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(54) **Title:** PHARMACEUTICAL COMPOSITION COMPRISING CANDESARTAN CILEXETIL AND METHOD FOR MANUFACTURING THEREOF

(57) **Abstract:** Stable pharmaceutical composition comprising candesartan cilexetil as the active pharmaceutical ingredient and graft copolymer of polyvinyl alcohol with polyethylene glycol as a stabilising agent. A method for manufacturing of pharmaceutical composition comprising candesartan cilexetil as the active pharmaceutical ingredient comprising the following steps: - a mixture comprising candesartan cilexetil, filler and binder is wet granulated with the solution of the graft copolymer of polyvinyl alcohol with polyethylene glycol acting as a granulating agent with optionally addition of a colourant, - the resulting granulate is dried, - a disintegrant and optionally another active pharmaceutical ingredient selected from diuretics, optionally a colourant, and a lubricant are added to the dried granulate and the resulting mixture is mixed and subsequently tableted.

Pharmaceutical composition comprising candesartan cilexetil and method for manufacturing thereof

The subject of the invention includes a pharmaceutical composition comprising candesartan cilexetil as the active pharmaceutical ingredient and graft copolymer of polyvinyl alcohol with polyethylene glycol as a stabilising agent as well as the method for manufacturing thereof.

1-(cyclohexyloxycarbonyloxy)ethyl 2-ethoxy-1-{[2'-(1H-tetrazolyl-5)biphenylyl-4]methyl}-7-benzimidazolecarboxylate known under the INN of candesartan cilexetil and process for producing thereof was first disclosed in patent EP 459136B. Being a pro-drug it converts via hydrolysis into the active form of candesartan upon absorption from the gastrointestinal tract and proves efficient in the treatment of i.a. arterial hypertension together with other angiotensin II receptor antagonists.

The problem which occurs is the stability of candesartan cilexetil in pharmaceutical compositions. This was described in detail in patent EP 546358B. The solution, which is claimed herein, is the addition of an oily substance with a low melting point of between 20° and 90°C to the pharmaceutical composition along with the active pharmaceutical ingredient. According to patent EP 546358B the method for manufacturing of the composition includes pre-mixing the active pharmaceutical ingredient with the oily substance with a low melting point of between 20° and 90°C and subjecting the mixture to the further forming process.

In the international publication of patent application WO 2005/084648 a pharmaceutical composition was disclosed comprising candesartan cilexetil with one or more water soluble polymers acting as stabilising agents. The method for manufacturing of the composition consists in the formation of candesartan cilexetil dispersion with one or more water soluble polymers in the solution of a binder, granulation, drying and granulate tableting.

In the international publication of patent application WO 2005/079751 a pharmaceutical composition was disclosed comprising candesartan cilexetil with fatty substances acting as stabilising agents. The fatty substances listed in the publication include phospholipids, fatty acids and their esters. The method for manufacturing of the composition consists in the formation of candesartan cilexetil dispersion with one or more fatty substances in the solution of a binder, granulation, drying and granulate tableting.

The objective of the present invention is to develop a new, stable pharmaceutical composition comprising candesartan cilexetil as the active pharmaceutical ingredient whose manufacturing process is simple and may be conducted using standard formulation methods.

Surprisingly it has been found that the presence of a graft copolymer of polyvinyl alcohol with polyethylene glycol, originally meant as a coating agent for rapid disintegration tablets, ensures stability of pharmaceutical compositions comprising candesartan cilexetil. Furthermore, surprisingly it has been found that the solution of the graft copolymer of polyvinyl alcohol with polyethylene glycol used as a granulating agent during the manufacturing process compensates for the negative properties of the candesartan cilexetil active pharmaceutical ingredient which consist in its electrostatic behaviour and fluffiness which result in the uncontrolled loss of the active pharmaceutical ingredient during the manufacturing process.

The graft copolymer of polyvinyl alcohol with polyethylene glycol present in the pharmaceutical composition according to the present invention has a melting point of between 150° and 300°C, preferably between 180° and 250°C, more preferably between 200° and 220°C.

The pharmaceutical composition according to the present invention has a content of candesartan cilexetil in the weight ratio to the graft copolymer of polyvinyl alcohol with polyethylene glycol of 4:1 to 1:3, preferably 1:2 to 2:1.

Additionally, the pharmaceutical composition according to the present invention comprisies pharmaceutically acceptable excipients selected from a

group comprising fillers, binders, disintegrants, lubricants and optionally colourants. It may additionally comprise another active pharmaceutical ingredient acting as a diuretic.

The graft copolymer of polyvinyl alcohol with polyethylene glycol present in the pharmaceutical composition according to the present invention has hydrophilic properties. Preferably, it is the known copolymer under the trade name of Kollicoat® IR comprising 75% polyvinyl alcohol residues and 25% polyethylene glycol residues. The molecular weight of the copolymer is approximately 45,000 Daltons with a melting point of 209°C. Kollicoat® IR is hydrophilic powder readily soluble in water, white to light yellow. To improve its flow, approximately 0.3% of colloidal silica is added.

