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- (71) **Applicant:** HANMI PHARM. CO., LTD. [KR/KR]; 214, Muha-ro, Paltan-myeon, Hwaseong-si, Gyeonggi-do 445-910 (KR).
- (72) **Inventors:** KIM, Yong Il; 147-2201, 57, Hwasan-ro, Paldal-gu, Suwon-si, Gyeonggi-do 442-872 (KR). JEONG, Ki Woo; 306-ho, 6-9, Haryul-ro 1beon-gil, Janggan-gu, Suwon-si, Gyeonggi-do 440-330 (KR). JEONG, Hayoung; 107-404, 21-9, Jingwan 1-ro, Eunpyeong-gu, Seoul 122-731 (KR). KIM, Kyeong Soo; 113-1902, 85, Hwasan-ro, Janggan-gu, Suwon-si, Gyeonggi-do 440-710 (KR). PARK, Jae Hyun; 311-404, 460, Yeongtong-ro, Yeongtong-gu, Suwon-si, Gyeonggi-do 443-737 (KR). WOO, Jong Soo; 120-2303, 85, Hwasan-ro, Janggan-gu, Suwon-si, Gyeonggi-do 440-710 (KR).

(74) **Agent:** FIRSTLAW P.C.; 60 Mabang-Ro, Seocho-Ku, Seoul 137-739 (KR).

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(54) **Title:** CHEWABLE TABLET COMPRISING A PHOSPHODIESTERASE-5 INHIBITOR

(57) **Abstract:** The present invention provides a chewable tablet comprising a phosphodiesterase-5 (PDE-5) inhibitor and a disintegrant having a swelling coefficient ranging from 4 to 8 L/kg which can be taken without water, causing no feeling of irritation in the oral cavity, and thus can improve compliance and patient satisfaction; it also exhibits a rapid disintegration in the oral cavity, therefore can be useful as a therapeutic agent in the treatment of human male erectile dysfunction.



DESCRIPTION

CHEWABLE TABLET COMPRISING A PHOSPHODIESTERASE-5 INHIBITOR

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FIELD OF THE INVENTION

The present invention relates to a chewable tablet comprising a
10 phosphodiesterase-5 (PDE-5) inhibitor or a pharmaceutically acceptable salt
thereof and a disintegrant having controlled swelling coefficient.

BACKGROUND OF THE INVENTION

15 Erectile dysfunction is a medical condition of inability to achieve or
maintain a penile erection sufficient for satisfactory sexual intercourse 25% or
more of the time. This prevalent type of sexual dysfunction is caused by
reduced blood flow to corpus cavernosum, or failure to build up intracavernous
pressure even if the blood flow is sufficient because the supplied blood is not
20 trapped by corpus cavernosum but flows back to vein due to various reasons.
Erectile dysfunction is a very common condition which may occur at any age,
especially occurs more frequently in men over the age of 55. Generally, it is
known that approximately 5 to 10% of adult males suffer from erectile
dysfunction.

25 There is a number of PDE-5 inhibitors developed, which are known for
treatment of erectile dysfunction, as a selective inhibitor of cyclic guanosine
3',5'-monophosphate phosphodiesterase type 5 (cGMP PDE-5), including
Vardenafil, 1-[[3-(1,4-dihydro-5-methyl-4-oxo-7-propylimidazo[5,1-
f][1,2,4]triazin-2-yl)-4-ethoxyphenyl]sulfonyl]-4-ethyl, $C_{23}H_{32}N_6O_4S$;
30 Sildenafil, 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-
d]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methylpiperazine, $C_{22}H_{30}N_6O_4S$;
Tadalafil, (6R,12aR)-6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-
methyl-pyrazino[1',2':1,6]pyrido[3,4-b]indol-1,4-dione, $C_{22}H_{19}N_3O_4$; Udenafil,

$C_{25}H_{36}N_6O_4S$. Accordingly, the use of Vardenafil, Sildenafil, Tadalafil and Udenafil for treating erectile dysfunction is disclosed in KR Pat. Nos. 0430355, 0262926, 0357411 and 0353014, respectively.

Most of the PDE-5 inhibitors are available in tablet form for oral administration. Vardenafil is sold under the name Levitra[®] by Bayer; Sildenafil is sold under the name Viagra[®] by Pfizer; and Tadalafil is sold under the name Cialis[®] by Lilly. Also, Udenafil is sold under the name Zydena[®] by Dong-A Pharmaceutical. The average onset time of these drugs is approximately 60 to 90 minutes, causing great inconvenience to the patients because they have to calculate the time and take the drug in advance of having intercourse. Also, these drugs are in the form of tablet which causes some inconvenience because they must be taken with water. Therefore, there is a strong demand for a research on development of a PDE-5 inhibitor formulation that rapidly disintegrates in the oral cavity which can be taken without water.

