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SUPERINTENDENCIA Y COMERCIO
Radicación : 00050630 00000004 Folio 1
Fecha (ASDI): 2004-12-28 16:04:12
Trámite : 002 PATENTES D 1 REGISTRO/ 503 PETICION
SUPERINTENDENCIA Y COMERCIO
Fecha (ASDI): 2004-12-28 16:04:12
Trámite : 002 PATENTES D 1 REGISTRO/ 503 IMPULSO P
Dependencia: 0005 DIVISION DE NUEVAS CREACIONES

Evento :001

Actuación :593

Referencia : Expediente No. 00.050.630

Asunto : Solicitud de patente para
"PROCEDIMIENTO PARA LA OBTENCIÓN DE
PREPARADOS FARMACÉUTICOS SÓLIDOS DE
DISGREGACIÓN RÁPIDA"

Solicitante : BAYER AKTIENGESELLSCHAFT

Fecha de Solicitud : 06 de julio de 2000

Yo, Emilio FERRERO, obrando como apoderado de la solicitante en referencia, atentamente, solicito a Usted se sirva ordenar la agilización del trámite de esta solicitud de patente y se sirva realizar el examen de patentabilidad de la misma. La última actuación que obra en el expediente es mi memorial número 00050630 00000003 radicado el 25 de febrero de 2003, mediante el cual solicité se efectuara el examen de patentabilidad de la solicitud en referencia.

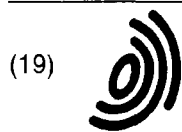
Bogotá, 28 DIC. 2004
Señora Jefe,



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D COLO 00698 801 118 2
DLM/DLM/ID-001579/WPCL0698

00 050 630
0-30630



Europäisches Patentamt

(19)

European Patent Office

Office européen des brevets



(11)

EP 0 627 218 B1

(12)

EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention
of the grant of the patent:
19.12.2001 Bulletin 2001/51

(51) Int Cl.7: **A61K 9/20**, A61K 47/10,
A61K 47/26, A61K 9/00

(21) Application number: **93904312.1**

(86) International application number:
PCT/JP93/00192

(22) Date of filing: **17.02.1993**

(87) International publication number:
WO 93/15724 (19.08.1993 Gazette 1993/20)

(54) **Process for producing fast soluble tablets and fast soluble tablets comprising xylitol**

Verfahren zur Herstellung von schnelllöslicher Tabletten und schnelllöslichen Tablette beinhaltend
Xylitol

Procédé de preparation de tablettes à dissolution rapide et tablettes solubles rapidement comprenant
xylitol

(84) Designated Contracting States:

**AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL
PT SE**

(30) Priority: **18.02.1992 JP 6956592**

(43) Date of publication of application:
07.12.1994 Bulletin 1994/49

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EP-A- 0 371 466

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JP-A- 61 205 208

627 218 B1

Note: Within nine months from the publication of the mention of the grant of the European patent, any person may give

Description

[0001] The present invention relates to a drug-containing fast soluble tablet that dissolves rapidly in the oral cavity.

[0002] The fast soluble tablet usually dissolves in the oral cavity within 15 seconds to 3 minutes, and is suitable for administration to infants, the aged, severely affected patients and others who have difficulty in taking tablets.

[0003] Oral dosage forms of drugs include tablets, granules, powders and liquids. Liquids, such as syrups, are suitable for administration to the physically weakened aged and infants because they are easily swallowable. However, they are not convenient because they must be accurately weighed for each use. Another drawback is that the tendency to deteriorate easily upon exposure to heat or atmosphere degrades the drug's chemical and physical stability.

[0004] Granules and powders are free of the above drawbacks, but they are not easily swallowable, and taking the accurate dose is difficult unless they are taken with water etc.

[0005] Tablets are suitable for administration of a certain accurate volumes and offers excellent chemical and physical stability for the drug contained, but they have a drawback of difficult swallow for infants, the aged, severely affected patients and others. Overcoming the drawback of poor swallowability would make it possible to provide an excellent preparation free of the above-described drawbacks in other dosage forms.

[0006] As a solution to the problem of poor swallowability in tablets, freeze-dried preparations in a tablet form, based on a water-soluble polymer, have recently been developed (e.g., Japanese Patent Unexamined Publication Nos. 44619/1978 and 86837/1991). They have overcome the drawback of poor swallowability in tablets by causing the preparation to dissolve rapidly in the oral cavity. However, they require a special preparation technology known as freeze-drying, resulting in drawbacks such as difficulty in industrial mass-production, high production cost and poor physical stability.