The fillers in the pharmaceutical composition according to the present invention are selected from a group comprising lactose, starch, cellulose, mannitol, sorbitol, tricalcium phosphate, calcium carbonate or other pharmaceutically acceptable fillers or their combination.

The binders in the pharmaceutical composition according to the present invention are selected from a group comprising hydroxypropylcellulose, povidone, hydroxypropylmethylcellulose or other pharmaceutically acceptable binders or their combination.

The disintegrants in the pharmaceutical composition according to the present invention are selected from a group comprising carmellose sodium or calcium, croscarmellose sodium, crospovidone, sodium starch glycolate or other pharmaceutically acceptable disintegrants or their combination.

The lubricants in the pharmaceutical composition according to the present invention are selected from a group comprising magnesium stearate, calcium stearate, stearyl fumarate, stearic acid or other pharmaceutically acceptable lubricants or their combination.

The colourants in the pharmaceutical composition according to the present invention are selected from a group comprising iron oxides or other pharmaceutically acceptable colourants or their combination.

The other active pharmaceutical ingredient acting as a diuretic in the pharmaceutical composition according to the present invention is hydrochlorothiazide.

The pharmaceutical composition according to the present invention is preferably a solid, oral pharmaceutical form, preferably tablet, capsule or powder.

Additionally, the invention includes a method for manufacturing of a pharmaceutical composition comprising candesartan cilexetil as the active pharmaceutical ingredient. The process comprises three steps. In the first step a mixture comprising candesartan cilexetil, filler and binder is wet granulated with the solution of the graft copolymer of polyvinyl alcohol with polyethylene glycol acting as a granulating agent with optionally addition of a colourant. In the second step, the resulting granulate is dried. In the third step a disintegrant and optionally another active pharmaceutical ingredient selected from diuretics, optionally a colourant, and a lubricant are added to the dried granulate and the resulting mixture is tableted.

The first step of the method for manufacturing of the pharmaceutical composition according to the invention is preferably carried out using fluid bed granulation method with the aqueous solution of the graft copolymer of polyvinyl alcohol with polyethylene glycol acting as a granulating agent with optionally addition of the colourant. The granulating solution constitutes 15% to 100% of the dry mass subjected to granulation, preferably 25% to 50%. The fillers utilised in the step are selected from a group comprising lactose, starch, cellulose, mannitol, sorbitol, tricalcium phosphate, calcium carbonate or other pharmaceutically acceptable fillers or their combination. The binders utilised in the step are selected from a group comprising hydroxypropylcellulose, povidone, hydroxypropylmethylcellulose or other pharmaceutically acceptable binders or their combination. The graft copolymer of polyvinyl alcohol with polyethylene glycol utilised in the step has a melting point of between 150° and 300°C, preferably between 180° and 250°C, more preferably between 200° and 220°C.

The colourants utilised in the step are selected from a group comprising iron oxides or other pharmaceutically acceptable colourants or their combination.

The second step of the method for manufacturing of the pharmaceutical composition according to the present invention is preferably carried out using fluid-bed drying until the moisture content is below 2%, preferably below 1%.

The third step of the method for manufacturing of the pharmaceutical composition according to the present invention is carried out by using a disintegrant selected from a group comprising carmellose sodium or calcium, croscarmellose sodium, crospovidone, sodium starch glycolate or other pharmaceutically acceptable disintegrants or their combination. The other active pharmaceutical ingredient selected from diuretics used in this step is hydrochlorothiazide. The colourants utilised in the step are selected from a group comprising iron oxides or other pharmaceutically acceptable colourants or their combination. The lubricants used in this step are selected from a group comprising magnesium stearate, calcium stearate, stearyl fumarate, stearic acid or other pharmaceutically acceptable lubricants or their combination.

The method for manufacturing of the pharmaceutical composition according to the present invention is characterised by the use of candesartan cilexetil active pharmaceutical ingredient in the weight ratio to the graft copolymer of polyvinyl alcohol with polyethylene glycol of 4:1 to 1:3, preferably between 1:2 and 2:1.

The invention is illustrated by the following examples which in no way restrict its scope:

Example 1

	[%/tablet]
Candesartan cilexetil	8
Lactose monohydrate	60
Corn starch	17
Hydroxypropylcellulose	3
Kollicoat® IR	4
Iron oxide	0.1
Carmellose calcium	7
Magnesium stearate	0.9

The weighed quantity of candesartan cilexetil, lactose monohydrate, corn starch and hydroxypropylcellulose is wet granulated using aqueous solution of Kollicoat® IR and iron oxide in the GLATT GPCG3 fluid-bed granulator. The resulting granulate is dried using fluid-bed method. The weighed quantity of carmellose calcium is added to the dried granulate. The content is mixed and weighed magnesium stearate is added. The content is again thoroughly mixed. The resulting tablet mass is tableted using the Kilian S100 rotary tablet press. 8 mm flat-concave punches are used in the tableting process. The resulting tablets have a weight of 200 mg.