Further, PDE-5 inhibitors used for treating human male erectile dysfunction, so called a happy drug, can improve patients' quality of life. Thus, therapeutic effect as well as factors including compliance and satisfaction level of patients must be considered during the development of the formulation. Conventional orally disintegrating tablets or chewable tablets showed a fast disintegration time, however, it was difficult to completely eliminate the unpleasant gritty or sandy sensation in the mouth when the tablet was released in the mouth.

Therefore, the present inventors have endeavored to improve compliance and patient satisfaction of the PDE-5 inhibitor formulation, which can be taken without water, causing no feeling of irritation in the oral cavity with rapid onset of therapeutic effect due to fast-disintegrating property, and have accomplished the present invention.

SUMMARY OF THE INVENTION

Therefore, it is an object of the present invention to provide a chewable tablet comprising a phosphodiesterase-5 inhibitor which rapidly disintegrates in the oral cavity without causing feeling of irritation for convenient

administration.

In accordance with one object of the present invention, there is provided a chewable tablet comprising a phosphodiesterase-5 inhibitor or a pharmaceutically acceptable salt thereof; and a disintegrant having a swelling coefficient ranging from 4 to 8 L/kg.

Also, there is provided a chewable tablet which further comprising sugar, sugar alcohol or a mixture thereof.

The chewable tablet comprising PDE-5 inhibitor in accordance with the present invention can be taken without water, causing no feeling of irritation in the oral cavity, and thus can improve compliance and patient satisfaction; it also exhibits a rapid disintegration in the oral cavity, therefore can be useful as a therapeutic agent in the treatment of human male erectile dysfunction.

DETAILED DESCRIPTION OF THE INVENTION

The chewable tablet in accordance with the present invention comprising a PDE-5 inhibitor or a pharmaceutically acceptable salt thereof as an active ingredient together with a disintegrant having controlled swelling coefficient has an advantage of rapid onset time of therapeutic effect which rapidly disintegrates in the oral cavity without causing feeling of irritation, and thus shows a high level of patient satisfaction.

The active ingredient of the chewable tablet of the present invention may be a PDE-5 inhibitor including Vardenafil, Sildenafil, Tadalafil, Udenafil or a pharmaceutically acceptable salt thereof, preferably Sildenafil free base.

The PDE-5 inhibitor or a pharmaceutically acceptable salt thereof may be employed in an amount ranging from 5 to 100 mg per tablet, 0.1 to 80% by weight, preferably 1 to 70% by weight, based on the total weight of the formulation.

The disintegrant is an essential ingredient used for rapid disintegration of the chewable tablet of the present invention, which may be employed in an amount ranging from 1.5 to 15% by weight, based on the total weight of the

formulation. If the amount of the disintegrant exceeds 15%, tableting properties of the formulation deteriorate and it becomes difficult to maintain the shape of the tablet. On the contrary, if the amount used is less than 1.5%, it does not act as a disintegrant effectively, causing delayed disintegration of the
5 tablet.

There are three major mechanisms how disintegrant disintegrate tablets:

(1) Swelling: particles of a disintegrant swell on coming in contact with a medium such as saliva and a swelling force of a disintegrant develops which leads to break-up the tablet. The examples of this type of disintegrants are
10 sodium croscarmethylcellulose, sodium starch glycolate, pregelatinized starch, *etc.*;

(2) Porosity and capillary action: when the tablet was put into a medium such as saliva, the medium penetrates into the tablet through capillary action causing the tablet to break apart. The examples of this type of disintegrants are
15 corn starch, sodium alginate, *etc.*; and

(3) Deformation: particles of a disintegrant get deformed during tablet compression and the particles recover their normal structure when they come in contact with a medium such as saliva. The examples of this type of disintegrants are crospovidone, starch grain, *etc.* (*see John C Carter, The role of*
20 *disintegrants in solid oral dosage manufacturing, Carter Pharmaceutical Consulting, Inc.*).

