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(54) Title: PHARMACEUTICAL COMPOSITION COMPRISING TADALAFIL AND A CYCLODEXTRIN

(57) Abstract: The invention relates to a co-granulate of tadalafil with beta-cyclodextrin in a free flowing particulate form, to a process of making it, to pharmaceutical compositions and dosage forms comprising such co-granulate and to use of the same in medicine.

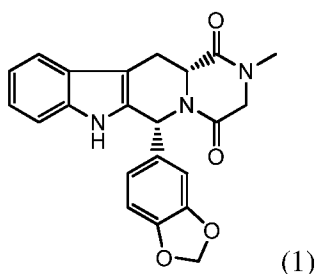


PHARMACEUTICAL COMPOSITION COMPRISING TADALAFIL AND A CYCLODEXTRIN

The present invention relates to a pharmaceutical composition comprising a co-granulate of tadalafil and beta-cyclodextrin as the main components.

BACKGROUND OF THE INVENTION

Tadalafil of formula (1)



is a known pharmaceutically active compound, which is marketed, e.g., under brand name CIALIS®, for treatment of erectile dysfunction and pulmonary arterial hypertension. The marketed product is a film-coated tablet for oral administration comprising 2.5, 5, 10 or 20 mg of the active substance. Inactive ingredients in CIALIS® are lactose monohydrate, croscarmellose sodium, hydroxypropylcellulose, microcrystalline cellulose, sodium laurylsulfate and magnesium stearate.

Tadalafil and its pharmaceutical compositions have been disclosed, e.g., in WO 95/19978 and WO 00/66099.

From a therapeutic point of view, tadalafil is in a certain aspect a follow-up product to the well known compound sildenafil (Viagra). Its main advantage is longer duration of action and minimized potential for side effects such as vision abnormalities.

Its main disadvantage is its very low aqueous solubility (about 2 micrograms per ml), which may cause formulation problems in making solid dosage forms and irreproducible clinical response. Various attempts aiming to solve this problem have been published in the prior art.

One possibility of improving the dissolution rate of tadalafil from solid pharmaceutical compositions is to use an active ingredient having a low average particle size. For instance, the patent application WO 01/08688 and WO 01/08686 disclose a population of tadalafil particles characterized by an average particle size (expressed as d_{0.9}) less than 40 micrometers. Such particulate form of tadalafil may exhibit better dissolution from pharmaceutical compositions.

The patent application WO 2007/033239 discloses tadalafil particles having an effective average size of less than 2000 nm (= 2 μm).

The patent applications WO 2006/069419 and WO 2008/000042 disclose a tadalafil nanoparticle composition, wherein the nanoparticles have an average size less than 200 nm, and a process for making such composition, respectively.

Another possibility of improving the dissolution rate of tadalafil from solid dosage forms is to provide an intimate mixture of the compound with a suitable solid carrier. In general, tadalafil is thereby finely dispersed in the carrier, which may result in improved dissolution due to the enhanced surface area of the drug substance. Several examples of solid dispersions comprising tadalafil have been disclosed, e.g., in WO 96/38131. Molecular dispersions of tadalafil in a polymeric carrier have been disclosed, e.g., in WO 2009/000493. An adsorbate of tadalafil on the surface of silica has been disclosed in EP 2238979.

Still another possibility of improving the dissolution rate of tadalafil from solid dosage forms is to formulate it into quickly disintegrating sublingual dosage forms. Examples of such compositions have been disclosed, e.g., in WO 00/20033, WO 01/41807, WO 2007/002125 or WO 2008/005039.

While many possibilities of enhancing the dissolution rate of tadalafil from solid oral pharmaceutical compositions have been addressed in the prior art, an improvement in the matter is still desirable. In particular, it is desirable to make a solid dosage form, which is not dependent on micronizing tadalafil into a population of low average particle size, or which requires complicated methods of providing a well defined intimate mixture of tadalafil with a solid carrier.

BRIEF DESCRIPTION OF THE PRESENT INVENTION.

The present invention relates to pharmaceutical compositions comprising a co-granulate of tadalafil with a cyclodextrin as the pharmaceutically active component.

5 In the first aspect, the present invention provides a solid pharmaceutical composition comprising a co-granulate of tadalafil with beta-cyclodextrin, in a molar ratio higher than 1:1, typically a molar ratio of about 1:1.25, 1:1.3, 1:1.5, 1:2, 1:2.5, 1:3, and at least one pharmaceutically acceptable excipient.

In a particular aspect, the tadalafil starting material comprises a population of tadalafil particles characterized by a particle size $d(0.9) > 40$ microns.

10 In a particular aspect, the invention provides a compressed dosage form, which typically is a tablet for oral administration of tadalafil, comprising the dose amount of the above defined composition.

In a yet particular aspect, the tablet comprises from 1 to 50 mg of tadalafil.

15 In a yet particular aspect, the dosage form exhibits a dissolution rate of at least about 75 wt% within about 15 min when tested by Ph.Eur. paddle method in 1000 ml of aqueous medium containing 0.35% of SLS with paddle rotating at a speed of 50 rpm.

In a second aspect, the invention provides a co-granulate of tadalafil with beta-cyclodextrin, in molar ratio higher than 1:1, typically a molar ratio of about 1:1.25, 1:1.3, 1:1.5, 1:2, 1:2.5, 1:3, in a free flowing particulate form.

