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(54) Title: NOVEL GRANULE FORMULATION CONTAINING SILDENAFIL OR PHARMACEUTICALLY ACCEPTABLE SALTS THEREOF AS AN ACTIVE INGREDIENT

(57) Abstract: Disclosed is a rapidly dissolving granule formulation that is rapidly dissolved in the oral cavity. The granule formulation is rapidly dissolved in the oral cavity within 20 seconds after oral administration without leaving a feeling of foreign matter and a residual feeling. The granule formulation is produced by mixing an active ingredient with a rapidly dissolving carrier and granulating the mixture. The rapidly dissolving carrier meets the requirements: an instantaneous solubility of at least 30 mg/ml; a solubility after 5 minutes of at least 50 mg/ml; and the instantaneous solubility being 90% or less of a maximum solubility. The granule formulation can accomplish the desired effects irrespective of the kind of active ingredient. Therefore, the granule formulation is applicable to various active ingredients. In addition, the granule formulation can be produced in a relatively simple manner. This allows for an economical and efficient production process.



Description

Title of Invention: NOVEL GRANULE FORMULATION CONTAINING SILDENAFIL OR PHARMACEUTICALLY ACCEPTABLE SALTS THEREOF AS AN ACTIVE INGREDIENT

Technical Field

- [1] The present invention relates to a novel rapidly dissolving granule formulation that contains sildenafil or a pharmaceutically acceptable salts thereof as an active ingredient and is characterized by rapid dissolution in the oral cavity. Specifically, the present invention relates to a novel rapidly dissolving granule formulation that contains sildenafil or a pharmaceutically acceptable salts thereof as an active ingredient and is characterized by rapid dissolution in the oral cavity within 20 seconds after oral administration without leaving any feeling of foreign matter and a residual feeling. More specifically, the present invention relates to a novel rapidly dissolving granule formulation that contains sildenafil or a pharmaceutically acceptable salts thereof as an active ingredient and is produced by granulation of the active ingredient together with a rapidly dissolving carrier meeting particular requirements wherein the dissolution and absorption of the active ingredient are promoted, the time required for the active ingredient to reach a maximum blood concentration (T_{max}) is 1 hour or less, and the granule formulation gives a feeling of refreshment without leaving a feeling of foreign matter and a residual feeling in the oral cavity. Still more specifically, the present invention relates to a novel rapidly dissolving granule formulation that has a small deviation in T_{max} between individuals after administration, specifically an R(T_{max},1h) of at least 80%, and is not bitter in taste.

Background Art

- [2] The chemical structures, production methods and medical applications of sildenafil and pharmaceutically acceptable salts thereof (hereinafter collectively referred to as sildenafil and individually referred to only when necessary to distinguish therebetween) are described in Korean Patent Nos. 78931 and 262926. Sildenafil is a drug useful in the treatment of impotence and pulmonary hypertension. Sildenafil is known to exhibit selectivity for inhibition of cGMP phosphodiesterase subtype V (cGMP PDE_v). This selective inhibition delays the degradation of cGMP to regulate the amount of blood flow to the penis, achieving therapeutic effects on erectile dysfunction. Sildenafil citrate was approved by the United States Food and Drug Administration (FDA) in March, 1998 and has been commercialized. Since then, sildenafil citrate has been used as a primary selective medicine related to erectile dysfunction treatment. Sildenafil citrate is administered about 1 to about 4 hours before sexual

activity.

- [3] Sildenafil is irregularly administered before sexual activity. Accordingly, a shorter onset time of sildenafil with enhanced administration convenience would be more desirable in view of the characteristics of sildenafil. Under such circumstances, research has been conducted on sildenafil formulations for oral administration that exhibit the efficacy of sildenafil within a shorter time.
- [4] Generally, rapid disintegration of a formulation and fast absorption of an active ingredient of the formulation in the stomach and intestines are required to shorten the onset time of the active ingredient. For rapid disintegration, dosage formulations can be designed in various manners. For example, an orally rapidly disintegrating tablet is designed such that it is easily disintegrated in the oral cavity before reaching the gastrointestinal tract. As another example, a strip formulation is designed such that it is attached or not attached to the mucosa of the oral cavity where the film is disintegrated to allow for rapid drug absorption.
- [5] However, it generally takes at least 30 seconds for the orally rapidly disintegrating tablet to be completely disintegrated and dissolved in the oral cavity. Particularly, the orally rapidly disintegrating tablet causes a patient to feel a severe feeling of foreign matter in the oral cavity before completion of disintegration. The patient can take the orally rapidly disintegrating tablet along with water, but administration convenience of the tablet is not substantially enhanced. If an active ingredient of the orally rapidly disintegrating tablet has a bitter taste, an additional technique should be applied to mask the bitter taste. Therefore, it is difficult to say that an orally rapidly disintegrating tablet of sildenafil has enhanced administration convenience because sildenafil has a bitter taste. Particularly, in attempts to mask the bitter taste of sildenafil, sildenafil free base has been included in orally rapidly disintegrating tablets or strip formulations. These formulations stay at particular sites of the oral cavities in view of their characteristics. This leads to an increase in the concentration of sildenafil at the sites and causes patients to still taste the bitterness of sildenafil. Thus, further technical considerations for masking the bitter taste of sildenafil are needed.
- [6] Strip formulations are produced by loading active ingredients in film-shaped strips. Strip formulations have been used as mouthwashes, etc., but the amount of active ingredients loaded therein is fundamentally limited. Further, sticky polymers forming the films cause inconvenience for patients due to their feeling of foreign matter and residual feeling in the oral cavities. Like orally rapidly disintegrating tablets, it is difficult to satisfactorily constitute strip formulations of bitter active ingredients, such as sildenafil, if an additional technique for masking the bitter taste is not applied. As stated above, despite the use of sildenafil free base, an increase in the concentration of sildenafil at particular sites of the oral cavities where the formulations are located is in-

evitable because of the characteristics of the formulations, making it impossible to completely mask the bitter taste of sildenafil.

- [7] Korean Patent No. 435514 discloses a fast-acting formulation of sildenafil lactate and describes the use of sugars, disintegrants, binder, excipients and lubricants known in the art as pharmaceutically acceptable carriers. As examples of the sugars, lactose, mannitol, sorbitol, xylitol, erythritol, dextrose, sucrose, fructose, levulose, maltodextrin and palatinose are mentioned. Particularly, this patent describes that the use of porous sugars prepared by a suitable process, such as spray drying, is preferred because of high solubility of the carriers in the oral cavity.
- [8] Korean Patent Publication No. 2001-0036527 discloses formulations for oral administration containing sildenafil citrate. Particularly, this patent publication mentions the necessity of developing new formulations that can be taken in an improved manner and exhibit their efficacy within a shorter time, and it discloses liquid, foaming tablet, chewing gum and chocolate forms as the formulations for oral administration. The time taken for a sildenafil preparation, particularly, a Viagra tablet, to reach a maximum blood concentration (T_{max}) is typically from 60 to 90 minutes. Accordingly, a patient must bear the onset time of the drug in mind before sexual intercourse. The sildenafil formulation can be taken in a much simpler manner than formulations for urethral administration or self-injectable formulations. The patent publication mentions a disadvantage in that the sildenafil formulation should be taken along with water because it is a tablet for oral administration. However, the liquid formulation is difficult to apply when the active ingredient exhibits poor stability in water, and the foaming tablet should be taken after it is foamed in water because of characteristics thereof. In the case of the chewing gum formulation, sufficient chewing is needed until the active ingredient is absorbed, but the chewing time is substantially unclear and is dependent on the degree of chewing. In a severe case, the active ingredient may be rarely dissolved from the gum base. The chocolate formulation is very susceptible to heat, making it difficult to say that the administration convenience of the formulation is enhanced.
- [9] Granule formulations for oral administration are not formulations aimed at shortening the onset time of drugs. Examples of such granule formulations include those containing crude drug extracts. Since these granule formulations are not rapidly dissolved in the oral cavities immediately after administration, they should be taken along with water and leave a severe feeling of foreign matter in the oral cavities. For these reasons, the granule formulations are thought to deviate from the enhancement of administration convenience in patients. Most conventional granule formulations are mixed with drinks or are considered to be suitable for taking along with foods. Few granule formulations have been reported as independent means for oral administration

that are capable of replacing tablet or capsule formulations. Granules are commonly regarded in the art as intermediates necessary for making tablets or filling capsules. Granules as final dosage formulations are generally recognized to be very poor in terms of administration convenience. It is difficult to find reports on granules as independent dosage formulations with enhanced administration convenience or improved in vivo pharmacokinetics of active ingredients.

- [10] For example, U.S. Patent Publication No. 2011/0027377 discloses a granule formulation that is produced by granulation of a sparingly soluble drug classifiable as Class II or Class IV of the Biopharmaceutical Classification System (BCS) to achieve increased solubility of the drug. This formulation is produced by mixing maltodextrin and polyethylene glycol having a particular molecular weight, together with the active ingredient, extruding the mixture using a screw extruder, and granulating the extrudate. The granules have a size of 100 to 2,500 μm . The granule formulation is dissolved in water and administered to animals. Alternatively, the granule formulation is compressed to produce a tablet or is filled in a capsule. That is, it is difficult to regard the granule formulation as an independent formulation. No disclosure is found regarding means for the enhancement of administration convenience.
- [11] U.S. patent publication No. 2011/0117193 discloses rapidly dissolving granule formulations of an antiretroviral drug for the treatment of children exposed to HIV/AIDS. The rapidly dissolving granule formulations are produced using saccharin as a sweetener and Ludiflash, croscarmellose sodium and Kollidon as disintegrants. This patent publication describes the administration of a suspension of the granules in water as a final dosage form but fails to disclose a granule formulation that can be taken without water.
- [12] Korean Patent Publication No. 10-2007-0062978 discloses granules containing paracetamol, NSAID and a sugar alcohol, made by melt extrusion. Specifically, the granules are produced by a process involving: dry blending alcohol, paracetamol and NSAID salts, optionally with other excipients which may be present in the granular component; heating the mixture at a temperature of 100 to 165 $^{\circ}\text{C}$ in an extruder to melt the sugar alcohol fully, thereby mixing the molten sugar alcohol with non-molten NSAID salts, paracetamol and other optional excipients; pouring the molten mass onto cooled stainless steel trays or a cooled moving belt at 10 $^{\circ}\text{C}$ to allow the molten mass to cool; solidifying the molten mixture; and milling the solid mass. However, this patent publication discloses the use of the granules as intermediates for the production of tablets but does not disclose any technical idea to use the granules as final formulations. Special consideration is needed regarding high production costs and equipment involved in the processes of melting the sugar alcohol at a high temperature, mixing the molten sugar alcohol with the active ingredients and cooling the mixture.