[0007] In recent years, tablets have been produced by subjecting tablet components to compressive shaping under high pressure in a dry state. This is because tablets are essentially intended to be disintegrated in the gastrointestinal tract to cause drug absorption and must be physically and chemically stable from completion of tableting to reach to the gastrointestinal tract, so that the tablet components must be strongly bound together by a compressive pressure. In early times, wet tablets were available, which were molded and shaped into tablets while in a wet state, followed by drying. However, such tablets were not rapidly soluble in the oral cavity because they were intended to be disintegrated in the gastrointestinal tract. Also, as these tablets are not strongly compressed mechanically and lack shape retention, they are not practically applicable to modern use.

[0008] EP-A1-0371466 discloses a fast dissolving buccal tablet for administering a medicament which includes the active ingredient, a lubricant and a water soluble sugar, such as sorbitol, combined such that the buccal tablet dissolves in about one minute.

[0009] Patent Abstracts of Japan 1256 C78, No. 53-44618 discloses the preparation of a disintegratable, easily administrable small-sized tablet with high productivity, by mixing granules obtained by the wet-granulation of propionic acid maridomycins with a specific binder, and adjusting the water-content to 4-8%.

[0010] The object of the present invention is to provide a method of producing a fast soluble tablet by a simple method without the above-described special preparation technology known as freeze-drying.

[0011] Accordingly, the invention provides a process for producing pharmaceutical tablets and a tablet as claimed in claims 1 and 7 respectively.

[0012] Through intensive investigation, the present inventors found that the above object could be accomplished by producing tablets based on a pharmaceutical additive rapidly soluble in water by a modification of the conventional tableting method based on wet granulation and completed the present invention.

[0013] A gist of the present invention is characterized by two features: 1) the tablet base component is a pharmaceutical additive rapidly soluble in water, and 2) a kneaded mixture of a drug and a pharmaceutical additive rapidly soluble in water is subjected to compressive shaping while in a wet state.

[0014] The present invention is hereinafter described in detail. In the method of the present invention the pharmaceutical additive rapidly soluble in water may be any water-soluble crystalline or powdery solid, exemplified by substances in common use as excipients. It is preferable, however, that the pharmaceutical additive is a sweetening substance, since the fast soluble tablet of the present invention dissolves rapidly in the oral cavity. Such substances include saccharides such as sucrose, lactose, glucose and fructose, and sugar alcohols such as xylitol, sorbitol and mannitol.

[0015] Of the above-mentioned sugar alcohols, xylitol is preferred because it has a good taste and dissolves most rapidly in the oral cavity. Mannitol and lactose are excellent in the compressive property described later, although they are inferior to xylitol in taste and dissolution rate.

[0016] In the present invention, these substances may be used in combination. Appropriate combination can offer only a combination of advantages thereof.

[0017] The fast soluble tablet relating to the present invention is produced by subjecting a kneaded mixture of a pharmaceutical additive rapidly soluble in water as described above and a drug to compressive shaping before drying when compressive shaping is performed in the conventional tableting method based on wet granulation. The present

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tablets are different from conventional tablets in that the shaping and drying operations are reversed in order; conventional tablets are produced by mixing starting materials, adding a binder, kneading and drying the mixture and subjecting the mixture to compressive shaping.

[0018] The compressive shaping pressure for shaping the fast soluble tablet relating to the present invention may be relatively low, e.g., 490 - 9800 N (50 - 1,000 kg) is sufficient. Although decreasing the pressure tends to yield tablets of shorter oral cavity dissolution time, compressive shaping pressures lower than 490 N (50 kg) result in formation of practically unapplicable tablets with insufficient tensile strength. Although increasing the pressure tends to yield more tough tablets of improved tensile strength, compressive shaping pressures exceeding 9800 N (1,000 kg) usually result in formation of tablets of longer oral cavity dissolution time. In some cases, however, tablets with practically acceptable strength are obtained from an appropriate combination of two or more the pharmaceutical additives, even when the compressive shaping pressure is lower than 490 N (50 kg). Also, in some cases tablets with shorter oral cavity dissolution time may be obtained from an appropriate combination of two or more the pharmaceutical additives, even when the compressive shaping pressure exceeds 9800 N (1,000 kg). Fast soluble tablets produced under a compressive shaping pressure out of the range of 490 - 9800 N (50 - 1,000 kg) are therefore included in the scope of the present invention.