20 In a third aspect, the invention provides a process of making a co-granulate of tadalafil with beta-cyclodextrin in a free flowing particulate form comprising

- wetting, under stirring, beta-cyclodextrin with 5 to 30% of water (w/w),
- mixing tadalafil with the wet beta-cyclodextrin in molar ratio higher than 1:1, typically a molar ratio of about 1:1.25, 1:1.3, 1:1.5, 1:2, 1:2.5, 1:3 and homogenizing
25 the mixture for at least 30 minutes, typically from 2 to 5 hours,
- drying the resulting mixture, preferably to a moisture content of less than 4%,
- optionally, milling or sieving of the resulting dry granulate.

In a specific aspect, the above process steps are followed by the next step of formulating the produced co-granulate into a solid pharmaceutical composition and/or into a solid dosage form for oral administration, e.g. to compressed dosage form, which typically is a tablet.

5 Preferably, the formulation step into the tablet comprises direct compression.

In a next aspect, the invention relates to use of co-granulate of tadalafil with beta-cyclodextrin, in a molar ratio higher than 1:1, typically a molar ratio of about 1:1.25, 1:1.3, 1:1.5, 1:2, 1:2.5, 1:3, and preferably in a free flowing particulate form, in medicine, particularly in combination with a disintegrant.

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BRIEF DESCRIPTION OF DRAWINGS

Figure 1 - Dissolution curves of tablets prepared in Example 3 in comparison with commercially available Cialis tablet.

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DETAILED DESCRIPTION OF THE PRESENT INVENTION

The present invention relates to a discovery that a complex of tadalafil with beta-cyclodextrin may be prepared by a simple and reliable process and in a form, which is well suitable for formulation into solid pharmaceutical compositions and for making tablets for oral administration of tadalafil.

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Cyclodextrins are compounds made up of sugar molecules bound together in a ring and are composed of 5 or more α -D-glucopyranoside units linked 1->4. Cyclodextrins are produced from starch by means of enzymatic conversion. Three naturally occurred cyclodextrins are known, one of these three, the so-called beta-cyclodextrin, has seven sugar molecules in the ring. As the natural beta-cyclodextrin exhibits relatively low aqueous solubility, various semi synthetic derivatives with enhanced aqueous solubility have been developed. One example is 2-hydroxy-propyl-beta-cyclodextrin (2-HPCD), which is a partially substituted poly(2-hydroxypropyl) ether of beta-cyclodextrin. Its aqueous solubility is quite high, exceeding 600 mg/ml.

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Cyclodextrins may form stable complexes with various chemicals, in which the molecule of the chemical is encapsulated inside the cyclodextrin ring and forms a so called inclusion complex. Thereby, original properties of the chemical vis-a-vis the cyclodextrin-

complexed chemical may be modified (For more details, see e.g., Arthur H. Kibbe (Ed.), Handbook of Pharmaceutical Excipients, Third Edition 2000, p. 165-168).

The possibility of formulating certain cyclodextrin complexes of tadalafil was studied in an article of Badr-Eldin et al. (*S.M. Badr-Eldin et al: Inclusion complexes of tadalafil with natural and chemically modified beta-cyclodextrins, I. Preparation and in vitro evaluation, European Journal of Pharmaceutics and Biopharmaceutics 70(2008), 819-827*). It was concluded by the authors that hydroxypropyl-beta-cyclodextrin complex with tadalafil was the most suitable for pharmaceutical applications; nevertheless this article did not provide any suitable pharmaceutical composition. Accordingly, inclusion complexation between tadalafil and cyclodextrins in the presence of various excipients was studied in more detail by the present inventor and resulted in the products and processes of the invention.

The present invention provides a solid pharmaceutical composition comprising a co-granulate of tadalafil with beta-cyclodextrin, in a molar ratio higher than 1:1, typically of molar ratio of about 1:1.25, 1:1.3, 1: 1.5, 1:2, 1: 2.5, 1:3, and at least one pharmaceutically acceptable excipient.

Formulation of the tadalafil and beta-cyclodextrin in a form of a co-granulate is advantageous as it avoids using complicated and expensive freeze-drying. The co-granulation assures a proper degree of complexation of tadalafil, which may be demonstrated by the fact that the co-granulate exhibits better dissolution rates than a plain physical mixture of both components. The co-granulate may be obtained as a free flowing particulate product, which is an advantageous form because it is well manageable in the process of formulating pharmaceutical compositions.

The composition of the present invention is a result of comparative study of the behaviour of tadalafil in solid granulated compositions comprising various cyclodextrins in the presence of pharmaceutically acceptable extragranular fillers, diluents and disintegrants, for instance in the presence of excipients found in Cialis. Contrary to the expectations predicted by Badr-Eldin et al., it was a co-granulate with natural beta-cyclodextrin, which provided the fastest dissolution of tadalafil when tested in an aqueous environment comprising 0.35% sodium lauryl sulfate (SLS), by a Ph.Eur. paddle method. Quite surprisingly, the high aqueous solubility of semi-synthetic cyclodextrins such as hydroxypropyl-beta-cyclodextrin is apparently not essential for making tadalafil-comprising solid pharmaceutical compositions with a good dissolution, e.g. with a dissolution

comparable to Cialis tablets. Without wishing to be bound by any theory, the inventor speculates that the presence of certain excipients in the solid composition, apparently mainly disintegrants, also contributes to the overall dissolution rate; when combining this contribution with an effective complexation of the tadalafil by beta-cyclodextrin, a proper synergy is obtained. As a result, far cheaper, albeit less soluble, natural beta-cyclodextrin may be successfully used in this particular case.