- [13] Korean Patent Publication No. 10-2009-0086469 discloses a powder formulation for valganciclovir. This formulation includes valganciclovir, povidone, fumaric acid, sodium benzoate, saccharin and mannitol. The formulation is also mixed with a particular solution before administration. Therefore, the final dosage form is not a granule formulation but a liquid formulation.
- [14] U.S. Patent No. 5,169,643 discloses a thiolcarbamate-containing granule formulation and U.S. Patent No. 5,532,209 discloses a propanil-containing granule formulation. These granule formulations do not take into account rapid dissolution and administration convenience because they are not applied to drugs for administration to humans.
- [15] As is evident from the above prior art publications, many attempts have been conducted to develop formulations that contain sildenafil as an active ingredient and exhibit the efficacy of the active ingredient within a short time. However, none of the attempts have succeeded in developing sildenafil-containing granules as final dosage formulations that shorten the onset time of sildenafil, leave no feeling of foreign matter and no residual feeling, and mask the bitter taste of sildenafil, achieving enhanced administration convenience. To the best of our knowledge, no special review has been done on granule formulations containing sildenafil as an active ingredient that are rapidly dissolved in the oral cavity, exhibit the efficacy of the active ingredient within a short time, have a small deviation in the onset time of sildenafil between individuals, leave no feeling of foreign matter and no residual feeling in the oral cavity, and are imparted with a feeling of refreshment.

Disclosure of Invention

Technical Problem

- [16] It is thus an object of the present invention to provide a formulation for oral administration containing sildenafil or a pharmaceutically acceptable salts thereof as an active ingredient that is rapidly dissolved in the oral cavity, can be taken without water and is administered in the form of a granule as a final dosage form. Specifically, it is an object of the present invention to provide a novel rapidly dissolving granule formulation that is rapidly dissolved in the oral cavity within 20 seconds after oral administration, leaves no feeling of foreign matter and no residual feeling, and is imparted with a feeling of refreshment. Furthermore, it is an object of the present invention to provide a novel rapidly dissolving granule formulation that is produced by mixing sildenafil or a pharmaceutically acceptable salts thereof with a sugar meeting particular requirements and granulating the mixture wherein the dissolution and absorption of the active ingredient are promoted, Tmax is shortened, deviation in Tmax between individuals is small, no feeling of foreign matter and no residual feeling are left in the

oral cavity, and the bitter taste of the active ingredient is masked.

Solution to Problem

- [17] To achieve the above object of the present invention, there is provided a rapidly dissolving granule formulation that is produced by granulation of sildenafil or a pharmaceutically acceptable salts thereof as an active ingredient and at least one rapidly dissolving carrier selected from the group consisting of sugars and sugar alcohols, and is rapidly dissolved in the oral cavity after oral administration.
- [18] The granule formulation is dissolved in the oral cavity within 20 seconds after administration.
- [19] The sugars and the sugar alcohols are xylitol, mannitol, isomaltose, sorbitol, maltitol, refined sugar, lactose, inositol, erythritol, crystalline fructose, trehalose, ribitol, arabitol, galactitol, lactitol, maltotritol, and mixtures thereof.
- [20] The granule formulation is a final dosage form that leaves no feeling of foreign matter and no residual feeling even when taken without water.
- [21] The rapidly dissolving carrier meets the following requirements:
- [22] (1) an instantaneous solubility of at least 30 mg/ml;
- [23] (2) a solubility after 5 minutes of at least 50 mg/ml; and
- [24] (3) the instantaneous solubility being 90% or less of a maximum solubility.
- [25] The rapidly dissolving granule formulation has a Tmax of 1 hour or less.
- [26] The rapidly dissolving granule formulation has an R(Tmax,1h) of at least 80%.
- [27] The sildenafil is present in an amount of 10% or less of its original amount in the oral cavity 30 seconds after administration.
- [28] The active ingredient is sildenafil free base and bitterness thereof is masked.

Advantageous Effects of Invention

- [29] Unlike conventional granules for oral administration, the novel rapidly dissolving granule formulation of the present invention is rapidly dissolved in the oral cavity after oral administration, leaves no feeling of foreign matter and no residual feeling, and gives a feeling of refreshment, contributing to a marked improvement in administration convenience. In addition, the rapidly dissolving granule formulation of the present invention is very suitable for oral administration of sildenafil without water due to its shortened Tmax, small deviation in Tmax between individuals and non-bitter taste. Furthermore, the rapidly dissolving granule formulation of the present invention is produced in a relatively simple manner, thus being very advantageous in terms of cost-effectiveness.

Best Mode for Carrying out the Invention

- [30] The term "sildenafil" as used herein is intended to include sildenafil free base and pharmaceutically acceptable salts thereof, which are used individually when necessary

to specifically distinguish therebetween, for example, sildenafil free base or sildenafil citrate as a specific salts.

- [31] The term “granules” as used herein is used as a generic name for powder formulations, fine granule formulations and granule formulations prescribed in the Korean Pharmacopoeia, and it refers to particulate formulations composed of fine particles or general particles. Granules can be produced by two processes, i.e. dry and wet processes. According to the dry process, an active ingredient, an excipient and a binder are mixed to form a slab- or sheet-like material, followed by granulation. According to the wet process, a binder solution is added to an active ingredient or a mixture of an active ingredient and an excipient, and the resulting mixture is mixed using a kneader, followed by granulation and drying. Fluidized bed granulation in which a raw material powder is formed into a fluidized bed using an air current, a binder solution is sprayed onto the fluidized bed, followed by granulation, is mainly used as a wet process. This method is advantageous in that mixing, granulation and drying processes are carried out in a single machine. There is no particular restriction on the method for producing the granule formulation of the present invention, but the use of a fluidized layer granulator is preferred.
- [32] The term “feeling of foreign matter” as used herein refers to an unpleasant feeling perceived by a patient who recognizes an orally administered drug as a foreign substance different from substances that the patient usually eats. The feeling of foreign matter is intended to include, for example, a prickly feeling of sand, a feeling of irritation in the oral mucosa and tongue, and a sticky feeling of viscous matter.
- [33] The term “residual feeling” as used herein refers to a feeling perceived by a patient who senses as if a formulation including an active ingredient stays partially or entirely in the oral cavity or a trace (e.g., a taste or a feeling) of the formulation remains unremoved although the formulation is already dissolved and absorbed over a long time (e.g. 20 seconds) after oral administration. The residual feeling does not reach a feeling of foreign matter but it also causes an unpleasant feeling for some patients. In the case where a patient feels a residual feeling, the patient may desire to drink water or a beverage. This case is contradictory to the intended purpose of taking a formulation without water. Therefore, a residual feeling, together with a feeling of foreign matter, is a factor that should be taken into consideration in order to improve the quality of a formulation.
- [34] The term “feeling of refreshment” as used herein refers to a cool and refreshed feeling perceived by a patient over the entire area of the oral cavity including a topical site where a formulation is located after the formulation has been administered orally. The feeling of refreshment is attributed to an endothermic reaction occurring when a formulation is dissolved in the saliva and is caused by a correlation among heat of dis-

solution, dissociation energy and dissolution rate of constituent ingredients of the formulation.

- [35] The term “bitter taste” as used herein refers to a taste inherent to sildenafil. A general tablet or capsule formulation causes no great administration inconvenience because it is swallowed immediately after administration. In contrast, in the case of an orally rapidly disintegrating tablet, a strip formulation or a granule formulation that is disintegrated and dissolved in the oral cavity while staying to some extent in the mouth, bitterness masking is an important factor that should be taken into consideration during formulation design.
- [36] The term “instantaneous solubility” as used herein is a new concept defined in the present invention to determine the dissolution pattern of the formulation of the present invention immediately after oral formulation. The instantaneous solubility is calculated as follows. First, 20.0 g of the rapidly dissolving carrier is added to 250 ml of purified water at a temperature of 37 ± 0.5 °C, and then the solubility values of the rapidly dissolving carrier (the weights (mg) of the rapidly dissolving carrier per ml of the purified water) after 1, 3, 5, 10 and 15 minutes are measured at a fixed paddle speed of 50 rpm. The solubility values are plotted. Thereafter, a linear regression curve is fitted according to the least square method and is extrapolated to obtain a value of the Y axis intercept. That is, the instantaneous solubility is a theoretical solubility value when time approaches zero infinite. The concept “instantaneous solubility” was conceived by the present inventors, based on the finding that the formulation of the present invention is rapidly dissolved immediately or within a few seconds after oral administration, and the dissolution effect, the feeling of foreign matter and the residual feeling of the formulation vary depending on the dissolution behaviors of the carrier, including change in the dissolution rate of the carrier at a microscopic level.
- [37] The term “solubility after 5 minutes” as used herein refers to a solubility of the rapidly dissolving carrier measured at 5 minutes after 20.0 g of the rapidly dissolving carrier is added to 250 ml of purified water at a temperature of 37 ± 0.5 °C and stirred at a fixed paddle speed of 50 rpm. The concept “solubility after 5 minutes” was conceived by the present inventors, based on the finding that the formulation of the present invention is rapidly dissolved immediately after oral administration, and the dissolution effect, the feeling of foreign matter and the residual feeling of the formulation vary depending on the dissolution behaviors of the carrier, including change in the dissolution rate of the carrier at a microscopic level. The solubility after 5 minutes, together with the instantaneous solubility, is a parameter defined to understand the time-dependent dissolution behaviors of the rapidly dissolving carrier in the oral cavity at a microscopic level.
- [38] The term “maximum solubility” as used herein refers to the highest solubility of the