[0019] Tablets whose tensile strength exceeds 49×10^4 Pa (5 kg/cm²) are practically applicable. In some cases, however, tablets with even lower tensile strength are practically applicable if they are packaged in suitable forms.

[0020] The mechanical strength of the fast soluble tablet relating to the present invention is retained mainly by the crosslinking force of the pharmaceutical additive rapidly soluble in water.

[0021] Conventional tablets are produced under compressive shaping pressures of about 9800 - 29400 N (500 - 3,000 kg).

[0022] When a sugar alcohol is applied in the present invention, e.g., xylitol is used alone, it is preferable that the compressive shaping pressure is about 490 - 2940 N (50 - 300 kg). Lower compressive shaping pressures make tablet shaping difficult. Higher compressive shaping pressures result in formation of practically unapplicable tablets of insufficient tensile strength (see Figure 1).

[0023] When xylitol alone is used as a sugar alcohol, compressive shaping pressures exceeding 2940 N (300 kg) result in formation of tablets with decreased tensile strength and increased oral cavity dissolution time. When xylitol is used in a mixture with lactose, mannitol or the like, tablets with sufficiently high tensile strength and short oral cavity dissolution time can be obtained even when the compressive shaping pressure exceeds 2940 N (300 kg).

[0024] For example, when xylitol is used in combination with lactose, tablets with shorter oral cavity dissolution time and sufficient tensile strength can be obtained by mixing them in a ratio of, for example, 8:2 (see Figure 2).

[0025] For example, when xylitol is used in combination with mannitol, tablets with shorter oral cavity dissolution time and sufficient tensile strength can be obtained by mixing them in a ratio of, for example, 8:2 (see Figure 3).

[0026] As mentioned above, when xylitol is used in a mixture with lactose or mannitol, better results are obtained than those obtained with xylitol alone. These results, however, have not been expected from the results with mannitol alone or lactose alone. This is because using mannitol alone or lactose alone results in considerably increased oral cavity dissolution time as well as increased tensile strength when the compressive shaping pressure exceeds 2940 N (300 kg) (see Figure 4).

[0027] The fast soluble tablet relating to the present invention displays rapid dissolution in the oral cavity. For example, when it is intended to incorporate a drug which may cause a problem, if used as such, e.g., a drug which has a high bitterness, a masking treatment such as microcapsulation or crystal surface coating is performed as appropriate, after which the drug is incorporated in the fast soluble tablet of the present invention, result in elimination of such problem.

[0028] The kneaded mixture of a drug and a pharmaceutical additive rapidly soluble in water is usually prepared by mixing the pharmaceutical additive rapidly soluble in water and the appropriately treated drug, adding and uniformly dispersing water, a binder solution or a saturated sugar solution, and kneading. The amount of water added is preferably about 1 - 10% by weight, most preferably about 3% by weight, in the tablet composition before compressive shaping. Excess water results in dissolution of sugar alcohol or sugar, or decreased shape retention, which in turn adversely affect the compressive shaping that follows and make it difficult to dry the shaped product. Insufficient water results in tableting failures such as cracking at shaping, thus hampering preferred embodiment. The shaped tablet, even if obtained, lacks mechanical strength, and is fragile. The water added is preferably purified water, for instance.

[0029] Compressive shaping can be achieved, irrespective of the form of the kneaded mixture, whether particulate, granular, soft lumpy or the like, as long as the kneaded mixture of the drug and the pharmaceutical additive rapidly soluble in water is wet. Compressive shaping machines which can be used include ordinary tableting machines, automatic compressive shaping machines for Japanese cakes and lump sugar machines.

[0030] The fast soluble tablet relating to the present invention can be produced more simply and in larger amounts, in comparison with the above-described tableting method using freeze-drying technique, because they can be produced by a modification of the conventional tableting method based on wet granulation compression, as stated above.

[0031] In the present invention, to further improve the physical properties of the preparation, known binders may be

added in the process of the kneading operation. Although the binder for the present invention is not subject to limitation, preference is given to substances of relatively high dissolution rate. Such binders include polyvinylpyrrolidone (PVP), hydroxypropyl cellulose (HPC) and hydroxypropyl methylcellulose (HPMC) and the like. Acacia etc. may also be incorporated as appropriate.