The disintegrants are generally water-insoluble, and thus, they are largely responsible for causing unpleasant feeling of irritation when taken orally as a chewable tablet. Hence, the diameter and swelling coefficient of
25 disintegrants are considered as two critical factors which affect feeling of irritation of a chewable tablet. An increase in the diameter of a disintegrant causes an increase in the feeling of irritation; and, similarly, when the swelling coefficient of a disintegrant is increased, so is the feeling of irritation. However, if the swelling coefficient of a disintegrant is too small, the
30 disintegrant may not effectively serve its original purpose and cause bigger particles to remain in the mouth, thereby resulting greater feeling of irritation. It is essential to use disintegrants having suitable diameters and swelling coefficients in the preparation of a chewable tablet with fast-disintegrating

properties without causing too much feeling of irritation in the oral cavity.

In the present invention, the swelling coefficient of the disintegrant may be in the range of 2 to 12 L/kg, preferably 4 to 8 L/kg. Also, the diameter of the disintegrant may vary depending on the swelling coefficient as described
5 above, for example, in the range of 5 to 250 μm .

In accordance with one embodiment of the present invention, the disintegrants employable include the following examples in said range as described above: Polyplasdone XL-10 (crospovidone) (5.4 L/kg), Polypladone XL (crospovidone) (5.8 L/kg), Kollidon CL (crospovidone) (4.3 L/kg), Kollidon
10 CL-M (crospovidone) (7.2 L/kg), Ac-Di-Sol (sodium croscarmethylcellulose) (13.5 L/kg), and StarCap 1500 (corn starch) (1.8 L/kg).

However, the disintegrants employable in the present invention are not limited to the said particular examples; and any disintegrant having suitable
15 diameter and swelling coefficient may be used in the present invention.

The chewable tablet of the present invention may further comprise sugar, sugar alcohol or a mixture thereof. Said sugar, sugar alcohol or a mixture thereof is considered as an important ingredient because it gives sweet taste in the mouth and affects solubility, texture, etc, and thus, it should possess sweet
20 flavor as well as good solubility. Examples of the sugar in the present invention include lactose, glucose, sucrose, fructose, levulose, maltodextrin, palatinose and the like. Examples of the sugar alcohol in the present invention include mannitol, sorbitol, xylitol, erythritol and the like. The porous sugar or sugar alcohol is prepared by spray drying, *etc.* is preferable to increase
25 solubility thereof in the oral cavity. In one embodiment of the present invention, spray dried mannitol (Mannitol SD 200) is used. In the present invention, the sugar, sugar alcohol or a mixture thereof may be employed in an amount ranging from 10 to 98% by weight, preferably 20 to 95% by weight, based on the total weight of the formulation. If the amount employed is less
30 than 10%, then the sweet taste and texture in the oral cavity may deteriorate.

In addition to the ingredient explained above, the composition in accordance with the present invention may further comprise one or more of

pharmaceutically acceptable additives, for example, those selected from the group consisting of a flavoring agent, a coloring agent, a sweetening agent and a lubricant.

5 The flavoring agent may be employed to improve the taste by giving a good flavor when the chewable tablet is administered orally. Specific examples may include peppermint flavor, spearmint flavor, various fruit flavors, *etc.*

10 The coloring agent may be employed to improve the appearance of the chewable tablet. Examples of the coloring agent include Green No. 3, Red No. 2, Red No. 3, Blue No. 1, Blue No. 2, Yellow No. 4, Yellow No. 5, caramel, titanium dioxide, ferric oxide or other natural coloring agents.

15 The sweetening agent may be employed to give a sweet flavor and soften the texture for improving patient compliance. Specific examples may include stevioside, xylitol, sucralose, aspartame, acesulfame potassium, sucrose, erythritol and a mixture thereof.

Specific examples of the lubricant include stearic acid, metal stearate salt such as calcium stearate or magnesium stearate, talc, colloidal silica, sugar fatty acid ester, hydrogenated vegetable oil, wax with high melting point, glyceryl dibehenate and a mixture thereof.

20

The average hardness of the chewable tablet in accordance with the present invention may be controlled for rapid disintegration in the oral cavity, preferably in the range of 2 kp to 17 kp. In accordance with one embodiment of the present invention, the average hardness of the chewable tablet may be in the range of 2 to 15 kp, more preferably 8 to 15 kp. If the value is less than 2 kp, the chewable tablet easily shatters, thereby causing a difficulty during packaging and distribution processes. Whereas, the hardness of greater than 17 kp causes a delay in disintegration of chewable tablet in the oral cavity, thereby lowering patient compliance.

30

Hereinafter, the present invention is described more specifically by the following examples, but these are provided only for illustration purposes, and the present invention is not limited thereto.