As to the relative amounts between tadalafil and beta-cyclodextrin in the co-granulate, an optimal molar ratio is higher than 1:1, and preferably is about 1:1.25, 1:1.3, 1:1.5, 1:2, 1:2.5, 1:3. Compositions comprising the tadalafil-beta-cyclodextrin co-granulate of molar ratio lower than 1:1 exhibited an undesirably slow dissolution rate, probably due to less complexation. Higher absolute amounts of beta-cyclodextrin in final compositions, e.g. higher than 65% w/w, may also cause certain technological problems, particularly when the tadalafil-beta-cyclodextrin co-granulate is formulated into a tablet composition, due to a lack of flowability. Thus, if the tadalafil-beta-cyclodextrin co-granulate is intended to be formulated into tablet composition, the molar ratio between tadalafil and beta-cyclodextrin should not exceed 1:8, preferably not exceed 1:5. Advantageously, the total amount of beta-cyclodextrin in a single tablet made from the co-granulate does not exceed 150 mg, preferably does not exceed 75 mg.

A useful process of making the co-granulate of tadalafil and beta-cyclodextrin in a free-flowing particulate form comprises the following steps:

1] Wetting, under stirring, beta-cyclodextrin with 5 to 30%, preferably with 10 to 25% and most preferably with about 20% of water (w/w).

Contact with water is performed in a suitable mixer at ambient temperature, for about 15 to 30 minutes, typically for about 20 minutes. As a result a wet, but still solid, homogeneous mass is obtained.

2] Mixing tadalafil with the wet beta-cyclodextrin in molar ratio higher than 1:1, typically of molar ratio of about 1:1.25, 1:1.3, 1:1.5, 1:2, 1:2.5, 1:3, and homogenizing the mixture by stirring for at least 30 minutes, typically from 2 to 5 hours.

The mixing and homogenization is typically performed in the same equipment, at a speed of about 100 to 200 rpm. The time of mixing plays a certain role as a well homogenized mixture with a high degree of complexation must be provided. Therefore, mixing for at least 30 minutes is necessary and mixing for at least 2 hours is preferred.

3] Drying the resulting mixture, advantageously to a moisture content of less than 4%.

Advantageously, the drying step is performed in fluid bed equipment, at a temperature of about 40°C to about 50°C.

4] Optionally, the dry co-granulate may be milled and/or sieved on a suitable
5 equipment.

In some embodiments, the co-granulate may also comprise some auxiliary intra-granulate excipients. In a first option, it may also comprise a suitable solubilizer. Such solubilizer may enhance the effect of cyclodextrin and/or may save the overall amount of the relatively expensive cyclodextrin. The examples of solubilizers are, without limitation,
10 hydroxypropylmethyl cellulose, polyethylene glycol (PEG 4000, PEG 6000), polyvinylpyrrolidone or polyoxyethylene(20)sorbitan monooleate (Tween 80) . The amount of a solubilizer in the co-granulate is advantageously less than 10%, in some embodiments less than 5%. In further, the co-granulate may also comprise an intragranular disintegrant, e.g.
15 is advantageously less than 10%, Furthermore, the co-granulate may comprise a suitable binder/diluent such as microcrystalline cellulose or lactose.

The auxiliary excipients may be incorporated into the granulate both in the wetting and in the mixing / homogenization step.

In a specific embodiment, the process of making the co-granulate comprises the
20 following steps:

1] Wetting, under stirring, beta-cyclodextrin with 5 to 30%, preferably with 10 to 25% and most preferably with about 20% of water (w/w), wherein the water contains dissolved solubilizer, e.g. PEG 4000, optionally in the presence of binder/diluent and/or disintegrant.

25 2] Mixing tadalafil with the wet beta-cyclodextrin plus other excipient(s) mixture in a tadalafil: beta-cyclodextrin molar ratio higher than 1:1, typically of molar ratio of about 1:1.25, 1:1.3, 1:1.5, 1:2, 1:2.5, 1:3, and homogenizing the mixture by stirring for at least 30 minutes, typically from 2 to 5 hours.

3] Drying the resulting mixture, advantageously to a moisture content of less than 4%.

4] Optionally, the dry co-granulate may be milled and/or sieved on a suitable
30 equipment.

Alternatively, in another embodiment, the process comprises the following steps:

1] Wetting, under stirring, beta-cyclodextrin with 5 to 30%, preferably with 10 to 25% and most preferably with about 20% of water (w/w), wherein the water contains dissolved solubilizer, e.g. PEG 4000, optionally in the presence of binder/diluent.

5 2] Mixing tadalafil with the wet beta-cyclodextrin plus other excipient(s) mixture in a tadalafil:beta-cyclodextrin molar ratio higher than 1:1, typically of molar ratio of about 1:1.25, 1:1.3, 1:1.5, 1:2, 1:2.5, 1:3, and homogenizing the mixture by stirring for at least 30 minutes, typically from 2 to 5 hours.

3] Adding an intragranular disintegrant and mixing additional for at least 30 minutes.

10 4] Drying the resulting mixture, advantageously to a moisture content of less than 4%.

5] Optionally, the dry co-granulate may be milled and/or sieved on a suitable equipment.

Quite surprisingly, the co-granulate of the present invention may be formulated into well dissoluble solid pharmaceutical compositions without a requirement that the starting
15 tadalafil must be of a small particle size. Specifically, it is not necessary to provide a population of tadalafil particles of an particles size (when expressed by the d(0.9) value) of less than 40 micrometers. Instead, it is possible and in certain aspects advantageous, to use batches of tadalafil having the average particle size d(0.9) higher than 40 micrometers, e.g. tadalafil directly produced by a chemical synthesis. For clarity, the "d(0.9) " in an association
20 with a number means that the size of 90% of particles of the population is less than or equal to the size expressed by that number when measured by a light scattering method.