[0032] The binder for the present invention may be contained at 0.1 to several percent by weight, preferably about 0.5 - 1% by weight, in the tablet composition before compressive shaping.

[0033] The fast soluble tablet relating to the present invention may be glazed by steam exposure for one to several seconds after compressive shaping and drying, to smooth the tablet surface for good appearance and prevent abrasion of the tablet surface.

[0034] Any drug is applicable to the fast soluble tablet relating to the present invention, as long as it is orally administered. Such drugs include the following:

1. Antipyretic analgesic anti-inflammatory agents

Indomethacin, aspirin, diclofenac sodium, ketoprofen, ibuprofen, mefenamic acid, dexamethasone, dexamethasone sodium sulfate, hydrocortisone, prednisolone, azulene, phenacetin, isopropylantipyrin, acetaminophen, benzydramine hydrochloride, phenylbutazone, flufenamic acid, mefenamic acid, sodium salicylate, choline salicylate, sasapyrine, clofezone, etodolac.

2. Antiulcer agents

Sulpiride, cetraxate hydrochloride, gefarnate, irsogladine maleate, cimetidine, unitidine hydrochloride, famotidine, nizatidine, roxatidine acetate hydrochloride.

3. Coronary vasodilators

Nifedipine, isosorbide dinitrate, diltiazem hydrochloride, trapidil, dipyridamole, dilazep dihydrochloride, methyl 2,6-dimethyl-4-(2-nitrophenyl)-5-(2-oxo-1,3,2-dioxaphosphorinan-2-yl)-1,4-dihydropyridine-3-carboxylate, verapamil, nicardipine, nicardipine hydrochloride, verapamil hydrochloride.

4. Peripheral vasodilators

Ifenprodil tartrate, cinepazide maleate, cyclandelate, cinnarizine, pentoxyfylline.

5. Antibiotics

Ampicillin, amoxicillin, cefalexin, erythromycin ethylsuccinate, bacampicillin hydrochloride, minocycline hydrochloride, chloramphenicol, tetracycline, erythromycin.

6. Synthetic antibacterial agents

Nalidixic acid, piromidic acid, pipemidic acid trihydrate, enoxacin, cinoxacin, ofloxacin, norfloxacin, ciprofloxacin hydrochloride, sulfamethoxazole trimethoprim, 6-fluoro-1-methyl-7-[4-(5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl-1-piperazinyl]-4-oxo-4H[1,3]thiazeto[3,2-a]quinoline-3-carboxylic acid.

7. Antispasmodics

Propantheline bromide, atropine sulfate, oxopium bromide, time-bidium bromide, butylscopolamine bromide, trospium chloride, butropium bromide, N-methylscopolamine methylsulfate, methyloctatropine bromide, butropium bromide.

9. Antitussive anti-asthmatic agents

Theophylline, aminophylline, methylephedrine hydrochloride, procaterol hydrochloride, trimetoxinol hydrochloride, codeine phosphate, sodium cromoglicate, tranilast, dextromethorphan hydrobromide, dimemorfan phosphate, clobutinol hydrochloride, fominoben hydrochloride, benproperine phosphate, dimemorfan phosphate, tiapedidine hibenzate, eprazinone hydrochloride, clofedanol hydrochloride, ephedrine hydrochloride, noscapine, calbetapentane citrate, oxeladin tannate, isoaminile citrate, eprazinone hydrochloride.

10. Bronchodilators

Diprophylline, salbutamol sulfate, clorprenaline hydrochloride, formoterol fumarate, orciprenalin sulfate, pirbuterol hydrochloride, hexoprenaline sulfate, bitolterol mesylate, clenbuterol hydrochloride, terbutaline sulfate, mabuterol hydrochloride, fenoterol hydrobromide, methoxyphenamine hydrochloride.

11. Diuretics

Furosemide, acetazolamide, trichlormethiazide, thyclothiazide, hydrochlorothiazide, hydroflumethiazide, ethiazide, cyclopenthiazide, spironolactone, triamterene, fluorothiazide, piretamide, mefrumide, ethacrynic acid, azosemide, clofenamide.

12. Muscle relaxants

Chlorphenesin carbamate, tolperisone hydrochloride, eperisone hydrochloride, tizanidine hydrochloride, mephenesin, chlorozoxazone, phenprobamate, methocarbamol, chlormezanone, pridinol mesylate, afloqualone, baclofen, pridinol mesylate, dantrolene sodium.