rapidly dissolving carrier measured after 20.0 g of the rapidly dissolving carrier is added to 250 ml of purified water at a temperature of 37 ± 0.5 °C and stirred at a fixed paddle speed of 50 rpm. That is, the maximum solubility is 80 mg/ml. The reason why the maximum solubility is defined in the present invention is as follows. Since the rapidly dissolving carrier used in the formulation of the present invention is dissolved immediately after oral administration, it was expected that the higher instantaneous solubility would be more preferable. However, the formulation was unexpectedly found to be poor in terms of a feeling of foreign matter and a residual feeling even at a high instantaneous solubility. Based on this finding, the present inventors established a correlation between the maximum solubility and the instantaneous solubility to set the requirements of the rapidly dissolving carrier that is rapidly dissolved in the oral cavity and leaves no feeling of foreign matter and no residual feeling.

[39] The term “Tmax” as used herein means the time required for a drug to reach a maximum blood concentration after administration. Tmax is determined through actual clinical tests. Specifically, Tmax is calculated by taking blood samples from subjects at particular time intervals after a drug is administered to the subjects, measuring the concentrations of the drug in the blood samples, and averaging the measured blood concentrations. The reason why the blood concentrations are averaged is because there are slight differences in blood concentration between the subjects.

[40] The term “R(Tmax,1h)” as used herein means the proportion of subjects in which Tmax is within 1 hour, relative to the total number of subjects from whom a statistically significant confidence can be ensured after the formulation of the present invention has been administered to the subjects. Considering that one of the main technical features of the formulation according to the present invention is to reduce deviation in Tmax between individuals, R(Tmax,1h) is a concept defined by the present inventors. In principle, Tmax values of a drug may vary from person to person. Therefore, Tmax determined through clinical tests has a statistical meaning. A large deviation in Tmax between individuals means that the onset time varies widely between individuals. In a drug that is regularly administered or a drug whose onset time difference is insignificant, deviation in Tmax may be negligible. In contrast, since sildenafil as the active ingredient of the formulation of the present invention is administered before sexual activity, its onset time is of great importance. Currently commercially available Viagra tablets reach Tmax at one hour after administration. In actual cases, Viagra tablets may have a Tmax of 4 hours in some individuals, showing that there is a large deviation in the onset time of the drug depending on individuals. Under such circumstances, the present inventors have surprisingly found that the presence of sildenafil in the formulation of the present invention shortens Tmax and reduces deviation in Tmax between individuals. Based on this finding, the present

inventors have introduced $R(T_{max}, 1h)$ as a new parameter to specifically define a main technical element by which the proportion of individuals in which T_{max} is less than one hour after administration of the drug can be maintained above a particular level.

- [41] The term “rapidly dissolving carrier” as used herein refers to a constituent carrier of the formulation of the present invention that is rapidly dissolved after oral administration, leaves no feeling of foreign matter and no residual feeling, and can give a feeling of refreshment. It is particularly preferred that the instantaneous solubility, the solubility after 5 minutes and the heat of dissolution of the rapidly dissolving carrier are at least 30 mg/ml, at least 50 mg/ml and -4 Kcal/g or less, respectively. The instantaneous solubility of the rapidly dissolving carrier is preferably 90% or less of the maximum solubility thereof. The rapidly dissolving carrier meeting all of the requirements is suitable for accomplishing the desired effects of the present invention. The rapidly dissolving carrier is not especially limited so long as it is pharmaceutically acceptable, is rapidly dissolved in the oral cavity, leaves no feeling of foreign matter and no residual feeling, and can give a feeling of refreshment. The rapidly dissolving carrier is preferably a sugar or a sugar alcohol. Examples of such rapidly dissolving carriers include, but are not limited to, pharmaceutically acceptable sugars and sugar alcohols, such as xylitol, mannitol, isomaltose, sorbitol, maltitol, refined sugar, lactose, inositol, erythritol, crystalline fructose, trehalose, ribitol, arabitol, galactitol, lactitol, and maltotritol. These rapidly dissolving carriers may be used alone or as a mixture thereof. Any sugar or sugar alcohol meeting the requirements defined in the present invention may be used without limitation, based on the compatibility with the active ingredient and other pharmaceutical considerations. The present invention will now be explained in detail.
- [42] The novel rapidly dissolving granule formulation of the present invention enables administration of sildenafil as the active ingredient without water, achieves greatly enhanced administration convenience, and does not suffer from the inconvenience of orally rapidly disintegrating tablets and strip formulations capable of being taken without water.
- [43] The most popular formulations for oral administration are tablets and capsules that are taken along with water. For drugs, such as sildenafil, that are irregularly administered and require a short onset time, preferred are easy-to-carry formulations that can be taken without water. Under such circumstances, research and development has been conducted on orally rapidly disintegrating tablets and strip formulations containing sildenafil as an active ingredient. Contrary to the expectation that an orally rapidly disintegrating tablet will be rapidly disintegrated in the oral cavity, a patient should hold an orally rapidly disintegrating tablet in the mouth for a considerable time

with an unavoidable feeling of foreign matter and the patient feels a residual feeling even after the tablet has been dissolved, which causes the patient to drink a beverage. For this reason, many patients tend to take orally rapidly disintegrating tablets along with water, which is contradictory to intended goals of the present invention. According to the present inventors' study, it was found that an orally rapidly disintegrating tablet of sildenafil exhibits the efficacy of sildenafil later than general tablets. This finding leads to the conclusion that an orally rapidly disintegrating tablet is not suitable for sildenafil.

- [44] An orally rapidly disintegrating tablet is basically produced by compressing an active ingredient together with a rapidly disintegrating excipient at a low pressure. However, the tablet tends to break during storage or distribution. This necessitates additional packaging of the tablet, which is undesirable in terms of cost-effectiveness. Particularly, sildenafil is not believed to be suitable for an orally rapidly disintegrating tablet due to bitterness thereof. Even in the case of using sildenafil free base to mask the bitterness of sildenafil, the concentration of sildenafil inevitably increases at a site of the oral cavity where an orally rapidly disintegrating tablet is located. This causes a patient to still taste bitterness. It is substantially difficult to prevent a patient from feeling a bitter taste of sildenafil.
- [45] Another representative formulation capable of being taken without water is a strip formulation produced by mounting an active ingredient in a film-like strip made of a film-forming polymer. The strip formulation is more rapidly dissolved than an orally rapidly disintegrating tablet but the amount of the active ingredient loaded therein is basically limited. There is a technical limitation in loading sildenafil, whose dose is typically 50 mg or 100 mg, in the strip formulation. The strip formulation is sensitive to humidity, which increases the possibility of severe distortion or deformation during storage after production. Therefore, special care should be taken in packaging the formulation. Like an orally rapidly disintegrating tablet, the strip formulation encounters a technical difficulty in that additional means is needed to mask the bitterness of a drug such as sildenafil. Sildenafil free base may be used for the purpose of suppressing the bitter taste of sildenafil to some extent. However, the strip formulation located on the tongue tends to keep its place until complete dissolution. As a consequence, sildenafil is dissolved and concentrated at the particular site, causing a patient to still taste its bitterness.
- [46] The stickiness of the film-forming polymer constituting the strip formulation leaves a feeling of foreign matter in the oral cavity after administration. If the formulation sticks to the roof of the patient's mouth, which is an unintended location, after administration, the location is difficult to change, thus failing to achieve greatly enhanced administration convenience.

- [47] On the other hand, since most conventional granule formulations are dissolved or suspended in beverage or water before administration, they are not substantially classified into formulations that can be taken without water. If a granule formulation needing no mixing with beverage or water for administration is taken without water, a feeling of foreign matter and a residual feeling are severely left in the oral cavity, inevitably leading to deterioration of medication compliance.
- [48] Thus, the present inventors have succeeded in developing a novel rapidly dissolving pharmaceutical granule formulation including sildenafil as an active ingredient that can overcome the drawbacks of orally rapidly disintegrating tablets, strip formulations and conventional granule formulations. Surprisingly, the present inventors have found that when a rapidly dissolving carrier meeting particular requirements is used, no feeling of foreign matter and no residual feeling are left and T_{max} is shortened with a small deviation between individuals compared to orally rapidly disintegrating tablets and strip formulations. The present invention has been accomplished based on this finding.
- [49] Specifically, the present invention discloses a novel rapidly dissolving granule formulation that is produced by mixing sildenafil with a rapidly dissolving carrier and wet granulating the mixture with a solution of a pharmaceutically acceptable binder. Alternatively, the rapidly dissolving granule formulation of the present invention may be produced by wet granulating a rapidly dissolving carrier with a solution or dispersion of a pharmaceutically acceptable binder and sildenafil. The rapidly dissolving carrier is preferably a sugar or a sugar alcohol, but is not limited thereto. Particularly preferred is a sugar or a sugar alcohol that meets the following requirements: (1) an instantaneous solubility of at least 30 mg/ml, (2) a solubility after 5 minutes of at least 50 mg/ml, and (3) the instantaneous solubility being 90% or less of a maximum solubility.
- [50] The instantaneous solubility of the rapidly dissolving carrier is calculated as follows. First, 20.0 g of the rapidly dissolving carrier is added to 250 ml of purified water at a temperature of 37 ± 0.5 °C, and then the solubility values of the rapidly dissolving carrier after 1, 3, 5, 10 and 15 minutes are measured at a fixed paddle speed of 50 rpm. The solubility values at 1, 3 and 5 minutes are plotted. Thereafter, a linear regression curve is fitted according to the least square method and is extrapolated to obtain a value of the Y axis intercept. That is, the instantaneous solubility is a theoretical solubility value when time approaches zero infinite. The solubility after 5 minutes means the solubility of the rapidly dissolving carrier measured at 5 minutes. The maximum solubility means the highest solubility of the rapidly dissolving carrier under the same conditions as described above.
- [51] The present inventors have discovered that when the rapidly dissolving carrier has an instantaneous solubility of at least 30 mg/ml and a solubility after 5 minutes of at least 50 mg/ml, the granule formulation of the present invention is rapidly dissolved in the