The co-granulate of the present invention may be formulated into solid pharmaceutical compositions, preferably to tablet compositions, by combining it, typically by dry mixing or by wet granulation/mixing, with at least one extragranular pharmaceutical excipient. As rapid
25 dissolution of tadalafil from the composition is therapeutically advantageous, the composition typically does not comprise any excipient serving as a release-controlling agent.

The at least one extragranular excipient(s) may be selected from

- At least one disintegrant. The examples are, without any limitation, starches, modified celluloses or crosslinked polymers such as starch, modified starch,
30 croscarmellose sodium, carboxymethylcellulose calcium, crospovidone, sodium

starch glycolate, polacrilin potassium, sodium alginate, guar gum, etc. A preferred disintegrant is croscarmellose sodium.

The extragranular disintegrant is an important excipient. As discussed above, it appears that the disintegrant potentiates the effect of the cyclodextrin and improves the overall release rate. Preferred amount of the disintegrant is from 1 to 5 weight %, based on the total mass of the composition. In some embodiments, the final composition may comprise both an extragranular disintegrant and an intragranular disintegrant, which may be the same or different.

- At least one water soluble or water insoluble filler /binder. The examples are, without any limitation, lactose, lactose monohydrate, mannitol, sorbitol, microcrystalline cellulose, methyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, dextrose, fructose, lactitol, maltitol, maltodextrins, maltose, calcium phosphates, xylitol, starch, modified starch, polyvinylpyrrolidone, copovidone, sodium alginate, etc.
- At least one solubilizer. The examples are, without any limitation, hydroxypropyl methylcellulose, polyvinylpyrrolidone, nicotinamide, polyoxyethylene (20) sorbitan monooleate (Tween 80), polyethylene glycol (PEG 4000), sodium lauryl sulfate, etc.
- At least one lubricant. The examples are, without any limitation, talc, magnesium stearate, calcium stearate, stearic acid, hydrogenated vegetable oils, palmitic acid, carnauba wax, mineral oil, sodium stearyl fumarate, polyethylene glycol, etc.

The relative amount of the tadalafil/beta-cyclodextrin co-granulate, optionally comprising auxiliary excipients as described above, in the composition is typically from about 30 to about 80 weight %, preferably from about 40 to about 60 weight %, based on the total weight of the composition. The relative amount of the beta-cyclodextrin as such in the composition should not exceed 65%.

In pharmaceutical use, the composition of the present invention is advantageously formulated into a compressed dosage form, which is typically a tablet, preferably by a process of direct compression. This process comprises adjusting the composition to portions – dose units – comprising dose amount of the active substance and compressing the doses of the composition to tablets on a suitable tablet press. The preferred hardness of tablets is higher than 50N, advantageously higher than 75N.

The resulting compressed tablet for oral administration of tadalafil typically comprises a dose amount comprising from 1 to 50 mg of tadalafil, preferably 2.5, 5, 10, 20 or 40 mg of tadalafil. Yet typically, a tablet comprises in total less than 150 mg of beta-cyclodextrin, in some embodiments the amount of beta-cyclodextrin does not exceed 75 mg.

5 The compressed dosage form preferably exhibits a dissolution rate which is characterized by a dissolution of more than 75 wt% and in some embodiments more than 80 wt% of tadalafil in 15 min when tested by a Ph.Eur. paddle method in 1000 ml of an aqueous medium containing 0.35% of SLS (sodium lauryl sulfate) with paddle rotating at a speed of 50 rpm.

10 The tablets may be optionally further coated by a film-coat. The coating serves generally for cosmetic purposes. The coating material typically has no influence on the release rate, except of an inherent short initial delay in dissolution due to the time necessary to dissolve the coat.

15 The coating may be selected from amongst one or more of those suitable coating materials known in the art. Coating may be performed by applying one or more film forming polymers, with or without other pharmaceutically inert excipients, as a solution/suspension. Coating is done using any conventional coating technique known in the art, such as spray coating in a conventional coating pan or fluidized bed processor; or dip coating.

20 The co-granulate of tadalafil with beta-cyclodextrin of the present invention, advantageously in a combination with a disintegrant, may be typically used in making solid pharmaceutical dosage forms, e.g., for oral administration of tadalafil. Thus, in general, the co-granulate of tadalafil with beta-cyclodextrin in molar ratio higher than 1:1, typically of molar ratio of about 1:1.25, 1:1.3, 1:1.5, 1:2, 1:2.5, 1:3, as well as pharmaceutical compositions and dosage forms comprising such co-granulate, advantageously in
25 combination with a disintegrant, are useful in medicine, specifically for the treatment of diseases and conditions known to be treated with tadalafil. Typically, these conditions include erectile dysfunction and pulmonary arterial hypertension, but they are not limited thereto. Accordingly, the present invention provides a method of treatment, particularly that of
30 erectile dysfunction or pulmonary arterial hypertension, comprising orally administering to a patient of need thereof a solid pharmaceutical composition comprising a therapeutical amount of co-granulate of tadalafil with beta-cyclodextrin in a molar ratio higher than 1: 1, typically a

molar ratio of about 1:1.25, 1:1.3, 1:1.5, 1:2, 1:2.5, 1:3, advantageously in combination with a disintegrant.

The invention is further illustrated by the following examples but those should not be construed as limiting the scope of this invention in any way.

