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(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 the use of the same in medicine.



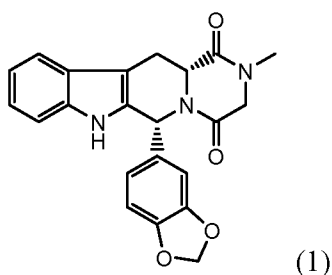
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PHARMACEUTICAL COMPOSITION COMPRISING TADALAFIL AND A CYCLODEXTRIN

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 the 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 lauryl sulfate 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 µ/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 the active ingredient with low average particle size. For instance, the patent applications 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 μm . Such particulated form of tadalafil may exhibit better dissolution from pharmaceutical compositions.

5 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 a composition, resp.

10 Another possibility for 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 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.

15 A pharmaceutical composition comprising a combination of tadalafil and starch has been disclosed in WO 2008/134557. An adsorbate of tadalafil on the surface of silica has been disclosed in EP 2238979.

Yet 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

20 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

25 dependent on micronizing tadalafil into a population of low average particle size or which does not require complicated methods of providing a well defined intimate mixture of tadalafil with a solid carrier.

SUMMARY OF THE INVENTION

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

In a 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 : 2, typically of molar ratio of about 1 : 3, and at least one pharmaceutically acceptable excipient.

5 In a particular aspect, the tadalafil starting material comprises a population of tadalafil particles characterized by a particle size $d(0.9) > 40 \mu\text{m}$.

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

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

In another 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 an aqueous medium containing 0.35% of SLS with the paddle rotating at a speed of 50 rpm.

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

In a third aspect, the invention provides a process for 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)
- 20 - mixing tadalafil with the wet beta-cyclodextrin in a molar ratio higher than 1 : 2, typically a molar ratio of about 1 : 3 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%
- optionally, milling or sieving of the resulted dry granulate.

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

Preferably, the formulation of the tablet comprises a direct compression.

30 In a next aspect, the invention relates to the use of the co-granulate of tadalafil with beta-cyclodextrin, in a molar ratio higher than 1 : 2, typically a molar ratio of about 1 : 3, and

preferably in a free-flowing particulate form, in medicine, particularly in combination with a disintegrant.

BRIEF DESCRIPTION OF DRAWINGS

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

DETAILED DESCRIPTION OF THE PRESENT INVENTION

10 The present invention relates to a complex of tadalafil with beta-cyclodextrin 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.

Cyclodextrins are a family of compounds made up of sugar molecules bound together in a ring. Cyclodextrins 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 occurring cyclodextrins are known, whereby 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. An 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.

15 20

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, the 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).

25

The possibility of formulating certain cyclodextrin complexes of tadalafil was studied in an article of Bahr-Eldin *et al.* (*S.M. Bahr-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* 20 (2008), 819-827). It was concluded by the authors that the hydroxypropyl-beta-cyclodextrin complex with tadalafil was the most suitable for pharmaceutical applications; nevertheless the article did not provide

30

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 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 : 2, typically a molar ratio of about 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, well manageable in the process of formulating pharmaceutical compositions.

The composition of the present invention is a result of a 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 Bahr-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 of tadalafil and beta-cyclodextrin in the co-granulate, an optimal molar ratio is higher than 1 : 2 and preferably is about 1 : 3. Compositions comprising the tadalafil/beta-cyclodextrin co-granulate of a molar ratio lower than 1 : 2 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 to a tablet composition, due to a lack of flowability. Thus, when the

5 tadalafil/beta-cyclodextrin co-granulate is intended to be formulated into a tablet composition of higher tablet strengths, e.g. 10 to 20 mg, the molar ratio between tadalafil and beta-cyclodextrin should not exceed 1 : 8, preferably not exceed 1 : 5. For lower strengths (1 or 2.5 mg), the upper limit of the molar ratio may be higher, e.g., up to 1 : 20.

The useful process for making the co-granulate of tadalafil and beta-cyclodextrin in a

10 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).

The 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,

15 homogeneous mass is obtained.