Reference Example: Measurement of Swelling Coefficient of Disintegrant

10 grams of each of Polyplasdone XL-10 (ISP Pharmaceuticals, U.S.),
5 Polyplasdone XL (ISP Pharmaceuticals, U.S.), Kollidon CL (BASF, Germany),
Kollidon CL-M (BASF, Germany), sodium croscarmethylcellulose (Ac-Di-
Sol, DFE, Germany), and corn starch (StarCap 1500, Roquette, France) were
placed in separate 100 mL volumetric flasks, and added with water to the 100
mL mark. The resulting mixtures were stirred for 24 hours and degrees of
10 swelling in each sample were measured (Anisul Q. *et al.*, A comparative study
of current superdisintegrants, Pharmaceutical technology 2006). The results of
the measurement of the swelling coefficients of the samples are as follows:
Polyplasdone XL-10 (5.4 L/kg), Polyplasdone XL (5.8 L/kg), Kollidon CL (4.3
L/kg), Kollidon CL-M (7.2 L/kg), sodium croscarmethylcellulose (Ac-Di-
15 Sol) (13.5 L/kg), and corn starch (StarCap 1500) (1.8 L/kg).

Example 1 and Comparative Examples 1 and 2: Preparation of chewable tablets with different types of disintegrants

20 In accordance with the ingredients listed in Table 1 below, a chewable
tablet comprising sildenafil as an active ingredient was prepared by using
sildenafil free base (Dong Woo Pharm., Korea), spray dried mannitol (Roquette,
France), crospovidone, (diameter of 30 to 50 μm , Polyplasdone XL-10, ISP
Pharmaceuticals, U.S.), enzymatically modified stevia (Daepyeong, Korea),
25 peppermint powder (Samjung Flavor, Korea), Blue No. 2 aluminum lake (Bolak,
Korea) and magnesium stearate (NOF, Japan). Specifically, the ingredients
listed in Table 1 were mixed and tableted with the compression force of about
5 kN using a tableting machine (MRC-45, Sejong Pharmatech, Korea) to obtain
the chewable tablet having a hardness of about 15 kp.

30 Also, for Comparative Examples 1 and 2, the above procedure was
repeated, except for using sodium croscarmethylcellulose (diameter of 45
to 74 μm , DFE, Germany) and corn starch (diameter of 74 to 125 μm , Roquette,
France) to obtain chewable tablets.

[Table 1]

	Example 1		Comparative Example 1		Comparative Example 2	
	Amount (mg)	Weight%	Amount (mg)	Weight%	Amount (mg)	Weight %
Sildenafil	100	18.17	100	18.17	100	18.17
Spray dried mannitol	400	72.66	400	72.66	400	72.66
Crospovidone (Polyplasdone XL-10)	30	5.45	-	-	-	-
Sodium croscarmethylcellulose	-	-	30	5.45	-	-
Corn starch	-	-	-	-	30	5.45
Enzymatically modified stevia	10	1.82	10	1.82	10	1.82
Peppermint powder	5	0.91	5	0.91	5	0.91
Blue No. 2 aluminum lake	0.5	0.09	0.5	0.09	0.5	0.09
Magnesium stearate	5	0.91	5	0.91	5	0.91

Examples 1 to 4: Preparation of chewable tablets with different diameter of crospovidone

In accordance with the ingredients listed in Table 2 below, chewable tablets were prepared by repeating the procedure of Example 1, except for using commercially available crospovidone with different diameters: Polyplasdone XL (diameter of 100 to 130 μm , ISP Pharmaceuticals, U.S.), Kollidon CL (diameter of 50 to 250 μm , BASF, Germany) and Kollidon CL-M (diameter of 5 to 15 μm).

[Table 2]

	Example 1		Example 2		Example 3		Example 4	
	Amt. (mg)	Wt%	Amt. (mg)	Wt%	Amt. (mg)	Wt%	Amt. (mg)	Wt%
Sildenafil	100	18.17	100	18.17	100	18.17	100	18.17
Spray dried mannitol	400	72.66	400	72.66	400	72.66	400	72.66
Crospovidone (Polyplasdone XL-10)	30	5.45	-	-	-	-	-	-
Crospovidone (Polyplasdone XL)	-	-	30	5.45	-	-	-	-
Crospovidone (Kollidon CL)	-	-	-	-	30	5.45	-	-
Crospovidone (Kollidon CL-M)	-	-	-	-	-	-	30	5.45

Enzymatically modified stevia	10	1.82	10	1.82	10	1.82	10	1.82
Peppermint powder	5	0.91	5	0.91	5	0.91	5	0.91
Blue No. 2 aluminum lake	0.5	0.09	0.5	0.09	0.5	0.09	0.05	0.09
Magnesium stearate	5	0.91	5	0.91	5	0.91	5	0.91

Examples 1, 5 to 7 and Comparative Examples 3, 4: Preparation of chewable tablets with different amounts of crospovidone

- 5 In accordance with the ingredients listed in Table 3 below, chewable tablets were prepared by repeating the procedure of Example 1, except for changing the amounts of crospovidone used.