oral cavity without leaving a feeling of foreign matter and a residual feeling, leading to extreme enhancement of administration convenience. The present inventors have also discovered that when the rapidly dissolving carrier meets the requirements in terms of instantaneous solubility and solubility after 5 minutes but the instantaneous solubility exceeds 90% of the maximum solubility, the granule formulation leaves a feeling of foreign matter and a residual feeling. Particularly, the present inventors have become aware that the two requirements (i.e. rapid dissolution, and no feeling of foreign matter and no residual feeling) of the formulation according to the present invention are associated with not only the solubility of the carrier but also a change in the dissolution rate of the carrier at a microscopic level (that is, despite a high solubility of the carrier, a low dissolution rate or a slow change in dissolution rate at a microscopic level leads to a feeling of foreign matter or a residual feeling). Thus, the present inventors introduced the concept "instantaneous solubility" as a parameter for simultaneously evaluating the dissolution rate and solubility to reflect time-dependent factors at a microscopic level.

[52] Therefore, it should be noted that if the same kind of carrier does not meet the requirements in term of instantaneous solubility and solubility after 5 minutes defined in the present invention, it may be dissolved at a low rate in the oral cavity or may leave a feeling of foreign matter and a residual feeling despite its high dissolution rate in the oral cavity, thus failing to accomplish the desired effects of the present invention.

[53] Specific examples of rapidly dissolving carriers suitable for use in the present invention include, but are not limited to, pharmaceutically acceptable sugars and sugar alcohols, such as xylitol, mannitol, isomaltose, sorbitol, maltitol, refined sugar, lactose, inositol, erythritol, crystalline fructose, trehalose, ribitol, arabitol, galactitol, lactitol and maltotritol. These rapidly dissolving carriers may be used alone or as a mixture thereof. Any sugar or sugar alcohol whose instantaneous solubility and solubility after 5 minutes are at least 30 mg/ml and at least 50 mg/ml, respectively, and whose instantaneous solubility is 90% or less of a maximum solubility may be used to accomplish the desired effects of the present invention, namely, that there is no feeling of foreign matter and no residual feeling. If the rapidly dissolving carrier has an instantaneous solubility of less than 30 mg/ml or a solubility after 5 minutes of less than 50 mg/ml or the instantaneous solubility of the rapidly dissolving carrier exceeds 90% of a maximum solubility, the rapidly dissolving carrier may not be rapidly dissolved in the oral cavity or may leave a feeling of foreign matter and/or a residual feeling in the oral cavity. On the other hand, the dissolution rate of the rapidly dissolving carrier may vary depending on particle size, particle size distribution or specific surface area thereof. However, it is to be noted that the rapidly dissolving carrier can be used without particular limitation irrespective of the specific surface area and particle size

thereof so long as it meets the requirements in terms of instantaneous solubility and solubility after 5 minutes. For example, the sugar alcohol may be subjected to special spray drying to impart porosity. In this case, the porous sugar alcohol may have a high instantaneous solubility exceeding 90% of a maximum solubility due to its small particle size, leaving a feeling of foreign matter and a residual feeling. Therefore, the porous sugar alcohol is not suitable for use as the rapidly dissolving carrier. The requirements associated with instantaneous solubility and solubility after 5 minutes are concepts different from the specific surface area and particle size of the rapidly dissolving carrier. If the specific surface area is large or the particle size is small but the requirements defined in the present invention are not met, the desired effects of the present invention cannot be accomplished. It should be noted that an increase in dissolution rate resulting from a large specific surface area of the carrier is clearly distinguished from the use of the rapidly dissolving carrier meeting the requirements defined in the present invention.

- [54] From the standpoint of imparting a feeling of refreshment, the rapidly dissolving carrier preferably has a heat of dissolution of -4.0 kcal/g or less. For example, xylitol having a heat of dissolution of -36.6 kcal/g is preferred in terms of a feeling of refreshment.
- [55] The rapidly dissolving carrier may be present in an amount of 40 to 98.75% by weight, based on the weight of the granule formulation of the present invention.
- [56] Sildenafil as the active ingredient, together with the rapidly dissolving carrier, constitutes the formulation of the present invention. The term "sildenafil" is intended to include sildenafil free base and pharmaceutically acceptable salts of sildenafil. There is no restriction on the kind of the salts. Sildenafil free base is preferably used for the purpose of masking bitterness. Particularly, according the present inventors' study, an orally rapidly disintegrating tablet or a strip formulation using sildenafil free base is still bitter in taste whereas the granule formulation of the present invention using sildenafil free base completely masks bitterness. Therefore, it should be noted that one of the main technical features of the present invention is a combination of sildenafil free base and the rapidly dissolving carrier for masking bitterness.
- [57] The reason why sildenafil free base is included in the formulation of the present invention to completely mask bitterness, unlike in other formulations including sildenafil, is thought to be due to an organic combination of the rapid dissolution in the oral cavity, the relatively large surface area and the functions of a sugar or a sugar alcohol as the rapidly dissolving carrier.
- [58] The granule formulation of the present invention is particularly suitable when taking into consideration the fact that sildenafil is a more preferable active ingredient as its onset time is shorter and sildenafil is expected to be irregularly administered and needs

immediate medication in a situation where administration is needed.

- [59] Sildenafil needs to be administered urgently in many unexpected situations. There are frequent situations where sildenafil must be rapidly administered even when water is not available. Considering such situations, the formulation of the present invention allows patients to maximally enjoy sildenafil taken without water and leaves no feeling of foreign matter and no residual feeling.
- [60] When compared to other formulations, such as general tablets or orally rapidly disintegrating tablets, containing the same amount of sildenafil, the granule formulation of the present invention has a principal element that the time required to reach a maximum blood concentration (T_{max}) after administration is shortened. This is a very great advantage taking into consideration the characteristics of sildenafil that needs to be administered urgently and exhibits efficacy within a short time. In addition, the formulation of the present invention is effective in shortening T_{max} and reducing deviation in T_{max} between individuals, which are great technical features of the present invention.
- [61] That is, as described above, T_{max} has a standard deviation because it is an average value obtained from many subjects. A larger standard deviation of T_{max} indicates non-uniform in vivo pharmacokinetics of the drug between individuals. Accordingly, in the case of a large standard deviation, there is an inevitable difference in the onset time of the drug between patients. This difference makes it difficult to exactly decide when to administer the drug, such as sildenafil, requiring a short onset time, and as a result, it is substantially impossible to specify a time point for administration that is commonly applicable to individuals.
- [62] According to the present inventors' study, a general sildenafil tablet has a T_{max} of at least 1 hour with a standard deviation of 0.9 hours, implying the possibility of a T_{max} of 4 hours in some individuals. For this reason, the time for the administration of currently commercially available sildenafil-containing tablets is set within a broad range of 1 to 4 hours before sexual activity. Taking into consideration the fact that the half-life of sildenafil-containing tablets is about 2.2 hours, an arbitrary administration time selected from the broad range of 1 to 4 hours before sexual activity may not offer satisfactory efficacy to some patients. Thus, there is an urgent need to develop a formulation that shortens T_{max} and reduces the difference in T_{max} between individuals.
- [63] The present inventors have found that the sildenafil formulation of the present invention shortens T_{max} to one hour or less and minimizes deviation in T_{max} between individuals. Specifically, the present inventors have found that the formulation of the present invention has an R(T_{max},1h) of at least 80%, which indicates that the proportion of subjects in which T_{max} is within 1 hour, relative to the total number of subjects is at least 80% and demonstrates that there is an extremely small difference in

onset time between individuals to whom the formulation of the present invention has been administered. As a result, the formulation of the present invention has an advantage in that a common administration time can be provided to accomplish satisfactory efficacy in most patients, in comparison with conventional tablets.

[64] Sildenafil may be present in an amount of 1.25 to 60% by weight, based on the weight of the granule formulation of the present invention.

[65] Another feature of the formulation according to the present invention is that the formulation leaves a much smaller amount of the active ingredient in the oral cavity after administration than other orally rapidly disintegrating formulations. Specifically, the amount of sildenafil remaining in the oral cavity 30 seconds after administration of the formulation of the present invention is 10% or less of the amount of sildenafil in the formulation before administration. As described above, orally rapidly disintegrating tablets and strip formulations are considered as orally rapidly dissolving formulations containing sildenafil, based on the finding that it is preferred that sildenafil exhibits its efficacy within a short time and is taken without water. However, when orally rapidly disintegrating tablets and strip formulations are taken without water, the active ingredient remains in the oral cavities even after the passage of considerable time. This means that orally rapidly disintegrating tablets and strip formulations are rapidly disintegrated but leave a considerable amount of the active ingredient in the oral cavity unless they are taken along with water. In such a case, the desired efficacy of the active ingredient is not sufficiently exhibited or the onset time of the active ingredient is disadvantageously retarded. In contrast, even when the formulation of the present invention is taken without water, only a very small amount of the active ingredient remains in the oral cavity. When comparing the formulation of the present invention with an orally rapidly disintegrating tablet or a strip formulation containing the same amount of the same active ingredient as the formulation of the present invention, 30 seconds after oral administration without water, the active ingredient of the formulation of the present invention remains in an amount 10 to 20 times smaller than that of the orally rapidly disintegrating tablet or the strip formulation. That is, the active ingredient present in the formulation of the present invention can be rapidly moved to the gastrointestinal tract. In conclusion, the formulation of the present invention has noticeable effects in terms of efficacy and onset time over orally rapidly disintegrating tablets and strip formulations.