13. Brain metabolism improvers

Meclofenoxate hydrochloride.

14. Minor tranquilizers

diameter weighing 500 mg each. The shaped tablets were then dried at 55°C for 3 hours in a hot air circulation oven (GT-100, produced by Alp Corporation) to yield fast soluble tablets of the present invention.

Example 7

[0043] 2.5 g of acacia powder, 146 g of mannitol and 10 g of nifedipine were mixed in a micro-type through-vision mixer (W-8, produced by Tsutsui Rikagaku Kiki) for 8 minutes. 158.5 g of this mixture and 341.5 g of xylitol were mixed in a kneader (KM-1.5, produced by Kikusui Seisakusho, Ltd.) for 10 minutes, followed by kneading with 14 ml of purified water added. The resulting mixture was applied to a feather mill (FM-1, produced by Hosokawa Micron Corp.) equipped with a screen of 12 mm pores, to uniformize particle size. The resulting granules were subjected to compressive shaping at a compression force of 2156 N (220 kg), using a rotary tableting machine (RT-F-9, produced by Kikusui Seisakusho, Ltd.), to yield tablets of 15 mm diameter weighing 1,000 mg each. The shaped tablets were then dried at 55°C for 3 hours in a hot air circulation oven (GT-100, produced by Alp Corporation) to yield fast soluble tablets of the present invention.

Example 8

[0044] 1.5 g of polyvinylpyrrolidone, 412.5 g of xylitol, 111 g of lactose and 125 g of cefalexin were mixed in a kneader (KM-1.5, produced by Kikusui Seisakusho, Ltd.) for 10 minutes, followed by kneading with 20 ml of purified water added. The resulting mixture was applied to a feather mill (FM-1, produced by Hosokawa Micron Corp.) equipped with a screen of 12 mm pores, to uniformize particle size. The resulting granules were subjected to compressive shaping at a compression force of 1764 N (180 kg), using a rotary tableting machine (RT-F-9, produced by Kikusui Seisakusho, Ltd.), to yield tablets of 15 mm diameter weighing 1,300 mg each. The shaped tablets were then dried at 55°C for 3 hours in a hot air circulation oven (GT-100, produced by Alp Corporation) to yield fast soluble tablets of the present invention.

Comparative Example 1

[0045] 300 g of xylitol was passed through a 32-mesh sieve. 1 g of the powder was subjected to compressive shaping at a compression force of 490 - 9800 N (50 - 1,000 kg) and a compression rate of 20 mm/min, using a material testing machine (Autograph (trade mark):AG-5000, produced by Shimadzu Corporation), to yield tablets of 13 mm diameter for comparative testing.

Comparative Example 2

[0046] 300 g of mannitol was passed through a 32-mesh sieve. 1 g of the powder was subjected to compressive shaping at a compression force of 980 - 6860 N (100 - 700 kg) and a compression rate of 20 mm/min, using a material testing machine (Autograph (trade mark):AG-5000, produced by Shimadzu Corporation), to yield tablets of 13 mm diameter for comparative testing.

Test Example 1

[0047] For the inventive fast soluble tablets of Example 1, the tablets of Comparative Example 1, and the undried tablets of Example 1, tensile strength and oral cavity dissolution time were measured. Tensile strength was measured using a material testing machine (Autograph (trade mark):AG-5000, produced by Shimadzu Corporation) equipped with a 100 KGF load cell, at a compression rate of 20 mm/min, with a full scale of 10 - 20 KGF. The point at which the load reduction rate for 1 second lowered to 50% of the full scale was taken as the breaking point. On the basis of breaking point data, the tensile strength of each tablet preparation was calculated as the mean of 5 tablets using the following equation:

$$\tau = 2P / \pi DT$$

τ : Tensile strength $9.8 \times 10^4 \text{ Pa (kg/cm}^2\text{)}$

P: Hardness (kg)

D: Tablet diameter (cm)

T: Tablet thickness (cm)

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Claims

1. A process for the production of pharmaceutical tablets which rapidly dissolve in the oral cavity having a pharmaceutically active ingredient (drug) and an excipient, comprising wet granulating the drug and an excipient which is readily soluble in water, compressing the wet granulate into tablet form and drying the compressed tablet.
2. A process according to claim 1, wherein the excipient is a sugar alcohol or a sugar.
3. A process according to claim 2, wherein the sugar alcohol is xylitol.
4. A process according to claim 3, wherein the tablet is prepared at 480 - 2940 N (50-300 Kg) of the compressive shaping pressure.
5. A process according to claim 1, wherein the excipient is a mixture of xylitol and lactose.
6. A process according to claim 1, wherein the excipient is a mixture of xylitol and mannitol.
7. A pharmaceutical tablet which rapidly dissolves in the oral cavity obtainable by the process as defined in claim 1, having a pharmaceutically active ingredient (drug), and the mixture of xylitol and at least one member selected from the group consisting of lactose and mannitol.