[Table 3]

	Comparative Example 3		Example 5		Example 1		Example 6		Example 7		Comparative Example 4	
	Amt. (mg)	Wt%	Amt. (mg)	Wt%	Amt. (mg)	Wt%	Amt. (mg)	Wt%	Amt. (mg)	Wt%	Amt. (mg)	Wt%
Sildenafil	100	19.03	100	18.85	100	18.17	100	17.23	100	16.38	100	15.61
Spray dried mannitol	400	76.12	400	75.40	400	72.66	400	68.91	400	65.522	400	62.45
Crospovidone (Polyplasdone XL-10)	5	0.95	10	1.89	30	5.45	60	10.34	90	14.74	120	18.74
Enzymatically modified stevia	10	1.90	10	1.89	10	1.82	10	1.72	10	1.64	10	1.56
Peppermint powder	5	0.95	5	0.94	5	0.91	5	0.86	5	0.82	5	0.78
Blue No. 2 aluminum lake	0.5	0.1	0.5	0.09	0.5	0.09	0.5	0.09	0.5	0.08	0.5	0.08
Magnesium stearate	5	0.95	5	0.94	5	0.91	5	0.86	5	0.82	5	0.78

10

Examples 1, 8 and Comparative Examples 5, 6: Preparation of chewable tablets with different types of excipients

- 15 In accordance with the ingredients listed in Table 4 below, chewable tablets were prepared by repeating the procedure of Example 1, except for using anhydrous lactose (DFE, Germany), microcrystalline cellulose (Mingtai,

Taiwan), or anhydrous calcium hydrogen phosphate (Innophos, U.S.) instead of spray dried mannitol.

[Table 4]

	Example 1		Example 8		Comparative Example 5		Comparative Example 6	
	Amt. (mg)	Wt%	Amt. (mg)	Wt%	Amt. (mg)	Wt%	Amt. (mg)	Wt%
Sildenafil	100	18.17	100	18.17	100	18.17	100	18.17
Spray dried mannitol	400	72.66	-	-	-	-	-	-
Anhydrous lactose	-	-	400	72.66	-	-	-	-
Microcrystalline cellulose	-	-	-	-	400	72.66		
Anhydrous calcium hydrogen	-	-	-	-	-	-	400	72.66
Crospovidone (Polyplasdone LX-10)	30	5.45	30	5.45	30	5.45	30	5.45
Enzymatically modified stevia	10	1.82	10	1.82	10	1.82	10	1.82
Peppermint powder	5	0.91	5	0.91	5	0.91	5	0.91
Blue No. 2 aluminum lake	0.5	0.09	0.5	0.09	0.5	0.09	0.5	0.09
Magnesium stearate	5	0.91	5	0.91	5	0.91	5	0.91

5

Experimental Example: Degree of feeling of irritation in the oral cavity and disintegration test

(1) Degree of feeling of irritation in the oral cavity

10 The degree of feeling of irritation in the oral cavity was evaluated when chewable tablets obtained in Examples 1 to 8 and Comparative Examples 1 to 6 were administered, and the results are shown in Tables 5, 7, 9 and 11.

15 The test was performed on 10 healthy human male subjects in their 20s who volunteered. In order to minimize individual differences, an oral administration procedure was set up and applied to the test, which comprises the following steps of: (1) using approximately 20 mL of water to wet the oral cavity so as to prevent dry mouth; (2) administering the tablet in the mouth, followed by chewing the tablet within 20 seconds using teeth near incisor teeth

to prevent the tablet pieces to be stuck between teeth; and (3) evaluating a feeling of irritation in the oral cavity by rubbing the tablet particles formed against tongue and palate. The results were evaluated on a scale of 0 to 5 (1: feeling of irritation disappears within 15 sec, 2: feeling of irritation disappears within 30 sec, 3: feeling of irritation disappears within 45 sec, 4: feeling of irritation disappears within 60 sec, 5: feeling of irritation remains after 60 sec and difficult to swallow).

(2) Disintegration test of chewable tablet

The disintegration test was performed on the chewable tablets comprising sildenafil obtained in Examples 1 to 8 and Comparative Examples 1 to 6 and the results are shown in Tables 6, 8, 10 and 12 below. The test was conducted in accordance with the disintegration test method described in Korea pharmacopoeia using distilled water as a disintegration solution and the disintegration time was recorded when the tablet was completely dissolved on the bottom of the container.