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

The mixing and homogenization is typically performed in the same equipment, at a

20 speed of about 100 to 200 rpm. The time of mixing plays a certain role as well as a 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

25 of about 40°C to about 60°C, typically at about 50°C.

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

In some embodiments, the co-granulate may also comprise some auxiliary intra-granular excipients, e.g. a suitable binder such as microcrystalline cellulose and/or a suitable

30 disintegrant, e.g. crosscarmellose sodium. The content of these excipients, in sum, typically

does not exceed 10% of the weight of the dry granulate. The excipients may be incorporated into the granulate both in the wetting and in the homogenization step.

Quite surprisingly, the co-granulate of the present invention may be formulated into well dissoluble solid pharmaceutical compositions without the requirement that the starting
5 tadalafil must be of a small particle size. Specifically, it is not necessary to provide a population of tadalafil particles of an average particle size (when expressed by the d(0.9) value) of less than 40 μm . 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 μm , e.g. tadalafil
10 directly produced by a chemical synthesis. For clarity, the “d(0.9)” in association with a number means that the size of 90% of the particles of a population were 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, with at least one extragranular pharmaceutical excipient. As rapid dissolution of tadalafil from
15 the composition is therapeutically advantageous, the composition typically does not comprise any excipient serving as a release-controlling agent.

The extragranular excipients typically comprise

a) At least one disintegrant. The examples are, without any limitation, starches, modified celluloses or crosslinked polymers such as starch, modified starch, croscarmellose
20 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. The preferred amount of the disintegrant is from 1 to 5 weight %, based on the total mass
25 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.

b) At least one water soluble or water insoluble filler/binder. The examples are, without any limitation, lactose, lactose monohydrate, mannitol, sorbitol, microcrystalline
30 cellulose, methyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, dextrose, fructose, lactitol, maltitol, maltodextrins, maltose, calcium phosphates, xylitol, starch, modified starch, polyvinylpyrrolidone, copovidone, sodium alginate, etc.

c) 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 in the composition is typically from about 30 to about 70 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 about 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 or 20 mg of tadalafil.

The compressed dosage form preferably exhibits a dissolution rate which is characterized by a dissolution of more than 75 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 the paddle rotating at a speed of 50 rpm.

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.

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.

The co-granulate of tadalafil with beta-cyclodextrin of the present invention, advantageously in 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 a molar ratio higher than 1 : 2, typically a molar ratio of about 1 : 3, as well as pharmaceutical compositions and dosage forms comprising such co-granulate, advantageously in 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 are not limited thereto. Accordingly, the present invention provides a method of treatment, particularly that of erectile dysfunction or pulmonary arterial hypertension, comprising orally administering to a patient in need thereof a solid pharmaceutical composition comprising a therapeutical amount of co-granulate of tadalafil with beta-cyclodextrin in molar ratio higher than 1 : 2, typically a molar ratio of about 1 : 3, advantageously in combination with a disintegrant.

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

15 **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:

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 min. After that, tadalafil was added and mixed in the same equipment for 60 min. The granulate was dried in a fluid bed equipment using a temperature lower than 50°C.

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

Formulation:

Composition	20 mg strength	
	mg/tablet	%/tablet
Tadalafil	20.00	4.90
B-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
Final mass	408	100.0

5 **Process:**

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

Example 3 - Comparative tablet compositions

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

- 15 a) Active substance $d(0.9) = 62.2 \mu\text{m}$, 2 hours granulation
- b) Active substance $d(0.9) = 62.2 \mu\text{m}$, 2 hours granulation
- c) Active substance $d(0.9) = 40.6 \mu\text{m}$, 2 hours granulation

d) Active substance $d(0.9) = 48.9 \mu\text{m}$, 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 case b).