[66] The formulation of the present invention is produced by the following procedure. First, the rapidly dissolving carrier is mixed with sildenafil. The mixture is granulated in a granulator while a solution of a pharmaceutically acceptable binder in a solvent is sprayed thereonto. Subsequently, the granules thus produced are mixed with at least one pharmaceutically acceptable excipient, such as a sweetener or a flavor. The

resulting mixture is placed in a packaging container to obtain a granule formulation for one-time administration. Alternatively, the formulation of the present invention may be produced by the following procedure. First, a pharmaceutically acceptable binder and sildenafil are mixed/suspended in a solvent. The rapidly dissolving carrier is granulated in a granulator while the mixture/suspension is sprayed thereonto. Subsequently, the granules thus produced are mixed with at least one pharmaceutically acceptable excipient, such as a sweetener or a flavor. The resulting mixture is put into a packaging container to obtain a granule formulation for one-time administration. One bag of the granule formulation for one-time administration can be administered as a single dose. The granule formulation leaves no feeling of foreign matter and no residual feeling even when taken without water. In addition, the granule formulation gives a feeling of refreshment, eliminating the desire to drink water after administration.

- [67] The granule formulation of the present invention can be supplied as easy-to-carry sachets and three-sided packages (stick forms), but is not limited to these packaging types. A patient can carry the packaged granule formulation in a purse and can take it whenever and wherever the patient wants.
- [68] In any of the production methods, the binder is commonly used to facilitate the formation of particles during granulation. Examples of such binders include pharmaceutically acceptable ones, such as hydroxylpropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), polyvinylpyrrolidone (PVP) and hydroxyethyl cellulose. These binders may be used alone or as a mixture thereof. The binder may be used in the form of a solution in purified water. The binder may be used in an amount of 0.05 to 15% by weight, based to the total weight of the formulation.
- [69] In the present invention, one or more pharmaceutically acceptable flavoring agents may be used to improve the flavor of the formulation and to increase the medication compliance of the formulation. Examples of such pharmaceutically acceptable flavoring agents include orange, grape, apple, lemon, strawberry, cherry, pineapple, banana, tutti-frutti, blueberry, peppermint, cocoa, peach and milk flavoring agents. These flavoring agents may be used alone or as a mixture thereof. The flavoring agents may be used in an amount of 0.001 to 10% by weight, based on the total weight of the formulation.
- [70] In the present invention, one or more sweeteners may be used to enhance the sweetness of the formulation and to increase the medication compliance of the formulation. The sweeteners are important ingredients in direct connection with the administration convenience of formulations for oral administration. The formulation of the present invention uses a sugar or a sugar alcohol as the rapidly dissolving carrier, which acts as a sweetener. In addition to the sugar or sugar alcohol, natural sweeteners and synthetic sweeteners may also be used. Non-limiting examples of such sweeteners

include: pharmaceutically acceptable natural sweeteners, such as sucrose, dextrose, fructose, glucose, liquid glucose and maltose; and pharmaceutically acceptable synthetic sweeteners, such as saccharine, cyclamate, aspartame, acesulfame potassium (K), sucralose, alitame and neotame. The sweeteners may be used in an amount of 0.05 to 20% by weight, based on the total weight of the formulation.

[71] The present invention will be explained with reference to the following examples. However, these examples are provided for illustrative purposes only and are not intended to limit the scope of the invention. It is to be noted that various modifications can be made in the present invention without departing from the spirit and scope of the invention.

[72] Preparative Examples 1-33

[73] Large crystals of the sugars and sugar alcohols (xylitol, sorbitol, maltitol, mannitol, isomaltose, inositol, lactose, refined sugar, crystalline fructose, trehalose and erythritol) shown in Table 1 were pulverized into smaller pieces, followed by sieving to prepare rapidly dissolving carriers (Preparative Examples 1-33). The D50 values (expressed in μm) of the rapidly dissolving carriers are shown in Table 1.

[74] [TABLE 1]

Preparative Example No.	Ingredient	D50
Preparative Example 1	Xylitol	63.4
Preparative Example 2	Xylitol	150.6
Preparative Example 3	Xylitol	370.6
Preparative Example 4	Sorbitol	96.1
Preparative Example 5	Sorbitol	254.2
Preparative Example 6	Sorbitol	751.6
Preparative Example 7	Maltitol	25.4
Preparative Example 8	Maltitol	108.1
Preparative Example 9	Maltitol	235.2
Preparative Example 10	Mannitol	40.0
Preparative Example 11	Mannitol	141.5
Preparative Example 12	Mannitol	381.1
Preparative Example 13	Isomaltose	47.4
Preparative Example 14	Isomaltose	222.3
Preparative Example 15	Isomaltose	390.2
Preparative Example 16	Inositol	49.2
Preparative Example 17	Inositol	86.8
Preparative Example 18	Inositol	273.7
Preparative Example 19	Lactose	30.7
Preparative Example 20	Lactose	112.0
Preparative Example 21	Lactose	192.2
Preparative Example 22	Refined sugar	56.9
Preparative Example 23	Refined sugar	319.7
Preparative Example 24	Refined sugar	413.9
Preparative Example 25	Crystalline fructose	144.0
Preparative Example 26	Crystalline fructose	312.9
Preparative Example 27	Crystalline fructose	468.9
Preparative Example 28	Trehalose	129.7
Preparative Example 29	Trehalose	326.8
Preparative Example 30	Trehalose	512.0
Preparative Example 31	Erythritol	85.3
Preparative Example 32	Erythritol	447.8
Preparative Example 33	Erythritol	648.3

[75] Test Example 1

[76] In this example, the instantaneous solubility values of the rapidly dissolving carriers prepared in Preparative Examples 1-33 were measured. First, 20.0 g of each sample

was placed on a weighing dish and was slowly added to 250 ml of purified water at $37 \pm 0.5^\circ\text{C}$ with stirring at a paddle speed at 50 rpm. The solubility values of the sample after 1, 3, 5, 10 and 15 minutes were measured under the conditions shown in Table 2 and analyzed by the method shown in Table 3. The solubility values at the respective dissolution times are shown in Table 4.

[77]

[TABLE 2]

Parameter	Condition
Sample weight (g)	20
Dissolution test method	Dissolution test method II described in the Korean Pharmacopoeia
Solution volume (mL)	250
Solution temperature ($^\circ\text{C}$)	37 ± 0.5
Paddle speed (rpm)	50
Sampling time (min)	1, 3, 5, 10, 15
Sample volume (mL)	Each 15 (filtered after sampling)

[78]

[TABLE 3]

Parameter		Condition
Test solution preparation		0.3 mL of each sample was diluted to 25 mL with distilled water, and filtered
Standard solution preparation		24 mg of each standard was precisely weighed and was diluted to 25 mL with distilled water
HPLC conditions	Detector	ELSD (Temp.: 80°C , Gas: N_2 25 mL/min)
	Mobile phase	30% acetonitrile
	Flow rate	1 mL/min
	Column	Prevail carbohydrate ES. 250 x 4.6 mm
	Column temperature	40°C
	Loading volume	10 μL

[79]

[TABLE 4]

Preparative Example No.	1 min	3 min	5 min
Preparative Example 1	67	77	77
Preparative Example 2	51	70	74
Preparative Example 3	22	34	44
Preparative Example 4	73	72	76
Preparative Example 5	54	75	77
Preparative Example 6	34	54	66
Preparative Example 7	49	57	61
Preparative Example 8	47	61	72
Preparative Example 9	28	41	50
Preparative Example 10	64	71	73
Preparative Example 11	74	77	76
Preparative Example 12	33	45	49
Preparative Example 13	58	66	71
Preparative Example 14	56	74	79
Preparative Example 15	36	46	48
Preparative Example 16	58	74	80
Preparative Example 17	40	54	73
Preparative Example 18	23	47	52
Preparative Example 19	40	74	76
Preparative Example 20	36	42	51
Preparative Example 21	29	37	45
Preparative Example 22	44	52	60
Preparative Example 23	24	36	46
Preparative Example 24	23	35	45
Preparative Example 25	47	61	71
Preparative Example 26	35	44	52
Preparative Example 27	21	32	40
Preparative Example 28	57	66	72
Preparative Example 29	37	49	58
Preparative Example 30	15	29	39
Preparative Example 31	44	53	58
Preparative Example 32	13	34	51
Preparative Example 33	10	22	41

[80]

The solubility values at 1, 3 and 5 minutes shown in Table 4 were plotted. Thereafter, linear regression curves were fitted according to the least square method and were ex-

trapolated to obtain values of the Y axis intercept. These values were defined as instantaneous solubility values. The instantaneous solubility values and solubility values after 5 minutes of the rapidly dissolving carriers prepared in Preparative Examples 1-33 are shown in Table 5. A judgment was made as to whether the rapidly dissolving carriers met the requirements: instantaneous solubility ≥ 30 mg/ml, solubility after 5 minutes ≥ 50 mg/ml. The results are shown in Table 5.