(3) Result and analysis

The results of the degree of feeling of irritation in the oral cavity and disintegration test of the chewable tablets prepared by employing different types of disintegrant obtained in Example 1 and Comparative Examples 1 and 2 are shown in Tables 5 and 6 below.

[Table 5]

	Example 1	Comparative Example 1	Comparative Example 2
Subject 1	1	4	3
Subject 2	1	5	4
Subject 3	0	3	2
Subject 4	0	4	2
Subject 5	1	4	3
Subject 6	1	5	3
Subject 7	1	4	2
Subject 8	2	5	3
Subject 9	1	4	3
Subject 10	1	5	4
Average	0.9	4.3	2.9

[Table 6]

	Example 1	Comparative Example 1	Comparative Example 2
1	12	10	32
2	11	10	31
3	12	11	33
4	13	10	29
5	10	12	30
6	13	12	27
Average (sec)	11.8	10.8	30.3

As shown in Table 5 above, the satisfaction levels of patients for the chewable tablet comprising crospovidone of Example 1 were high, having the average degree of feeling of irritation value of 0.9, whereas the average degrees of feeling of irritation for Comparative Examples of 1 and 2 each comprising sodium croscarmethylcellulose and corn starch were 4.3 and 2.9, respectively, which are very high showing relatively low levels of patient satisfaction. The degrees of feeling of irritation of crospovidone were low because it has the average diameter of 30 to 50 μm and does not swell much after coming in contact with water. However, the average diameter of sodium croscarmethylcellulose is 45 to 74 μm and it swells to about 13.5 times its original volume on contact with water; and corn starch has the average diameter of about 74 to 125 μm , but its relatively weak swelling force caused high level of feeling of irritation in the oral cavity. Therefore, it can be concluded that the most preferred disintegrant in the present invention is crospovidone.

Also, as shown in Table 6 above, the disintegration times for the chewable tablets obtained in Example 1 and Comparative Example 1 all came out to be about 10 seconds. Thus, it can be concluded that crospovidone and sodium croscarmethylcellulose were suitable as a disintegrant, but corn starch of Comparative Example 2 seemed inappropriate to be used as a disintegrant due to its poor swelling force.

Meanwhile, the results of the degree of feeling of irritation in the oral cavity and disintegration test of the chewable tablets prepared by using different diameters of crospovidone obtained in Examples 1 to 4 and the results are shown in Tables 7 and 8 below.

[Table 7]

	Example 1	Example 2	Example 3	Example 4
Subject 1	1	1	1	2
Subject 2	1	2	2	2
Subject 3	0	1	1	2
Subject 4	0	1	1	1
Subject 5	1	1	1	2
Subject 6	1	2	2	3
Subject 7	1	1	1	2
Subject 8	2	2	1	3
Subject 9	1	2	1	3
Subject 10	1	1	1	2
Average	0.9	1.4	1.2	2.2

[Table 8]

	Example 1	Example 2	Example 3	Example 4
1	12	8	15	11
2	11	7	18	11
3	12	8	19	10
4	13	7	17	12
5	10	8	17	11
6	13	9	19	10
Average (sec)	11.8	7.8	17.5	10.8

5 As shown in Table 7 above, the satisfaction levels of patients for the chewable tablet comprising crospovidone with different diameters of Examples 1 to 4 were high, having the average degree of feeling of irritation value of 2.2 or less.

Also, as shown in Table 8 above, the disintegration time varied
 10 depending on the swelling coefficient. However, the chewable tablets of Examples 1 to 4 all demonstrated short disintegration times.

In summary of the results of Tables 7 and 8, the chewable tablets of the present invention showed high levels of patient satisfaction and short disintegration times when crospovidone having swelling coefficient ranging
 15 from 4 to 8 L/kg and having the diameter of 5 to 250 μm was employed.

Meanwhile, the results of the degree of feeling of irritation in the oral cavity and disintegration time test of the chewable tablets prepared by varying

the amount of crospovidone obtained in Examples 1, 5 to 7 and Comparative Examples 3 and 4 and the results are shown in Tables 9 and 10 below.