5

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

10 The results are summarized in the table below and the corresponding dissolution curves are shown in Fig. 1.

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

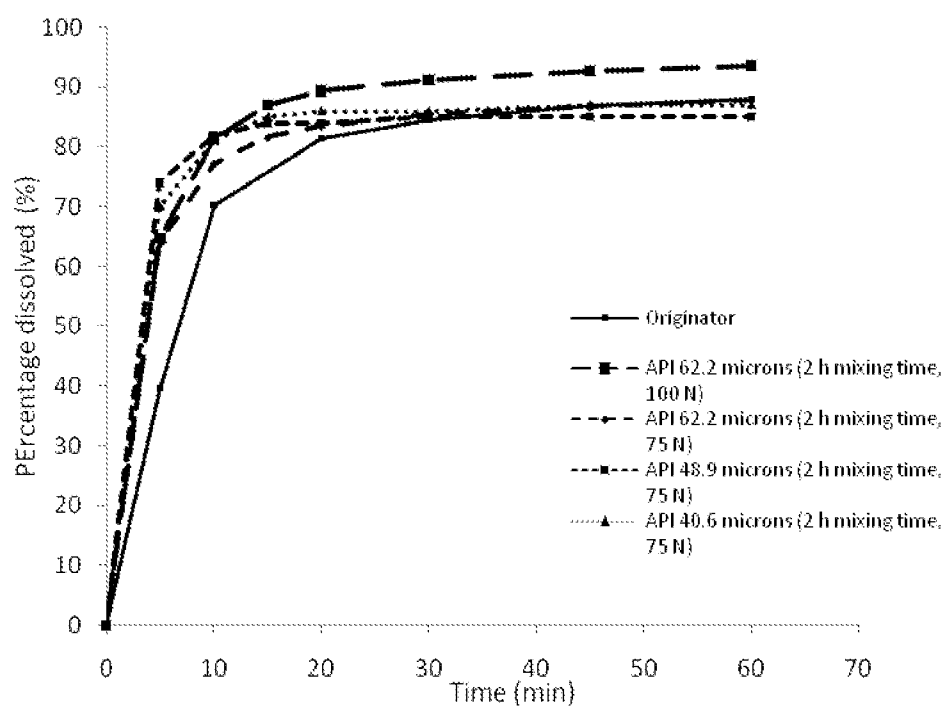
The invention having been described it will be obvious that the same may be varied in many ways and all such modifications are contemplated as being within the scope of the invention as defined by the following claims.

15

CLAIMS

1. A solid pharmaceutical composition comprising a co-granulate of tadalafil with beta-cyclodextrin in a molar ratio higher than 1 : 2 and at least one pharmaceutically acceptable extragranular excipient.
5
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 μm .
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 70 weight %, preferably from about 40 to about 60 weight %, based on the total weight of the composition.
15
6. A compressed tablet for oral administration of tadalafil, comprising a dose amount of the composition of claims 1-5.
7. The tablet according to claim 6 comprising from 1 to 50 mg of tadalafil.
- 20 8. The tablet according to claims 6-7, which exhibits a dissolution rate of at least about 75 wt% within about 15 min when tested by the Ph. Eur. paddle method in 1000 ml of an aqueous medium containing 0.35% of sodium lauryl sulfate with the paddle rotating at a speed of 50 rpm.
9. A co-granulate of tadalafil with beta-cyclodextrin in a molar ratio higher than 1 : 2, in a free-flowing particulate form.
25
10. The co-granulate according to claim 9, wherein the molar ratio is lower than 1 : 20.
11. The co-granulate according to claim 10-11, further comprising up to 10% of other excipients.
12. A process for making a co-granulate of tadalafil with beta-cyclodextrin in a free-flowing particulate form comprising the steps of:
30

- 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 : 2 and homogenizing the mixture for at least 30 minutes, typically from 2 to 3 hours;
 - 5 - drying the resulting mixture, preferably to a moisture content of less than 4%; and,
 - optionally, milling or sieving of the resulting dry granulate.
13. The process according to claim 12 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.
- 10 14. The process according to claim 13, wherein the formulation comprises a direct compression of the dry mixture of co-granulate and excipients.
15. 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
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A. CLASSIFICATION OF SUBJECT MATTER
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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, XP55005612, ISSN: 0939-6411, DOI: 10.1016/j.ejpb.2008.06.024	9,10
Y	abstract page 820, column 2 page 825 ----- -/--	1-15



Further documents are listed in the continuation of Box C.



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International application No
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