[81]

[TABLE 5]

Preparative Example No.	Instantaneous solubility	Solubility after 5 minutes	Whether or not the requirements of the present invention were met?
Preparative Example 1	66.2	77	○
Preparative Example 2	47.8	74	○
Preparative Example 3	16.8	44	×
Preparative Example 4	71.4	76	○
Preparative Example 5	51.4	77	○
Preparative Example 6	27.3	66	×
Preparative Example 7	46.7	61	○
Preparative Example 8	41.3	72	○
Preparative Example 9	23.2	50	×
Preparative Example 10	62.5	73	○
Preparative Example 11	74.2	76	×
Preparative Example 12	30.3	49	×
Preparative Example 13	55.3	71	○
Preparative Example 14	52.4	79	○
Preparative Example 15	34.3	48	×
Preparative Example 16	54.2	80	○
Preparative Example 17	30.9	73	○
Preparative Example 18	18.9	52	×
Preparative Example 19	36.3	76	○
Preparative Example 20	31.8	51	○
Preparative Example 21	25.0	45	×
Preparative Example 22	40.0	60	○
Preparative Example 23	18.8	46	×
Preparative Example 24	17.8	45	×
Preparative Example 25	41.7	71	○
Preparative Example 26	30.9	52	○
Preparative Example 27	16.8	40	×
Preparative Example 28	53.8	72	○
Preparative Example 29	32.3	58	○
Preparative Example 30	9.7	39	×
Preparative Example 31	41.2	58	○
Preparative Example 32	4.2	51	×
Preparative Example 33	1.1	41	×

[82]

Examples 1-33

[83]

In accordance with the compositions shown in Tables 6-9, hypromellose and polyvinylpyrrolidone were dissolved in purified water, and then the solution was sprayed onto a mixture of sildenafil and each of the rapidly dissolving carriers prepared in Preparative Examples 1-33 in a fluidized bed granulator (Glatt, Germany) to obtain granules. The granules were mixed with sucralose and peppermint flavor to produce final granules.

[84]

[TABLE 6]

Ingredients		Contents (mg/formulation)								
		Ex. 1	Ex. 2	Ex. 3	Ex. 4	Ex. 5	Ex. 6	Ex. 7	Ex. 8	Ex. 9
Active ingredient	Sildenafil	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0
Rapidly dissolving carrier	Prep. Ex. 1	390.3								
	Prep. Ex. 2		390.3							
	Prep. Ex. 3			390.3						
	Prep. Ex. 4				390.3					
	Prep. Ex. 5					390.3				
	Prep. Ex. 6						390.3			
	Prep. Ex. 7							390.3		
	Prep. Ex. 8								390.3	
	Prep. Ex. 9									390.3
Binder	Hypromellose	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Binder	Polyvinylpyrrolidone	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
Solvent	Purified water	87.5	87.5	87.5	87.5	87.5	87.5	87.5	87.5	87.5
Sweetener	Sucralose	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3
Flavoring agent	Peppermint flavor	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1
Total amount		450	450	450	450	450	450	450	450	450

[85]

[TABLE 7]

Ingredients		Contents (mg/formulation)									
		Ex. 10	Ex. 11	Ex. 12	Ex. 13	Ex. 14	Ex. 15	Ex. 16	Ex. 17	Ex. 18	
Active ingredient	Sildenafil	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0
Rapidly dissolving carrier	Prep. Ex. 10	390.3									
	Prep. Ex. 11		390.3								
	Prep. Ex. 12			390.3							
	Prep. Ex. 13				390.3						
	Prep. Ex. 14					390.3					
	Prep. Ex. 15						390.3				
	Prep. Ex. 16							390.3			
	Prep. Ex. 17								390.3		
	Prep. Ex. 18									390.3	
Binder	Hypromellose	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Binder	Polyvinylpyrrolidone	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
Solvent	Purified water	87.5	87.5	87.5	87.5	87.5	87.5	87.5	87.5	87.5	87.5
Sweetener	Sucralose	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3
Flavoring agent	Peppermint flavor	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1
Total amount		450	450	450	450	450	450	450	450	450	450

[86]

[TABLE 8]

Ingredients		Contents (mg/formulation)									
		Ex. 19	Ex. 20	Ex. 21	Ex. 22	Ex. 23	Ex. 24	Ex. 25	Ex. 26	Ex. 27	
Active ingredient	Sildenafil	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0
Rapidly dissolving carrier	Prep. Ex. 19	390.3									
	Prep. Ex. 20		390.3								
	Prep. Ex. 21			390.3							
	Prep. Ex. 22				390.3						
	Prep. Ex. 23					390.3					
	Prep. Ex. 24						390.3				
	Prep. Ex. 25							390.3			
	Prep. Ex. 26								390.3		
	Prep. Ex. 27									390.3	
Binder	Hypromellose	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Binder	Polyvinylpyrrolidone	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
Solvent	Purified water	87.5	87.5	87.5	87.5	87.5	87.5	87.5	87.5	87.5	87.5
Sweetener	Sucralose	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3	2.3
Flavoring agent	Peppermint flavor	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1
Total amount		450	450	450	450	450	450	450	450	450	450

[87]

[TABLE9]

Ingredients		Contents (mg/formulation)					
		Ex. 28	Ex. 29	Ex. 30	Ex. 31	Ex. 32	Ex. 33
Active ingredient	Sildenafil	50.0	50.0	50.0	50.0	50.0	50.0
Rapidly dissolving carrier	Prep. Ex. 28	390.3					
	Prep. Ex. 29		390.3				
	Prep. Ex. 30			390.3			
	Prep. Ex. 31				390.3		
	Prep. Ex. 32					390.3	
	Prep. Ex. 33						390.3
Binder	Hypromellose	5.0	5.0	5.0	5.0	5.0	5.0
Binder	Polyvinylpyrrolidone	1.3	1.3	1.3	1.3	1.3	1.3
Solvent	Purified water	87.5	87.5	87.5	87.5	87.5	87.5
Sweetener	Sucralose	2.3	2.3	2.3	2.3	2.3	2.3
Flavoring agent	Peppermint flavor	1.1	1.1	1.1	1.1	1.1	1.1
Total amount		450	450	450	450	450	450

[88] Example 34

[89] Granules were produced in the same manner as in Example 2, except that sildenafil citrate was used as an active ingredient instead of sildenafil free base and the contents of the ingredients were changed as shown in Table 10.

[90] [TABLE 10]

Ingredients	Contents (mg/formulation)	
	Example 34	
Active ingredient	Sildenafil citrate (corresponding to 50 mg of sildenafil free base)	70.23
Carrier	Preparative Example 2	390.07
Binder	Hypromellose	5.0
Binder	Polyvinylpyrrolidone	1.3
Solvent	Purified water	62.5
Sweetener	Sucralose	2.3
Flavoring agent	Peppermint flavor	1.1

[91] Example 35

[92] Granules were produced in the same manner as in Example 2, except that sildenafil free base as an active ingredient was dispersed in a binding solution of hypromellose and polyvinylpyrrolidone in purified water, and sprayed onto xylitol to obtain granules.

[93] Example 36

[94] Granules were produced in the same manner as in Example 35, except that sildenafil free base as an active ingredient was dispersed in a binding solution of hypromellose and polyvinylpyrrolidone in 75 wt% ethanol (ethanol 75 wt% and purified water 25 wt%), and sprayed onto xylitol to obtain granules.

[95] Comparative Example 1

[96] In accordance with the composition shown in Table 11, sildenafil free base, corn starch, crospovidone, hydroxypropyl cellulose, Ludiflash, Prosolv and citric acid hydrate were sieved via a 26 mesh screen (600 μ m), and mixed. Colloidal silicon dioxide and sodium stearyl fumarate were sieved via a 30 mesh screen (500 μ m), and mixed. The two mixtures were mixed. The resulting mixture was compressed using a single tablet press (XENA-I, RAON, KOREA).

[97] [TABLE 11]

Ingredients		Contents (mg/formulation)
Active ingredient	Sildenafil free base	50.0
Excipient	Corn starch	31.5
Disintegrant	Crospovidone	40.0
Binder	Hydroxypropyl cellulose	2.3
Excipient	Ludiflash ^{*1}	73.7
Fluidizing agent	Prosol ^{*2}	25.5
Sweetener	Citric acid hydrate	4.0
Fluidizing agent	Colloidal silicon dioxide	1.5
Lubricant	Sodium stearyl fumarate	6.5
Total amount		235

^{*1} Ludiflash, BASF, Germany

^{*2} Prosolve, JRS, Germany

[98] Comparative Example 2

[99] Granules were produced in the same manner as in Comparative Example 1, except that sildenafil citrate was used instead of sildenafil free base and the contents of the ingredients were changed as shown in Table 12.

[100]

[TABLE 12]

Ingredients		Content (mg/formulation)
Active ingredient	Sildenafil citrate (corresponding to 50 mg of sildenafil)	70.23
Excipient	Corn starch	31.5
Disintegrant	Crospovidone	40.0
Binder	Hydroxypropyl cellulose	2.27
Excipient	Ludiflash	53.5
Fluidizing agent	Prosolv	25.5
Sweetener	Citric acid hydrate	4.0
Fluidizing agent	Colloidal silicon dioxide	1.5
Lubricant	Sodium steary fumarate	6.5
Total amount		235

[101] Comparative Example 3

[102] A Viagra 50 mg tablet (corresponding to 50 mg of sildenafil free base) as a sildenafil citrate product was purchased from Pfizer Pharmaceuticals Korea (Australia).

[103] Comparative Example 4

[104] In accordance with the method of Preparative Example 4 presented in Korean Patent Publication No. 10-2011-0041412, an orally disintegrating film was produced using sildenafil free base, crystalline cellulose, carrageenan gum, Polysorbate, mentol, peppermint oil, aspartame, enzymatically modified stevia, glycerin and hydroxypropyl cellulose were used to produce. The film was found to have excellent film-forming properties, texture and solubility.