[Table 9]

	Comparative Example 3	Example 5	Example 1	Example 6	Example 7	Comparative Example 4
Subject 1	3	2	1	2	3	3
Subject 2	2	1	1	2	3	4
Subject 3	1	1	0	1	2	3
Subject 4	1	0	0	2	2	4
Subject 5	2	1	1	2	3	4
Subject 6	2	2	1	2	3	4
Subject 7	3	0	1	2	3	3
Subject 8	2	1	2	3	3	4
Subject 9	2	1	1	2	2	3
Subject 10	3	1	1	3	3	4
Average	2.1	1.0	0.9	2.1	2.7	3.6

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[Table 10]

	Comparative Example 3	Example 5	Example 1	Example 6	Example 7	Comparative Example 4
1	35	16	12	10	8	6
2	33	18	11	7	8	5
3	34	20	12	11	6	6
4	34	23	13	12	9	7
5	39	22	10	9	10	7
6	43	19	13	10	7	6
Average (sec)	36.3	19.7	11.8	9.8	8.0	6.2

As shown in Table 9 above, the satisfaction levels of patients for the chewable tablets comprising crospovidone in an amount of 5 to 90 mg of Examples 1, 5 to 7 and Comparative Example 3 were high, having the average degree of feeling of irritation value of 3 or less, whereas Comparative Example 4 which employed crospovidone in an amount of 120 mg (18.74% by weight), resulted relatively high degree of feeling of irritation. This is because crospovidone is insoluble in water, and as the amount of crospovidone increases, the amount remains in the oral cavity also increases.

Also, as shown in Table 10 above, the disintegration time was decreased as the amount of crospovidone increased. The disintegration time of Comparative Example 3, wherein the least amount of crospovidone was

employed, was 36.3 seconds and the degree of feeling of irritation in the oral cavity was relatively higher than other tablets considering the amount of crospovidone employed, as can be seen in Table 9, owing to the long disintegration time.

- 5 In summary of the results of Tables 9 and 10, the amount of crospovidone employed in the chewable tablet of the present invention is preferably 1.5 to 15% by weight, based on the total weight of the formulation.

10 Meanwhile, the results of the degree of feeling of irritation in the oral cavity and disintegration time test of the chewable tablets prepared by employing different types of excipients obtained in Examples 1, 8 and Comparative Examples 5 and 6, and the results are shown in Tables 11 and 12 below.

15 [Table 11]

	Example 1	Example 8	Comparative Example 5	Comparative Example 6
Subject 1	1	1	3	4
Subject 2	1	2	4	4
Subject 3	0	1	3	3
Subject 4	0	1	3	3
Subject 5	1	2	3	4
Subject 6	1	2	4	4
Subject 7	1	1	3	3
Subject 8	2	2	4	4
Subject 9	1	1	3	3
Subject 10	1	2	3	4
Average	0.9	1.5	3.3	3.6

[Table 12]

	Example 1	Example 8	Comparative Example 5	Comparative Example 6
1	12	12	39	42
2	11	14	42	45
3	12	15	38	39
4	13	14	38	46
5	10	12	44	48
6	13	15	36	41
Average (sec)	11.8	13.7	39.5	43.5

As shown in Table 11 above, the satisfaction levels of patients for the chewable tablets comprising spray dried mannitol and anhydrous lactose of Examples 1 and 8 were high, resulting the average degrees of feeling of irritation value of 0.9 to 1.5. Comparative Examples 5 and 6 comprising microcrystalline cellulose and anhydrous calcium hydrogen phosphate resulted relatively higher degrees of feeling of irritation in the oral cavity, 3.3 to 3.6 which was somewhat higher than Examples 1 and 8, yet test subjects did not experience difficulties when they took the tablets. The difference in the average degrees of feeling of irritation was due to water solubility. The spray dried mannitol and anhydrous lactose are highly soluble in water, whereas microcrystalline cellulose and anhydrous calcium hydrogen phosphate are almost insoluble in water. However, the average diameters of microcrystalline cellulose and anhydrous calcium hydrogen phosphate were in the range of 100 to 200 μm , which were small, and hence the test subjects did not experience unpleasant feelings caused by feeling of irritation.

Also, as shown in Table 12 above, the disintegration time was affected by the solubility of excipients. The chewable tablets of Examples 1 and 8 which employed spray dried mannitol and anhydrous lactose rapidly disintegrated, each having disintegration time of 11.8 and 13.7 seconds, respectively, whereas the chewable tablets of Comparative Examples 5 and 6 which employed microcrystalline cellulose and anhydrous calcium hydrogen phosphate disintegrated relatively slowly, each having disintegration time of 39.5 and 43.5 seconds.

As can be seen from the results of Tables 11 and 12 above, the preferred excipients employable for the chewable tablet in accordance with the present invention are spray dried mannitol and anhydrous lactose; and spray dried mannitol is the most effective in particular. This is due to a porous surface of spray dried mannitol obtained by the spray drying process as well as high solubility of mannitol which disintegrates rapidly in the oral cavity.