Patentansprüche

1. Verfahren für die Herstellung von pharmazeutischen Tabletten, die sich schnell in der Mundhöhle lösen, die einen pharmazeutisch aktiven Bestandteil (Arzneimittel) und einen Träger haben, umfassend Feuchtgranulieren des Arzneimittels und Trägers, der leicht in Wasser löslich ist, Komprimieren des Feuchtgranulats in Tablettenform und Trocknen der komprimierten Tablette.
2. Verfahren nach Anspruch 1, wobei der Träger ein Zuckeralkohol oder ein Zucker ist.
3. Verfahren nach Anspruch 2, wobei der Zuckeralkohol Xylitol ist.
4. Verfahren nach Anspruch 3, wobei die Tablette bei 480 - 2940 N (50-300 kg) des Kompressionsformdrucks hergestellt wird.
5. Verfahren nach Anspruch 1, wobei der Träger eine Mischung von Xylitol und Lactose ist.
6. Verfahren nach Anspruch 1, wobei der Träger eine Mischung aus Xylitol und Manitol ist.
7. Pharmazeutische Tablette, die sich schnell in der Mundhöhle löst, erhältlich durch das Verfahren, wie in Anspruch 1 definiert, die einen pharmazeutisch aktiven Bestandteil (Arzneimittel) und die Mischung aus Xylitol und mindestens einem Glied, ausgewählt aus der Gruppe, bestehend aus Lactose und Manitol, hat.

Revendications

1. Procédé pour la fabrication de cachets pharmaceutiques qui se dissolvent rapidement dans la cavité buccale contenant un ingrédient pharmaceutiquement actif (médicament) et un excipient, comprenant la granulation par voie humide du médicament et d'un excipient qui est facilement soluble dans l'eau, la compression des granulés humides sous la forme de cachets et le séchage des cachets comprimés.
2. Procédé suivant la revendication 1, dans lequel l'excipient est un alcool de sucre ou un sucre.
3. Procédé suivant la revendication 2, dans lequel l'alcool de sucre est du xylitol.
4. Procédé suivant la revendication 3, dans lequel les cachets sont préparés à 480-2940 N (50-300 kg) de pression de façonnage par compression.

5. Procédé suivant la revendication 1, dans lequel l'excipient est un mélange de xylitol et de lactose.
6. Procédé suivant la revendication 1, dans lequel l'excipient est un mélange de xylitol et de mannitol.
- 5 7. Cachet pharmaceutique qui se dissout rapidement dans la cavité buccale pouvant être obtenu par le procédé suivant la revendication 1, contenant un ingrédient pharmaceutiquement actif (médicament) et le mélange de xylitol et d'au moins un élément choisi dans le groupe constitué de lactose et de mannitol.

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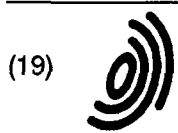
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Europäisches Patentamt

(19)

European Patent Office

Office européen des brevets



(11)

EP 0 788 791 A1

(12)

EUROPEAN PATENT APPLICATION

published in accordance with Art. 158(3) EPC

(43) Date of publication:
13.08.1997 Bulletin 1997/33

(51) Int. Cl.⁶: **A61K 9/46**, A61K 47/10

(21) Application number: 96927897.7

(86) International application number:
PCT/JP96/02372

(22) Date of filing: 23.08.1996

(87) International publication number:
WO 97/09037 (13.03.1997 Gazette 1997/12)

(84) Designated Contracting States:
CH DE ES FR GB IT LI NL

(30) Priority: 07.09.1995 JP 229802/95
17.05.1996 JP 123154/96

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(54) LOW-PRESSURE TABLETED EFFERVESCENT PREPARATION

(57) The present invention provides a low-pressure-tableted effervescent preparation which is satisfactory in tablet hardness and dissolution properties, the preparation comprising 10 to 35% by weight of sodium hydrogencarbonate and/or sodium carbonate, 10 to 70% by weight of a neutralizing agent and 0.02 to 40% by weight of at least one member selected from the group consisting of maltitol, sorbitol, maltose, trehalose, mannitol, lactitol and xylitol.