5

EXAMPLES

Example 1 Co-granulate of tadalafil and beta-cyclodextrin

A co-granulate of tadalafil with beta-cyclodextrin of a molar ratio of 1:3 was made by the following process:

- 10 20% of water (w/w of beta-cyclodextrin amount) was sprayed on a surface of beta-cyclodextrin and mixed in a high shear mixer for 20 minutes. After that, tadalafil was added and mixed in the same equipment for 60 minutes. The granulate was dried in a fluid bed equipment using a temperature lower than 50°C.

- 15 **Example 2 Pharmaceutical tablet comprising tadalafil-beta-cyclodextrin (1:3 m/m) co-granulate**

Formulation:

Composition	20 mg strength	
	mg/tablet	%/tablet
Tadalafil	20.00	4.90%
β-cyclodextrin (CAVAMAX W7)	200.00	49.02%
Lactose monohydrate spray dried (SUPERTAB 11 S)	137.09	33.60%
Croscarmellose sodium (AC-DI-SOL)	8.16	2.00%
Microcrystalline cellulose (AVICEL PH102)	40.80	10.00%
Magnesium stearate	2.040	0.50%
Water	qs	qs
Total mass (uncoated tablet)	408	100.0%

20

Process:

The co-granulate of tadalafil and beta-cyclodextrin was prepared according to the process of example 1. The extragranular excipients spray-dried lactose, microcrystalline cellulose, and croscarmellose sodium were mixed with the co-granulate in a free fall blender, subsequently magnesium stearate was added and mixed with the rest of excipients. The lubricated blend was compressed in an excentric press machine.

Example 3

Comparative tablets compositions were made with a co-granulate of tadalafil/beta-cyclodextrin (1:3 molar) made of:

- a) Active substance d(0.9)= 62.2. microns, 2 hours granulation
- b) Active substance d(0.9)= 62.2. microns, 2 hours granulation
- c) Active substance d(0.9) =40.6. microns, 2 hours granulation
- d) Active substance d(0.9) =48.9 microns, 2 hours granulation

The granulates were formulated, by direct compression, into tablets of the composition identical to that of Example 2

The tablet hardness was 75N in cases a], c] and d] and 100N in the case b]

All tablets were tested for dissolution by Ph.Eur. paddle method at paddle speed 50 rpm in 1000 ml of water comprising 0.35% sodium laurylsulfate. For comparison, a commercially available batch of tablets CIALIS 20 mg (the “Originator”) was used.

The results are summarized in the Table 1 and the corresponding dissolution curves are shown in Figure 1.

Table 1

		Time (min)							
		0	5	10	15	20	30	45	60
Originator	Batch/percentage dissolved (%)	0	40	70		81	85	87	88
API 62.2 microns (100 N)		0	74	82	84	84	85	85	85
API 62.2 microns (75 N)		0	64	77	82	84	85	87	88
API 48.9 microns (75 N)		0	70	81	85	86	86	87	87
API 40.6 microns (75 N)		0	65	81	87	89	91	93	94

Example 4

Pharmaceutical tablet comprising tadalafil-beta-cyclodextrin (1:2.5 m/m) co-granulate with an intragranular solubilizer.

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Composition:

Formulation	20 mg dose	
	mg	%
Tadalafil	20.00	4.17
β - cyclodextrin (Cavamax W7)	150.00	31.25
Lactose monohydrate spray dried (Supertab 11SD)	153.23	31.92
HPMC (Methocel E5 Premium LV)	0.85	0.18
Sodium Croscarmellose (Ac-di-sol)	9.60	2.00
Cellulose, microcrystalline (Avicel PH102)	144.00	30.00
Magnesium stearate	2.40	0.50
Total mass (uncoated tablet)	480	100%

HPMC was dissolved in water (20% w/w of the amount of cyclodextrin). This solution was mixed with cyclodextrin in a granulator for 20 minutes. Drug substance was added to the formed paste and blended for 4 h. After that, the wet mass was removed from the granulator,

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sieved through a conical sieve (BTS, 2.5 mm) and dried in a fluid bed at 50°C until getting a LOD < 14%. The granulate was sieved through 0.5 mm mesh (BTS) and was mixed with lactose monohydrate, microcrystalline cellulose and Na croscarmellose for 30 minutes.

Magnesium stearate was added to the blend and mixed for 5 additional minutes. Finally, the

5 lubricated blend was compressed in a rotary tablet press.

Example 5

Pharmaceutical tablet comprising tadalafil-beta-cyclodextrin (1:2.5 m/m) co-granulate with an extragranular solubilizer.

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Composition

Formulation	20 mg dose	
	mg	%
Tadalafil	20.00	4.17
β- cyclodextrin (Cavamax W7)	150.00	31.25
Lactose monohydrate spray dried (Supertab 11SD)	151.60	31.58
Nicotinamide	40.00	8.33
Sodium Croscarmellose (Ac-di-sol)	14.40	2.00
Cellulose, microcrystalline (Avicel PH102)	101.60	21.17
Magnesium stearate	2.40	0.50
Total mass(uncoated tablet)	480	100 %

Cyclodextrin and water (20% w/w of the amount of cyclodextrin) were mixed in a high shear mixer/granulator for 20 minutes. Tadalafil was added to the CD:water paste and blended for 4 h. After that, the granulate was sieved through conical sieve (BTS, 2.5 mm) and dried in fluid bed at 50°C until getting a LOD < 14%. Granulate was sieved through 0.5 mm mesh (BTS).

15

In a second granulation step, TDI:β-CD granulate was granulated with lactose monohydrate, half of microcrystalline cellulose and 40% of the sodium croscarmellose, using water (25% w/w of granulated mass) as the granulation liquid. Nicotinamide was partially dissolved in the granulation liquid and partially added as powder in the high shear mixer. The granulated product was dried in Glatt GPCG-1. The dried granulate was blended with the remaining microcrystalline cellulose and sodium croscarmellose for 30 minutes. Finally, magnesium stearate was added and the mixture was blended for 5 minutes. The lubricated blend was compressed in a rotative press machine to get 20, 10, 5 and 2.5 mg tablets.