What is claimed is:

1. A chewable tablet comprising a phosphodiesterase-5 (PDE-5) inhibitor or a pharmaceutically acceptable salt thereof; and a disintegrant having a swelling coefficient ranging from 4 to 8 L/kg.
2. The chewable tablet of claim 1, wherein the PDE-5 inhibitor is sildenafil free base.
3. The chewable tablet of claim 1, wherein the chewable tablets further comprises sugar, sugar alcohol or a mixture thereof.
4. The chewable tablet of claim 3, wherein the sugar is selected from the group consisting of lactose, glucose, sucrose, fructose, levulose, maltodextrin and palantinos; and the sugar alcohol is selected from the group consisting of mannitol, sorbitol, xylitol and erythritol.
5. The chewable tablet of claim 3, wherein the sugar alcohol is spray-dried mannitol.
6. The chewable tablet of claim 3, wherein the sugar, sugar alcohol or a mixture thereof is employed in an amount ranging from 10 to 98% by weight, based on the total weight of the formulation.
7. The chewable tablet of claim 1, wherein the diameter of the disintegrant employed is 5 to 250 μm .
8. The chewable tablet of claim 1, wherein the disintegrant is employed in an amount ranging from 1.5 to 15% by weight, based on the total weight of the formulation.
9. The chewable tablet of claim 1, wherein the average hardness of the tablet is in the range of 2 to 17 kp.

10. The chewable tablet of claim 3, wherein the chewable tablet comprises sildenafil free base, spray-dried mannitol and a disintegrant having a swelling coefficient ranging from 4 to 8 L/kg.

11. The chewable tablet of claim 1, wherein the chewable tablet further comprises one or more of pharmaceutically acceptable additives selected from the group consisting of a flavoring agent, a coloring agent, a sweetening agent and a lubricant.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2013/010739**A. CLASSIFICATION OF SUBJECT MATTER****A61K 9/68(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 9/68; A61K 31/4985; A61P 15/00; A61K 31/522; A61K 9/16; A61K 31/519; A61K 9/20

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: chewable tablet, phosphodiesterase-5 (PDE-5) inhibitor, swelling coefficient

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2011-030351 A2 (RUBICON RESEARCH PRIVATE LIMITED) 17 March 2011 See pages 8, 17 and 26-32; and claims 1-3, 5 and 22-24.	1-11
A	GOEL, H. et al., 'Orally disintegrating systems: innovations in formulation and technology', Recent Patents on Drug Delivery & Formulation, 2008, Vol. 2, pages 258-274. See abstract; and page 268.	1-11
A	US 2012-0295916 A1 (WINTER, S. et al.) 22 November 2012 See paragraphs [0007], [0014], [0062], [0117], [0154], [0169] and [0170]; and claims 1-4.	1-11
A	WO 2004-017976 A1 (PHOQUS PHARMACEUTICALS LIMITED) 04 March 2004 See pages 17 and 18; and claims 1, 2 and 21.	1-11
A	NEGI, J. S. et al., 'Effect of bioadhesion on initial in vitro buoyancy of effervescent floating matrix tablets of ciprofloxacin HCL', Journal of Advanced Pharmaceutical Technology & Research, 2011, Vol. 2, No. 2, pages 121-127. See abstract; and pages 122 and 123.	1-11



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

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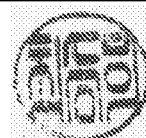
Korean Intellectual Property Office
189 Cheongsu-ro, Seo-gu, Daejeon Metropolitan City,
302-701, Republic of Korea

Facsimile No. +82-42-472-7140

Authorized officer

CHOI, Sung Hee

Telephone No. +82-42-481-8740



INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/KR2013/010739

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2011-030351 A2	17/03/2011	WO 2011-030351 A3	30/06/2011
US 2012-0295916 A1	22/11/2012	EP 2338474 A1	29/06/2011
		EP 2515852 A1	31/10/2012
		WO 2011-076411 A1	30/06/2011
WO 2004-017976 A1	04/03/2004	AU 2003-255822 A1	11/03/2004
		AU 2003-259336 A1	11/03/2004
		CA 2496106 A1	04/03/2004
		EP 1539112 A1	15/06/2005
		EP 1539173 A1	15/06/2005
		JP 2006-501233 A	12/01/2006
		JP 2006-501234 A	12/01/2006
		US 2006-0099250 A1	11/05/2006
		US 2006-0100214 A1	11/05/2006
		WO 2004-017947 A1	04/03/2004