tose, dextrin, etc.; polysaccharides capable of functioning also as an emulsifier, such as gum arabic, casein, etc.; and proteins. Examples of useful emulsifiers are lecithin, glycerin fatty acid ester, sucrose fatty acid ester, calcium stearoyl lactate, sorbitan fatty acid ester, propyleneglycol fatty acid ester, etc. The antioxidant-containing powder may contain an oxidation inhibitor for inhibiting the oxidation of carotin or like antioxidants, such as L-ascorbic acid palmitic acid ester, vitamin C, enzymatically modified rutin, etc. The incorporation of such oxidation inhibitor in the powder is desirable.

The matrix of the antioxidant-containing powder can be formed by conventional methods such as spray drying to give the desired powder having a suitable particle size.

Among the antioxidant-containing powders, powders containing catechin or like water-soluble antioxidant can be easily prepared merely, for example, by extracting the antioxidant with hot water or alcohol, concentrating the extract, and making the concentrate into particles by conventional methods such as spray drying.

The proportion of the antioxidant-containing powder in the preparation of the invention is not greater than 15%, preferably 0.1 to 5.0%. The proportion of the antioxidant (fat-soluble substance) in the powder is 0.2 to 20%, preferably 0.5 to 10%. This means that the balance 99.8 to 80% consists of the fat and oil, the base material for forming particles or emulsifier, and the oxidation inhibitor optionally added with these components. The oxidation inhibitor, when incorporated in the powder, is preferably used in a proportion of about 0.5 to about 20% of the antioxidant-containing powder. The proportion of catechin or like water-soluble antioxidant in the powder is at least 10%.

The effervescent preparation of the present invention may further comprise, in addition to the above essential components and optional additives, predetermined amounts of various vitamins to obtain an effervescent multivitamin preparation. The species and proportions of the vitamins to be used are as described above. Among these vitamins, vitamin A, vitamin D, vitamin E and β -carotin are incorporated into the preparation of the invention preferably in the form of a vitamin-containing powder, like the antioxidant-containing powder mentioned above. The reason is that such powder is uniformly dispersed in cold water (without floatation or precipitation) and less susceptible to deterioration caused by oxidation, since said powder has relatively good barrier property against oxygen.

Various kinds of said vitamin-containing powders are commercially available, and any of them can be employed in the present invention.

Thus, the effervescent multivitamin preparation of the present invention contains vitamins in suitable amounts according to the standard for daily quota of vitamins (RDI), within the range which can provide a commercially valuable product and maintain the characteristics (tablet properties, taste, etc.) of the product. Said multivitamin preparation of the invention can effectively supply vitamins.

The effervescent multivitamin preparation of the invention is advantageous in that it can supply vitamins with better taste than vitamin supplements to be taken with water, and can keep the vitamin components stable for a longer period than vitamin solutions, since the preparation of the invention is in a dry form. The incorporation of a plurality of vitamin components usually results in deterioration of the tableting properties (increase in pressure required for tableting, lower tablet hardness, longer dissolution time, etc.). The preparation of the present invention is advantageous also in that the amount of the specific components (such as maltitol) can be suitably selected to provide the optimum production conditions (such as suitability for the tableting machine) and the optimum tablet properties.

The effervescent preparation of the invention can be prepared by conventional methods using said essential components and optional additives. The conventional methods include a dry (direct) tableting process which comprises simply mixing the starting materials and tableting the mixture, and a wet tableting process which comprises wetting a part of the starting materials, kneading all of the starting materials, drying and sieving the kneaded mixture to form granules, and tableting the granules. The dry tableting process can be carried out easily, but has a drawback that when components are used which are likely to be modified by the reaction with each other, the resulting tablets have a problem with long-term storage stability. On the other hand, the wet tableting process, which is free from the above problem, can be carried out under lower pressure than the dry tableting process to produce tablets of the equivalent hardness. However, the wet tableting process disadvantageously involves troublesome procedures. Therefore, the effervescent tablets of the present invention can be prepared by a method suitably selected from the dry tableting process and wet tableting process depending on the kinds and proportions of the components. The wet tableting process is advantageous in that the tableting can be carried out under satisfactorily low pressure using the excipients, i.e., maltitol, sorbitol, maltose, trehalose, mannitol, lactitol and xylitol in a small amount within the above-specified range. The pressure for tableting is usually selected from the range of about 0.2 to about 0.35 ton/cm², preferably about 0.24 to about 0.31 ton/cm². It is recommendable that the pressure in said range result in tablets having hardness of about 4.0 to about 6.6 kp, preferably about 4.5 to about 5.9 kp. The hardness of the tablets is expressed in terms of a pressure under which the tablet was broken by compression of two sides at a specific loading speed (1.0 mm/sec) using a Schleuniger tablet hardness meter, Model 4M (Schleuniger-4M).