Example 6

Pharmaceutical tablet comprising tadalafil-beta-cyclodextrin (1:2.5 m/m) co-granulate with an extragranular solubilizer.

Composition

	Tablet mass	
	mg	%
TADALAFIL	20.00	4.17
Beta-cyclodextrin (CAVAMAX W7)	150.00	31.25
Lactose monohydrate spray dried (SUPERTAB 11SD)	151.60	31.58
TWEEN 80V PHARMA	2.40	0.50%
Sodium croscarmellose (Ac-di-sol)	14.40	3.00%
Microcrystalline cellulose (Avicel PH102)	139.20	29.00%
MAGNESIUM STEARATE	2.40	0.50%
Purified water	qs	qs
Total mass (uncoated tablet)	480	100%

Process:

Cyclodextrin and water (20% w/w of the amount of cyclodextrin) were mixed in a Mimipro high shear mixer/granulator for 20 minutes. Tadalafil was added to the cyclodextrin- water paste and blended for 4 h at an impeller speed of 150 rpm. After that, the

granulate was sieved manually through 1.4 mm mesh and dried in a fluid bed (Miniglatt) at 50°C until getting a LOD < 14%. The dried granulate was sieved through 0.710 mm mesh.

In a second granulation step, the tadalafil:β-CD granulate was granulated with lactose monohydrate, half of microcrystalline cellulose and 40% of the sodium croscarmellose in Mimipro. Tween was dissolved in the granulation liquid and added in the high shear mixer. The granulated product was dried in fluid bed equipment. The dried granulate was blended with the remaining microcrystalline cellulose and sodium croscarmellose for 10 minutes. Finally, magnesium stearate was added and blended for 5 minutes. The lubricated blend was compressed in a excentric press machine to get 20 mg tablets (mass 480 mg, hardness 150 N).

Example 7

Pharmaceutical tablet comprising tadalafil-beta-cyclodextrin (1:1.3 m/m) co-granulate with an intragranular solubilizer, binder and disintegrant.

Composition

	Tablet mass	
	mg	%
TADALAFIL	20.00	4.17
Beta-cyclodextrin (CAVAMAX W7)	75.00	15.63
Lactose monohydrate spray dried (SUPERTAB 11SD)	229,000	47.71
PEG 4000	4.8	1.00
Sodium croscarmellose (Ac-di-sol)	9.600	2.00
Microcrystalline cellulose (Avicel PH102)	139.20	29.00
MAGNESIUM STEARATE	2.40	0.50
Purified water	61.76	20
Total mass (uncoated tablet)	480	100

Process:

Cyclodextrin, lactose, half of the sodium croscarmellose was mixed with an aqueous solution of PEG 4000 (amount of water is 20% w/w of the total weight of the composition) in a VMA 10 high shear mixer/granulator for 20 min Tadalafil was added to the wet paste and

blended for 3 hours. After blending, the granulate was dried in a fluid bed at 50°C. The dried granulate was sieved through 1.0 mm sieve.

The dried granulate was blended with the microcrystalline cellulose and the rest of sodium croscarmellose for 10 minutes. Finally, magnesium stearate was added and blended.

- 5 The lubricated blend was compressed to get 20 mg tablets.

By the same process, proportional tablets of 10 mg, 5 mg and 2.5 mg tadalafil were also prepared.

Example 8

- 10 Pharmaceutical tablet comprising tadalafil-beta-cyclodextrin (1:1.3 m/m) co-granulate with an intragranular solubilizer, binder and disintegrant.

Composition

	Tablet mass	
	mg	%
TADALAFIL	40.00	8.33
Beta-cyclodextrin (CAVAMAX W7)	150.00	31.25
Lactose MH (SUPERTAB 11SD)	134.00	27.92
Na croscarmellose (ACDISOL)	9.60	2.00
Microcrystalline cellulose (AVICEL PH102)	139.20	29.00
PEG4000	4.80	1.00
Mg STEARATE	2.40	0.50
Water	61.76	20.00
Total mass (uncoated tablet)	480	100

- 15 Process:

The same as in Example 7.

Example 9

Pharmaceutical tablet comprising tadalafil-beta-cyclodextrin (1:1.3 m/m) co-granulate with an intragranular solubilizer, binder and disintegrant.

5 Composition

	Tablet mass				
	20 mg	10 mg	5 mg	2.5 mg	%
TADALAFIL	20.00	10.00	5.00	2.5	4.17
Beta-cyclodextrin (CAVAMAX W7)	75.00	37.50	18.75	9.38	15.63
Lactose MH (SUPERTAB 11SD or PHARMATOSE 200M)	219.41	109.70	54.85	27.43	45.71
Na croscarmellose (ACDISOL)	19.20	9.60	4.80	2.40	4.00
Microcrystalline cellulose (AVICEL PH102)	139.20	69.60	34.8	17.40	29.00
PEG4000	4.80	2.40	1.20	0.60	1.00
Mg STEARATE	2.40	1.20	0.60	0.30	0.50
Water	q.s.	q.s.	q.s.	q.s.	20.00
Total mass (uncoated tablet)	480	240	120	60	100.0

40 mg strength

	Tablet mass	
	40 mg	%
TADALAFIL	40.00	8.33
Beta-cyclodextrin (CAVAMAX W7)	150.00	31.25
Lactose MH (SUPERTAB 11SD or PHARMATOSE 200M)	124.42	25.92
Na croscarmellose (ACDISOL)	19.20	4.00
Microcrystalline cellulose (AVICEL PH102)	139.20	29.00
PEG4000	4.80	1.00
Mg STEARATE	2.40	0.50
Water	q.s.	20.00
Total mass (uncoated tablet)	480	100

Process:

Cyclodextrin, lactose and half of the croscarmellose was mixed with an aqueous solution of PEG 4000 (amount of water is 20% w/w of the mass) in a VMA 10 high shear mixer/granulator for 20 minutes. Tadalafil was added to the wet paste and blended for 3 hours. Subsequently, the granulate was sieved and dried in a fluid bed at 50°C. The dried granulate was sieved through a 1.0 mm sieve.