Example 2

	[%/tablet]
Candesartan cilexetil	8
Lactose monohydrate	56
Corn starch	17
Hydroxypropylcellulose	3
Kollicoat® IR	8
Iron oxide	0.1
Carmellose calcium	7
Magnesium stearate	0.9

Procedure identical to that in Example 1. The resulting tablets have a weight of 200 mg.

Example 3

	[%/tablet]
Candesartan cilexetil	8
Lactose monohydrate	48
Corn starch	17
Hydroxypropylcellulose	3
Kollicoat® IR	16
Iron oxide	0.1
Carmellose calcium	7
Magnesium stearate	0.9

Procedure identical to that in Example 1. The resulting tablets have a weight of 200 mg.

Example 4

	[%/tablet]
Candesartan cilexetil	8
Lactose monohydrate	61.5
Corn starch	17
Hydroxypropylcellulose	3
Kollicoat® IR	2.5
Iron oxide	0.1
Carmellose calcium	7
Magnesium stearate	0.9

Procedure identical to that in Example 1. The resulting tablets have a weight of 200 mg.

Example 5

	[%/tablet]
Candesartan cilexetil	8
Lactose monohydrate	40
Corn starch	17
Hydroxypropylcellulose	3
Kollicoat® IR	24
Iron oxide	0.1
Carmellose calcium	7
Magnesium stearate	0.9

Procedure identical to that in Example 1. The resulting tablets have a weight of 200 mg.

Example 6

	[%/tablet]
Candesartan cilexetil	8
Hydrochlorothiazide	6.25
Kollicoat® IR	4
Lactose monohydrate	59.25
Corn starch	12.5
Hydroxypropylcellulose	2
Iron oxide	0.1
Carmellose calcium	7
Magnesium stearate	0.9

The weighed quantity of candesartan cilexetil, lactose monohydrate, corn starch and hydroxypropylcellulose is wet granulated using aqueous solution of Kollicoat® IR in the GLATT GPCG3 fluid-bed granulator. The resulting granulate is dried using fluid-bed method. The weighed quantity of carmellose calcium, hydrochlorothiazide and iron oxide is added to the dried granulate. The

content is mixed and weighed magnesium stearate is added. The content is again thoroughly mixed. The resulting tablet mass is tableted using the Kilian S100 rotary tablet press. 8 mm flat-concave punches are used in the tableting process. The resulting tablets have a weight of 200 mg.

Example 7 (Comparative example)

	[%/tablet]
Candesartan cilexetil	8
Lactose monohydrate	64
Corn starch	17
Hydroxypropylcellulose	3
Iron oxide	0.1
Carmellose calcium	7
Magnesium stearate	0.9

Procedure identical to that in Example 1. The tablets are manufactured without Kollicoat® IR. In order to obtain tablets of the same weight the quantity of lactose monohydrate is increased to 64% of the single tablet weight.

Example 8 (Comparative example)

	[%/tablet]
Candesartan cilexetil	8
Hydrochlorothiazide	6.25
Lactose monohydrate	63.25
Corn starch	12.5
Hydroxypropylcellulose	2
Iron oxide	0.1
Carmellose calcium	7
Magnesium stearate	0.9

Procedure identical to that in Example 6. The tablets are manufactured without Kollicoat® IR. In order to obtain tablets of the same weight the quantity of lactose monohydrate is increased to 63.25% of the single tablet weight.

For all batches from Example 1 to 8 the stability tests are performed in stability chamber for four weeks, 50°C and 75% RH.

The tablets are tested for candesartan cilexetil content and stability using assay methods based on high-performance liquid chromatography. The results of the testing, which confirm the subject matter of the invention, are specified in Table 1 and Table 2.

Table 1. Candesartan cilexetil content in tablet before the stability tests.

	Example 1	Example 2	Example 3	Example 4	Example 5	Example 6	Example 7 (without Kollicoat IR)	Example 8 (without Kollicoat IR)
Content [%]	100.1	99.3	101.0	102.7	106.0	94.2	90.0	82.0

Table 2. Total impurities, percentage of candesartan cilexetil degradation products in tablets stored at 50°C and relative humidity of 75%.