Best Mode for Carrying Out the Invention

Given below are Test Examples and Examples to clarify the present invention in more detail. The parts in the Examples are all by weight.

107 104

Example 1

Wet tableting process

Granulated sugar	1900 mg
Maltitol	3 mg
L-Ascorbic acid	500 mg
L-Tartaric acid	1200 mg
Sodium hydrogencarbonate	1200 mg
Sweetener	q.s.
Vitamins	Predetermined amount
Flavor and pigment	Trace
Total	5100 mg

As the vitamins, the multivitamins A to E of the following compositions were used.

Table 3

Component	A	B	C	D	E
Vitamin A powder	0.03	0.06	0.45	0.2	0.2
Vitamin B ₁	0.01	0.8	0.05	0.5	0.02
Vitamin B ₂	0.03	0.3	0.2	0.1	0.03
Vitamin B ₆	0.04	0.2	0.1	0.08	0.04
Vitamin B ₁₂	0.00003	0.0012	0.0001	0.0003	0.0001
Pantothenic acid	0.05	0.8	0.5	0.4	0.2
Niacin	0.1	0.8	0.5	0.3	0.4
Vitamin C	0.1	0.8	0.5	0.3	10
Vitamin D powder	0.01	0.18	0.1	0.05	0.02
Vitamin E powder	0.3	0.8	1.0	0.5	0.4
Folic acid	0.001	0.08	0.88	0.01	0.008
Biotin	0.001	0.21	0.01	0.1	0.006
β-carotin powder	0.3	1.0	1.0	0.6	1.0

The β-carotin powder in the multivitamins was prepared by forming a matrix from 4 parts of β-carotin dissolved in 32 parts of vegetable fat and oil, 2 parts of L-ascorbic acid, 2 parts of tocopherol extract, 0.9 part of tea extract (containing tea polyphenol), 0.1 part of L-ascorbic acid palmitic acid ester and, as the base materials, 58 parts in total of gum arabic and saccharides.

A granulating liquid consisting of maltitol syrup, water and ethyl alcohol was added to a mixture of the above specified amounts of ascorbic acid, tartaric acid and granulated sugar to prepare granules, and the other components were admixed with the granules. The mixture was formed into effervescent tablets of the invention under a pressure of 0.27 ton/cm².

The tablets thus obtained (containing multivitamin E shown in Table 3) had hardness of 4.5 kp and dissolution time of 1 minute and 40 seconds.

composición (es decir principio activo, coadyuvante y líquido para granular) y la condición de humedad residual antes de la compresión (de 5 – 10 %) estos son obvios para una persona versada en la materia y (c) el problema planteado en esta solicitud era la necesidad de proporcionar un procedimiento para obtención de preparados de rápida disgregación en agua y saliva de modo que liberen rápidamente el principio activo y puesto que para resolver este problema técnico la solicitud proporciona un procedimiento para obtener preparados que contienen un principio activo, un coadyuvante, un líquido para granular, con una humedad residual antes de la compresión de 5 – 10 %, es decir de manera similar a como se resolvía en las anterioridades D1 – D3; entonces esta solicitud no tiene **nivel inventivo**.

6. Conclusión

En conclusión, los requisitos de patentabilidad de la presente solicitud están afectados así:

Item	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	EP 0 627 218	1 – 9	Nivel inventivo
D2	EP 0 788 791	1 – 9	Nivel inventivo
D3	EP 0 553 777	1 – 9	Nivel inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de la notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No. 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL

Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista, de fecha

14 JUL. 2005

CONCEPTO TÉCNICO No. 987	EXAMINADOR TÉCNICO Código 202007
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14 June/05

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