The dried granulate was blended with the microcrystalline cellulose and the rest of sodium croscarmellose for 10 minutes. Finally, magnesium stearate was added and the mixture was blended. The lubricated blend was compressed in a rotative compression machine to get 20 mg, 10 mg, 5 mg and 2.5 mg tablets.

(Same process for the 40 mg strength)

Example 10Composition

	Tablet mass				
	20 mg	10 mg	5 mg	2.5 mg	%
TADALAFIL	20.00	10.00	5.00	2.5	4.17
Beta-cyclodextrin (CAVAMAX W7)	75.00	37.50	18.75	9.38	15.63
Lactose MH (SUPERTAB 11SD or PHARMATOSE 200M)	219.41	109.70	54.85	27.43	45.71
Crospovidone (Polyplasdone XL)	19.20	9.60	4.80	2.40	4.00
Microcrystalline cellulose (AVICEL PH102)	139.20	69.60	34.8	17.40	29.00
PEG4000	4.80	2.40	1.20	0.60	1.00
Mg STEARATE	2.40	1.20	0.60	0.30	0.50
water	q.s.	q.s.	q.s.	q.s.	20.00
Total mass (uncoated tablet)	480	240	120	60	100

40 mg strength

	Tablet mass	
	40 mg	%
TADALAFIL	40.00	8.33
Beta-cyclodextrin (CAVAMAX W7)	150.00	31.25
Lactose MH (SUPERTAB 11SD or PHARMATOSE 200M)	124.42	25.92
Crospovidone (Polyplasdone XL)	19.20	4.00
Microcrystalline cellulose (AVICEL PH102)	139.20	29.00
PEG4000	4.80	1.00
Mg STEARATE	2.40	0.50
Water	q.s.	20.00
Total mass (uncoated tablet)	480	100.0

Process:

Cyclodextrin, lactose and half of the crospovidone was mixed with an aqueous solution of PEG 4000 (amount of water is 20% w/w of the mass) in a VMA 10 high shear mixer/granulator for 20 minutes. Tadalafil was added to the wet paste and blended for 3 hours. After that, the granulate was sieved and dried in a fluid bed at 50°C. The dried granulate was sieved through 1.0 mm sieve. The dried granulate was blended with the microcrystalline cellulose and the rest of sodium crospovidone for 10 minutes. Finally, magnesium stearate was added and blended. The lubricated blend was compressed in a rotative compression machine to get 20 mg, 10 mg, 5 mg and 2.5 mg tablets.

(Same process for the 40 mg strength)

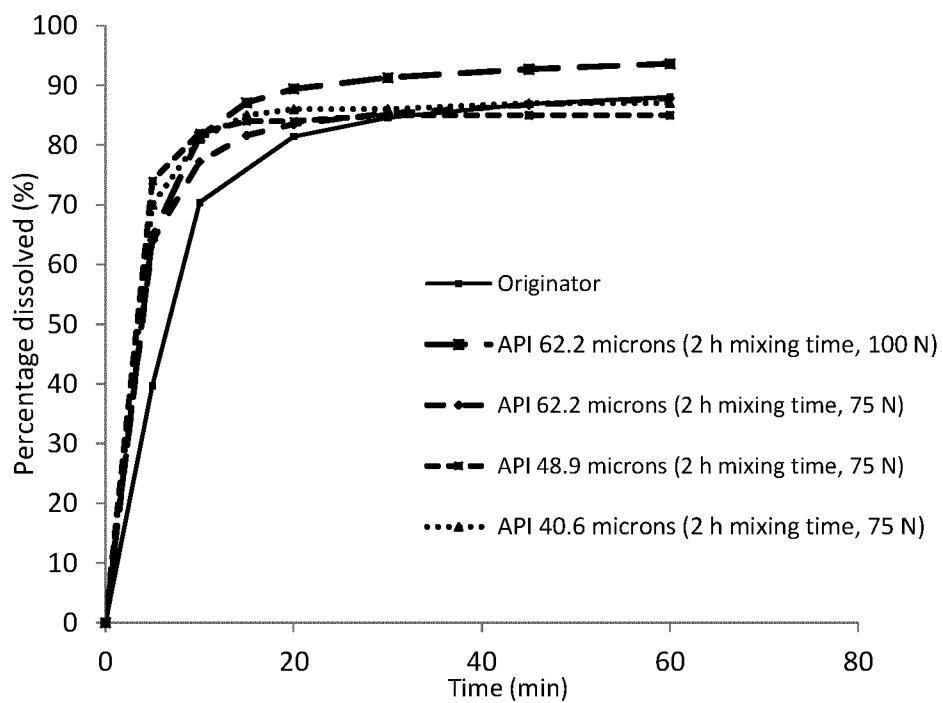
The invention having been described it will be obvious that the same may be varied in many ways and all such modifications are contemplated as being within the scope of the invention as defined by the following claims.

