drug release ability in the digestive tract-imitated test solution cannot be obtained when the mixing amount is smaller than 0.2% by weight, and the period of time required for the production is prolonged when it is larger than 50% by weight.

[0054] The polymer base to be used in the present invention is not particularly limited with the proviso that it is pharmaceutically acceptable and can achieve the object of the present invention, and is a water-insoluble polymer base, and its illustrative examples include pH-independent polymer bases such as hydroxypropylmethylcellulose, ethyl cellulose and aminoalkylmethane acrylate copolymers RS and RL and pH-dependent polymer bases such as hydroxypropylmethyl acetate succinate, carboxymethylethylcellulose, an aminoalkyl methacrylate copolymer E and a methacrylic acid copolymer S. More preferred are water-insoluble and pH-independent polymer bases such as an aminoacryl methacrylate copolymer RS (trade name Eudlagit RS), ethyl cellulose and aminoalkyl methacrylate copolymer E, of which ethyl cellulose is most preferred. In addition, the polymer bases can also be used alone or by optionally combining two or more of them.

[0055] Mixing amount of the polymer base varies depending, e.g., on the size of preparation particles so that cannot absolutely be defined, but is from 0.2 to 50% by weight, preferably from 1 to 40% by weight, based on the whole preparation. Excellent drug control ability in the buccal-imitated test solution will be spoiled when the mixing amount is smaller than 0.2% by weight, and the production time will be prolonged when it is larger than 50% by weight.

[0056] The drug to be used in the present invention is not particularly limited with the proviso that it is used as a medically active component and has a bitter taste. Examples of the medically active component include central nervous system drugs such as a hypnotic sedative, a sleep inductor, an anxiolytic drug, an antiepileptic, an antipyretic-analgesic-anti-inflammatory drug, an antidepressant, an antiparkinsonism drug and a psychoneurosis drug, circulatory drugs such as a skeletal muscle relaxant, an autonomic drug, an antispasmodic agent, a cardiotonic agent, an arrhythmia drug, a diuretic agent, an antihypertensive drug, a vasoconstrictor, a coronary vasodilator, a peripheral vasodilator and a hyperlipemia drug, allergy drugs such as an antitussive expectorant and a bronchodilator, digestive organ drugs such as an antidiarrheal drug, a drug for controlling intestinal function, an antiulcer drug, a stomatic digestive drug and an antacid agent and hormone drugs such as a pituitary hormone drug, a thyroid hormone drug and an anti-thyroid hormone drug, as well as a urogenital organ drug, a vitamin compound, a hemostatic drug, a blood coagulation inhibitor, a pulmonary disease drug, an antidote, a habitual intoxication drug, a gout treating drug, a diabetic drug, an antimalignant tumor drug, an antihistaminic drug, a crude drug, a Chinese orthodox medicine, an antibiotic, a chemotherapy drug, an anthelmintic drug and an anti-protozoan drug. Illustratively, meclofenoxate hydrochloride, chloramphenicol, aminophylline, erythromycin, josamycin, calcium hopantenate, phenobarbital, cimetidine, famotidine, etilefrine hydrochloride, diltiazem hydrochloride, propranolol hydrochloride, flufenamic acid, atolvastatin calcium, digitoxin, theophylline, promethazine hydrochloride, quinine hydrochloride, sulpyrine and ibuprofen can be exemplified. In addition, the drug can also be used alone or by optionally combining two or more of them.

[0057] Mixing amount of the drug is optionally selected generally in response to the kind of drugs or medical use (indication), though not particularly limited with the proviso that it is a therapeutically effective amount or a prophylactically effective amount. Mixing amount of the drug is preferably from 0.5% to 85% by weight, more preferably from 0.5% to 80% by weight, based on the whole pharmaceutical preparation. More preferred mixing amount of the drug is from 0.5% to 50% by weight, and most preferred mixing amount is from 0.5 to 10% by weight.

[0058] When the composition of the present invention is made into a pharmaceutical preparation, its dosage form is not particularly limited and various dosage forms generally used as medicaments can be selected. The composition of the present invention can be applied to any bitter drug and exerts particularly useful effects on a drug having a difficulty in preparing a medicament due to its bitterness, particularly on a drug having a markedly low threshold value. For example, it is a preferred embodiment to make the composition of the present invention into oral solid preparations such as granules, or dry syrups, capsules, tablets, troches or chewable tablets in which the granules are contained by a known method. In obtaining the pharmaceutical preparations, known methods generally used in this field can be used optionally, and one and/or two or more of conventionally used additives can be used by optionally combining them. Examples of such additives include binders, disintegrating agents, thickeners, fillers, lubricants, correctives and aromatics.

[0059] Also, the composition of the invention is a composition suitable for making intrabuccally quick disintegrating tablets by mixing it with an intrabuccally quick disintegrating tablet base and making the mixture into tablets. Examples of such intrabuccally quick disintegrating tablets include those which are described, e.g., in International Publication 95-20380, JP-A-8-19589 (corresponds to U.S. Pat. No. 5,672,364), JP-A-9-48726, Japanese Patent No. 2,919,771 and Japanese Patent No. 3,069,458 (corresponds to U.S. Pat. No. 5,720,974). Also, it is possible to make the