[105] Comparative Example 5

[106] Granules were produced in the same manner as in Comparative Example 4, except that sildenafil citrate was used instead of sildenafil free base and the contents of the ingredients were changed as shown in Table 13.

[107] [TABLE 13]

Ingredient	Comparative Example 4		Comparative Example 5	
	mg	w/w %	mg	w/w %
Crystalline cellulose	2.50	2.4	3.5	2.4
Carrageenan gum	0.73	0.7	1.0	0.7
Mentol	0.73	0.7	1.0	0.7
Polysorbate	3.33	3.2	4.7	3.2
Peppermint oil	4.06	3.9	5.7	3.9
Aspartame	3.33	3.2	4.7	3.2
Enzymatically modified stevia	0.73	0.7	1.0	0.7
Glycerin	1.67	1.6	2.3	1.6
Sildenafil free base	50.00	48.0	-	-
Sildenafil citrate (corresponding to 50 mg of sildenafil free base)	-	-	70.2	48.0
Hydroxypropyl cellulose	37.08	35.6	52.1	35.6

[108] Test Example 2

[109] The formulations produced in Examples 1-36 and Comparative Examples 1-4 were organoleptically evaluated for dissolution rate, feeling of foreign matter and residual feeling in the oral cavities of six healthy adults, based on the criteria shown in Table 14. The results are shown in Tables 15-17.

[110]

[TABLE 14]

Score	Dissolution rate	Feeling of foreign matter	Residual feeling	
0	After 1 g of each of the formulations was administered to the oral cavity, the time required for complete dissolution of the formulation was measured using stopwatch	No feeling of foreign matter	A	No residual feeling
1		Almost no feeling of foreign matter		
2		Slight feeling of foreign matter	B	Residual feeling
3		Feeling of foreign matter		
4		Feeling of foreign matter and feeling of repulsion	C	Severe residual feeling
5		Severe feeling of foreign matter and feeling of repulsion		

[111]

[TABLE 15]

	Prep. Ex.1	Prep. Ex.2	Prep. Ex.3	Prep. Ex.4	Prep. Ex.5	Prep. Ex.6	Prep. Ex.7	Prep. Ex.8	Prep. Ex.9	Prep. Ex.10	Prep. Ex.11
Dissolution time (sec)	4.8	7.2	14.7	8.0	8.0	17.3	13.0	16.3	22.8	9.0	15.0
Feeling of foreign matter	0.2	1.2	3.5	0.8	1.8	4.5	1.2	2.0	4.2	0.3	4.0
Residual feeling	A	A	B	A	A	B	A	A	B	A	B

[112]

[TABLE 16]

	Prep. Ex.12	Prep. Ex.13	Prep. Ex.14	Prep. Ex.15	Prep. Ex.16	Prep. Ex.17	Prep. Ex.18	Prep. Ex.19	Prep. Ex.20	Prep. Ex.21	Prep. Ex.22
Dissolution time (sec)	19.7	5.7	11.2	12.3	8.5	14.7	26.0	9.0	12.0	14.0	5.8
Feeling of foreign matter	2.5	0.3	1.8	2.6	1.0	1.7	4.3	0.3	0.7	3.2	0.2
Residual feeling	C	A	A	C	A	A	B	A	A	B	A

[113]

[TABLE 17]

	Prep. Ex.23	Prep. Ex.24	Prep. Ex.25	Prep. Ex.26	Prep. Ex.27	Prep. Ex.28	Prep. Ex.29	Prep. Ex.30	Prep. Ex.31	Prep. Ex.32	Prep. Ex.33
Dissolution time (sec)	9.3	13.2	4.7	7.5	9.8	6.3	12.3	14.7	6.7	11.2	17.7
Feeling of foreign matter	3.3	3.7	0.0	1.2	3.2	0.7	1.8	3.2	0.5	3.3	3.7
Residual feeling	B	B	A	A	B	A	A	B	A	B	B

[114] Test Example 3

[115] The formulations produced in Examples 1-36 and Comparative Examples 1-5 were organoleptically evaluated for dissolution rate, feeling of foreign matter and residual feeling in the oral cavities of six healthy adults, based on the criteria shown in Table 18. The results are shown in Table 19.

[116]

[TABLE 18]

Score	Dissolution rate	Feeling of foreign matter	Residual feeling	
0	After 1 g of each of the formulations was administered to the oral cavity, the time required for complete dissolution of the formulation was measured using stopwatch	No feeling of foreign matter	A	No residual feeling
1		Almost no feeling of foreign matter		
2		Slight feeling of foreign matter	B	Residual feeling
3		Feeling of foreign matter		
4		Feeling of foreign matter and feeling of repulsion	C	Severe residual feeling
5		Severe feeling of foreign matter and feeling of repulsion		

[117]

[TABLE 19]

Example No.	Dissolution rate in the oral cavity (sec)	Feeling of foreign matter	Residual feeling
Example 1	5.0	0.5	A
Example 2	7.7	1.3	A
Example 3	15.2	4.2	B
Example 4	8.1	1.2	A
Example 5	8.2	2.0	A
Example 6	17.8	4.7	B
Example 7	13.4	1.5	A
Example 8	16.6	2.0	A
Example 9	23.0	4.5	B
Example 10	9.5	0.8	A
Example 11	15.4	4.2	B
Example 12	20.4	2.5	C
Example 13	6.2	0.7	A
Example 14	11.4	2.0	A
Example 15	12.6	2.7	C
Example 16	9.3	1.2	A
Example 17	15.4	1.8	A
Example 18	26.6	4.8	B
Example 19	9.8	0.7	A
Example 20	12.8	1.2	A
Example 21	14.5	3.5	B
Example 22	6.5	0.8	A
Example 23	9.8	3.5	B
Example 24	13.8	4.3	B
Example 25	5.0	0.5	A
Example 26	7.9	1.7	A
Example 27	10.6	3.5	B
Example 28	6.9	1.0	A
Example 29	12.9	2.2	A
Example 30	15.0	3.5	B
Example 31	6.9	1.0	A
Example 32	12.0	3.8	B
Example 33	18.2	4.0	B
Example 34	8.0	1.5	A
Example 35	7.6	1.3	A
Example 36	7.7	1.5	A
Comparative Example 1	47.3	1.8	B
Comparative Example 2	43.7	1.8	C
Comparative Example 3	-	-	-
Comparative Example 4	127.3	4.5	C
Comparative Example 5	120.5	4.5	C

[118] From the above results, it can be seen that the granule formulations produced using the rapidly dissolving carriers failing to meet either of the requirements in terms of instantaneous solubility, solubility after 5 minutes, and the relationship between the instantaneous solubility and the maximum solubility did not achieve the desired effects of the present invention due to their severe feeling of foreign matter and residual feeling.

[119] Test Example 4

[120] The formulations produced in Examples 1-36 and Comparative Examples 1-5 were organoleptically evaluated for bitterness in 15 healthy male adults, based on the criteria shown in Table 20. The results are shown in Table 21.

[121]

[TABLE 20]

Score	Bitterness
0	No bitterness
1	Almost no bitterness
2	Slight bitterness
3	Bitterness
4	Bitterness and feeling of repulsion
5	Severe bitterness

[122]

[TABLE 21]

Example No.	Bitterness
Example 1	0.0
Example 2	0.2
Example 3	0.2
Example 4	0.0
Example 5	0.3
Example 6	0.2
Example 7	0.0
Example 8	0.3
Example 9	0.2
Example 10	0.2
Example 11	0.3
Example 12	0.2
Example 13	0.3
Example 14	0.2
Example 15	0.3
Example 16	0.2
Example 17	0.0
Example 18	0.2
Example 19	0.2
Example 20	0.0
Example 21	0.3
Example 22	0.0
Example 23	0.0
Example 24	0.2
Example 25	0.0
Example 26	0.0
Example 27	0.2
Example 28	0.2
Example 29	0.2
Example 30	0.2
Example 31	0.0
Example 32	0.0
Example 33	0.2
Example 34	4.0
Example 35	0.0
Example 36	0.0
Comparative Example 1	2.3
Comparative Example 2	4.8
Comparative Example 3	-
Comparative Example 4	2.1
Comparative Example 5	4.7

[123] As can be seen from the above test results, the inventive formulations including sildenafil free base did not have a bitter taste, whereas the formulations including sildenafil citrate as an active ingredient had a bitter taste. Meanwhile, the orally rapidly disintegrating tablets and the orally disintegrating films had a bitter taste despite the use of sildenafil free base as an active ingredient. These results suggest that bitterness can be masked by the combination of sildenafil citrate as an active ingredient and the formulation of the present invention.

[124] Test Example 5

[125] The formulations of Example 2 and Comparative Example 3 were subjected to dissolution tests at pH 1.2 (artificial gastric fluid, Korean Pharmacopoeia) and pH 4.0

(acetate buffer, Korean Pharmacopoeia). The dissolution profiles of the formulations were compared, and the results are shown in Table 22 (Example 2) and Table 23 (Comparative Example 3).

[126]

[TABLE 22]

Example 2	pH 1.2		pH 4.0	
	Dissolution rate (%)		Dissolution rate (%)	
	Mean	Standard deviation (SD)	Mean	Standard deviation (SD)
0	0.0	0.0	0.0	0.0
5	104.4	1.6	87.2	4.0
10	106.2	1.5	95.5	4.8
15	106.2	1.6	97.6	5.1
30	106.3	1.6	99.7	4.5

[127]

[TABLE 23]

Comparative Example 3	pH 1.2		pH 4.0	
	Dissolution rate (%)		Dissolution rate (%)	
	Mean	Standard deviation (SD)	Mean	Standard deviation (SD)
0	0.0	0.0	0.0	0.0
5	69.3	2.9	59.5	8.5
10	82.9	4.0	71.3	8.8
15	86.7	3.5	75.8	7.6
30	89.6	3.3	79.2	6.2

[128]

As a result of the dissolution tests, the formulation of Example 2 showed a complete dissolution rate within 10 minutes after initiation of the dissolution, but the formulation of Comparative Example 3 showed a dissolution rate of about 90% at 30 minutes after initiation of the dissolution. These results reveal that there is a significant difference in initial dissolution rate after initiation of the dissolution between the formulations of Example 2 and Comparative Example 3.