CLAIMS

1. A solid pharmaceutical composition comprising a co-granulate of tadalafil with beta-cyclodextrin in molar ratio higher than 1:1 and at least one pharmaceutically acceptable
5 extragranular excipient.
2. The composition according to claim 1, wherein the extragranular excipient is a disintegrant, preferably croscarmellose sodium.
3. The composition according to claim 2, wherein the amount of the disintegrant is from 1 to 5 weight %, based on the total mass of the composition.
- 10 4. The composition according to claims 1-3, wherein the tadalafil starting material comprises a population of tadalafil particles characterized by a particle size $d(0.9)$ higher than 40 microns.
5. The composition according to claims 1-4, wherein the relative amount of the tadalafil/beta-cyclodextrin co-granulate in the composition is from about 30 to about 80
15 weight %, preferably from about 40 to about 60 weight %, based on the total weight of the composition.
6. The composition according to claims 1-5, wherein the co-granulate comprises at least one other intragranular excipient.
7. The composition according to claims 1-6, wherein the intragranular excipient is a
20 solubilizer
8. The composition according to claims 1-7, wherein the molar ratio between tadalafil and beta-cyclodextrine is lower than 1: 8
9. The composition according to claims 1-8, wherein the molar ratio between tadalafil and beta-cyclodextrine is about 1:1.25, 1:1.3, 1: 1.5, 1:2, 1:2.5, 1:3.
- 25 10. A compressed tablet for oral administration of tadalafil, comprising a dose amount of the composition of claims 1-9.
11. The tablet according to claim 10 comprising from 1 to 50 mg of tadalafil.

12. The tablet according to claims 10-11, which exhibits a dissolution rate of at least about 75 wt% within about 15 min when tested by Ph.Eur. paddle method in 1000 ml of an aqueous medium containing 0.35% of sodium lauryl sulfate with paddle rotating at a speed of 50 rpm.
- 5 13. A co-granulate of tadalafil with beta-cyclodextrin in molar ratio higher than 1:1, in a free flowing particulate form.
14. The co-granulate according to claim 13, wherein the molar ratio between tadalafil and beta-cyclodextrin is lower than 1:20, preferably lower than 1:8, more preferably about 1:1.25, 1:1.3, 1: 1.5, 1:2, 1: 2.5, 1:3.
- 10 15. The co-granulate according to claim 13-14, further comprising at least one other excipient.
16. A process of making a co-granulate of tadalafil with beta-cyclodextrin in a free flowing particulate form comprising the steps of:
- 15 - wetting, under stirring, beta-cyclodextrin with 5 to 30%, preferably 10 to 25%, of water (w/w);
- mixing tadalafil with the wet beta-cyclodextrin in a molar ratio higher than 1:1 and homogenizing the mixture for at least 30 minutes, typically from 2 to 3 hours;
- drying the resulting mixture, preferably to a moisture content of less than 4%; and
- optionally, milling or sieving of the resulted dry granulate.
- 20 17. The process according to claim 16, wherein at least one other excipient is added to the granulate in the wetting and/or in the mixing/homogenization step.
18. The process according to claim 16 followed by a next step of formulating the produced co-granulate with extragranular excipients into a solid pharmaceutical composition and/or to a solid dosage form for oral administration, e.g. to a compressed dosage form.
- 25 19. The process according to claim 18, wherein the formulation comprises a direct compression of the dry mixture of co-granulate and excipients.
20. A co-granulate of tadalafil with beta-cyclodextrin as well as pharmaceutical compositions and dosage forms comprising such co-granulate according to any of the claims 1 to 11, for use in medicine.

FIGURE 1



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/052266

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/16 A61K9/20 A61K31/519
ADD.

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

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

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

EPO-Internal, BIOSIS, EMBASE, MEDLINE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SHAIMAA M. BADR-ELDIN ET AL: "Inclusion complexes of tadalafil with natural and chemically modified [beta]-cyclodextrins. I: Preparation and in-vitro evaluation", EUROPEAN JOURNAL OF PHARMACEUTICS AND BIOPHARMACEUTICS, vol. 70, no. 3, 1 November 2008 (2008-11-01), pages 819-827, XP055005612, ISSN: 0939-6411, DOI: 10.1016/j.ejpb.2008.06.024	13,14
Y	abstract page 820, column 2 page 825 ----- -/--	1-20

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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Date of the actual completion of the international search

6 March 2012

Date of mailing of the international search report

14/03/2012

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/052266

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2009/047330 A1 (BANGALORE RAMESH [US]) 19 February 2009 (2009-02-19) table 1 claims 1-9	1-20
Y	----- WO 2005/107810 A2 (EMOTIONAL BRAIN B V [NL]; TUITEN JAN JOHAN ADRIAAN [NL]) 17 November 2005 (2005-11-17) page 3, line 3 - page 4, line 15 -----	1-20

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2012/052266

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2009047330	A1	19-02-2009	NONE
-----	-----	-----	-----
WO 2005107810	A2	17-11-2005	AU 2005239962 A1 17-11-2005
		BR PI0511079 A	26-12-2007
		CA 2566699 A1	17-11-2005
		CN 101027061 A	29-08-2007
		EP 1750766 A2	14-02-2007
		JP 2007537247 A	20-12-2007
		KR 20070042920 A	24-04-2007
		NZ 551356 A	25-09-2009
		US 2007093450 A1	26-04-2007
		WO 2005107810 A2	17-11-2005
		ZA 200609974 A	30-07-2008
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