[129]

Test Example 6

[130]

After the formulations of Example 2 and Comparative Example 3 were orally administered to 40 healthy male adults, the pharmacokinetics of sildenafil in blood was measured.

[131]

- Subjects: 40 healthy male adults (nothing except water was allowed to eat after 8:00 p.m. on the evening before the testing)

[132]

- Test drug: Example 2, 1 bag (corresponding to 50 mg of sildenafil free base)

[133]

- Control drug: Comparative Example 3, 1 tablet (Viagra 50 mg tablet, corresponding to 50 mg of sildenafil free base, Pfizer Pharmaceuticals Korea (Australia))

[134]

- Administration mode: The test drug or the control drug was administered orally. Considering the loss half-life of the drug, one week after Phase 1, the test drug and the control drug were crossed with each other to conduct Phase 2 testing (2×2, crossover).

[135]

- Blood sampling: After a heparin-locked catheter was introduced into the brachial vein, blood was sampled at predetermined time intervals (each 10 mL).

[136]

- Blood sampling time: Before administration (0 hour), and 0.25, 0.50, 0.75, 1, 1.25, 1.50, 2, 3, 4, 6, 8, 10, 12 and 24 hours after administration.

[137]

- Sample storage: Each of the blood samples was placed in a vacuum heparin tube

(Vacutainer), mixed and centrifuged at 3,000 for 10 minutes. The supernatant (plasma) was placed in a container and stored in a quick freezer set at -70 °C.

[138] - Results: The analytical results are shown in Table 24.

[139] [TABLE 24]

Parameter	Comparative Example 3			Example 2		
	Mean	Standard deviation (SD)	Coefficient of variation (CV)	Mean	Standard deviation (SD)	Coefficient of variation (CV)
T_{max} (h)	1.1	0.9	85.0	0.7	0.4	59.5
C_{max} (ng/ml)	204.8	81.9	40.0	234.3	98.5	42.0
λ_z (h ⁻¹)	0.3	0.1	21.0	0.3	0.1	26.6
$T_{1/2}$ (h)	2.2	0.7	33.4	2.7	2.9	104.1
AUC_0 (ng*h/ml)	541.5	189.8	35.0	605.6	247.5	40.9
AUC_{inf} (ng*h/ml)	554.5	188.5	34.0	621.3	246.5	39.7
AUC_0/AUC_{inf} (%)	97.7	1.9	1.9	97.5	3.6	3.7

[140] As can be seen from the results in the above table, the time required for the formulation of Example 2 to reach the maximum blood concentration (T_{max}) was shortened by 0.4 hours compared to T_{max} of the formulation of Comparative Example 3. In addition, the standard deviation associated with the T_{max} of the formulation of Comparative Example 3 (0.9 hours) was twice or more as large as that of the formulation of Example 2 (0.4 hours). These results can also be confirmed from the CV values associated with T_{max} . The CV value associated with the T_{max} of the formulation of Example 2 was 59.5, whereas the CV value associated with the T_{max} of the formulation of Comparative Example 3 was 85.0. These results reveal that the inventive formulation remarkably reduced deviation in T_{max} between individuals compared to the general tablet.

[141] Meanwhile, Tables 25 and 26 show the numbers and proportions of subjects belonging to the respective T_{max} values, respectively.

[142] [TABLE 25]

T_{max}	Number of subjects (Comparative Example 3)	Number of subjects (Example 2)
0.5	14	19
0.75	9	15
1	5	2
1.25	3	2
1.5	4	1
2	1	0
3	0	1
4	4	0

[143] [TABLE 26]

T_{max}	Proportion of subjects (Comparative Example 3)	Proportion of subjects (Example 2)
0.5	35%	47.5%
0.75	22.5%	37.5%
1	12.5%	5%
1.25	7.5%	5%
1.5	10%	2.5%
2	2.5%	0%
3	0%	2.5%
4	10%	0%

[144] The above tables show that the proportion of subjects within a T_{max} of 1 hour was higher than 80% (Example 2), that is an $R(T_{max}, 1h)$ of at least 80%. This demonstrates that the presence of sildenafil in the inventive formulation led to a reduction in the deviation of T_{max} between individuals. From the results, the

conclusion can be drawn that the inventive formulation can provide a more general time point for drug administration.

[145] Test Example 7 :Analysis of the amounts of formulations remaining in oral cavities.

[146] In this example, the amounts of the formulations of Example 2, Comparative Example 1 and Comparative Example 4 remaining in the oral cavities of 6 healthy male adults were analyzed by the following procedure.

[147] Each of the subjects was allowed to take one bag of the formulation of Example 2, one tablet of the formulation of Comparative Example 1 or one sheet of the formulation of Comparative Example 4 (each corresponding to 50 mg of sildenafil free base) without water. After 30 seconds, the mouth of the subject was rinsed with 30 ml of water for 10 seconds. The water was collected in a beaker. The mouth of the subject was again rinsed with 30 ml of water for 10 seconds. The water was collected in the beaker (a total of 60 ml). When the residue remained unrecovered, mouth rinsing was repeated to completely remove the residue.

[148] Each of the three test solutions (each 60 ml) was put into a 100 ml flask, and then acetonitrile was added thereto until the final volume reached 100 ml. The content of sildenafil free base in the test solution was analyzed by liquid chromatography. The obtained value was defined as the retention of sildenafil free base in the oral cavity. Table 27 shows the retentions (%) of sildenafil free base in the oral cavities at 30 seconds after taking without water.

[149] [TABLE 27]

	Example 1	Comparative Example 1	Comparative Example 4
Subject 1	3.2	55.1	82.7
Subject 2	2.1	50.9	73.9
Subject 3	2.2	45.8	60.1
Subject 4	2.5	40.1	59.9
Subject 5	3.8	49.8	65.4
Subject 6	2.9	48.3	70.9
Average	2.8	48.3	74.1

[150] From the results in the above table, it can be seen that the retentions of the formulation of Example 2 in the oral cavities were much lower than those of the formulations Comparative Examples 1 and 4, showing that the formulation of Example 2 can be effectively administered without water within a short time.

Industrial Applicability

[151] The novel rapidly dissolving granule formulation of the present invention is rapidly dissolved in the oral cavity, leaves no feeling of foreign matter and no residual feeling, and gives a feeling of refreshment. Particularly, the formulation of the present invention can accomplish the desired effects irrespective of the kind of active ingredient. Therefore, the formulation of the present invention is applicable to various active ingredients. In addition, the formulation of the present invention can be produced in a relatively simple manner. This allows for an economical and efficient

production process.

Claims

- [Claim 1] A rapidly dissolving granule formulation that is produced by granulation of sildenafil or a pharmaceutically acceptable salts thereof as an active ingredient and at least one rapidly dissolving carrier selected from the group consisting of sugars and sugar alcohols, and is rapidly dissolved in the oral cavity after oral administration.
- [Claim 2] The rapidly dissolving granule formulation according to claim 1, wherein the granule formulation is dissolved in the oral cavity within 20 seconds after administration.
- [Claim 3] The rapidly dissolving granule formulation according to claim 1 or 2, wherein the sugars and the sugar alcohols are xylitol, mannitol, isomaltose, sorbitol, maltitol, refined sugar, lactose, inositol, erythritol, crystalline fructose, trehalose, ribitol, arabitol, galactitol, lactitol, maltotritol, and mixtures thereof.
- [Claim 4] The rapidly dissolving granule formulation according to claim 3, wherein the granule formulation is a final dosage form that leaves no feeling of foreign matter and no residual feeling even when taken without water.
- [Claim 5] The rapidly dissolving granule formulation according to claim 1, wherein the rapidly dissolving carrier meets the following requirements:
(1) an instantaneous solubility of at least 30 mg/ml;
(2) a solubility after 5 minutes of at least 50 mg/ml; and
(3) the instantaneous solubility being 90% or less of a maximum solubility.
- [Claim 6] The rapidly dissolving granule formulation according to claim 5, wherein the rapidly dissolving granule formulation has a Tmax of 1 hour or less.
- [Claim 7] The rapidly dissolving granule formulation according to claim 6, wherein the rapidly dissolving granule formulation has an R(Tmax,1h) of at least 80%.
- [Claim 8] The rapidly dissolving granule formulation according to claim 7, wherein the sildenafil is present in an amount of 10% or less of its original amount in the oral cavity 30 seconds after administration.
- [Claim 9] The rapidly dissolving granule formulation according to claim 8, wherein the active ingredient is sildenafil free base and bitterness thereof is masked.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2012/006086**A. CLASSIFICATION OF SUBJECT MATTER*****A61K 9/22(2006.01)i, A61K 9/16(2006.01)i, A61K 9/20(2006.01)i, A61K 31/519(2006.01)i***

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K 9/22; A61K 9/14; A61K 9/00; A61K 9/20; A61K 9/10; A61K 47/40; A61K 9/26; A61K 31/53

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Korean utility models and applications for utility models

Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKOMPASS(KIPO internal) & Keywords: sildenafil, sugar, rapidly dissolving, granule, oral cavity, bitterness, fast dissolving

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	WO 02-062315 A1 (PHARMACIA CORPORATION) 15 August 2002 See the whole document.	1-9

☐ Further documents are listed in the continuation of Box C.☒ See patent family annex.

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INTERNATIONAL SEARCH REPORT

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