Time	Example 1	Example 2	Example 3	Example 4	Example 5	Example 6	Example 7 (without Kollicoat IR)	Example 8 (without Kollicoat IR)
0	0.38	0.39	0.37	0.41	0.28	0.44	0.22	0.45
2 weeks	1.27	0.49	0.46	1.97	0.68	1.80	4.59	9.10
4 weeks	1.78	1.29	0.63	2.50	0.74	2.16	7.74	12.00

Claims

1. A pharmaceutical composition comprising candesartan cilexetil as the active pharmaceutical ingredient **characterised in that** it comprises a graft copolymer of polyvinyl alcohol with polyethylene glycol.

2. The pharmaceutical composition of Claim 1 **characterised in that** the melting point of the graft copolymer of polyvinyl alcohol with polyethylene glycol is between 150° and 300°C, preferably between 180° and 250°C, more preferably between 200° and 220°C.

3. The pharmaceutical composition of Claim 1 **characterised in that** the weight ratio of the active pharmaceutical ingredient to the graft copolymer of polyvinyl alcohol with polyethylene glycol is 4:1 to 1:3, preferably 1:2 to 2:1.

4. The pharmaceutical composition of Claim 1 **characterised in that** it also comprises one or more pharmaceutically acceptable excipients.

5. The pharmaceutical composition of Claim 4 **characterised in that** the pharmaceutically acceptable excipients are selected from a group comprising fillers, binders, disintegrants, lubricants and optionally colourants.

6. The pharmaceutical composition of Claim 1 **characterised in that** it also comprises another active pharmaceutical ingredient selected from diuretics.

7. The pharmaceutical composition of Claim 6 **characterised in that** the other active pharmaceutical ingredient selected from diuretics is hydrochlorothiazide.

8. The pharmaceutical composition of Claims 1-7 **characterised in that** it is a solid, oral pharmaceutical form, preferably tablet, capsule or powder.

9. A method for manufacturing of a pharmaceutical composition comprising candesartan cilexetil as the active pharmaceutical ingredient **characterised in that** the method comprises the following steps:

a) a mixture comprising candesartan cilexetil, filler and binder is wet granulated with the solution of the graft copolymer of polyvinyl alcohol with polyethylene glycol acting as a granulating agent with optionally addition of a colourant,

b) the granulate manufactured in step a) is dried,

c) a disintegrant and optionally another active pharmaceutical ingredient selected from diuretics, optionally a colourant, and a lubricant are added to the dried granulate produced in step b) and the resulting mixture is mixed and subsequently tableted.

10. The method for manufacturing of the pharmaceutical composition of Claim 9 **characterised in that** the melting point of the graft copolymer of polyvinyl alcohol with polyethylene glycol is between 150° and 300°C, preferably between 180° and 250°C, more preferably between 200° and 220°C.

11. The method for manufacturing of the pharmaceutical composition of Claim 9 **characterised in that** the other active pharmaceutical ingredient selected from diuretics is hydrochlorothiazide.

12. The method for manufacturing of the pharmaceutical composition of Claim 9 **characterised in that** the weight ratio of the active pharmaceutical ingredient to the graft copolymer of polyvinyl alcohol with polyethylene glycol is 4:1 to 1:3, preferably 1:2 to 2:1.

INTERNATIONAL SEARCH REPORT

International application No
PCT/PL2008/000026

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/20

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, WPI Data, FSTA, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2005/084648 A (RANBAXY LAB LTD [IN]; SINGH ROMI BARAT [IN]; KARANTH GIRISH [IN]; PRAS) 15 September 2005 (2005-09-15) cited in the application page 1, line 15 - line 25 page 2, line 1 - line 8 example 1 table 1	1-12
Y	WO 2005/079751 A (RANBAXY LAB LTD [IN]; SINGH ROMI BARAT [IN]; KARANTH GIRISH K [IN]; PR) 1 September 2005 (2005-09-01) cited in the application examples 1-3 table 1 claims 1-12 page 3, line 17 - line 23	1-12

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
12 August 2008	21/08/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Schüle, Stefanie

INTERNATIONAL SEARCH REPORT

International application No
PCT/PL2008/000026

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2005/070398 A (RANBAXY LAB LTD [IN]; SINGH ROMI BARAT [IN]; KARANTH GIRISH K [IN]; PR) 4 August 2005 (2005-08-04) example 1 page 4, line 8 - line 15 claims 1-17	1-12
Y	JANSSENS ET AL: "The use of a new hydrophilic polymer, Kollicoat IR<(>R), in the formulation of solid dispersions of Itraconazole" EUROPEAN JOURNAL OF PHARMACEUTICAL SCIENCES, ELSEVIER, AMSTERDAM, NL, vol. 30, no. 3-4, 23 February 2007 (2007-02-23), pages 288-294, XP005901598 ISSN: 0928-0987 abstract page 289, column 1, paragraph 3 - column 2, paragraph 1 page 289, paragraph 2.2	1-12
A	WO 2004/052345 A (RANBAXY LAB LTD [IN]; GANDHI RAJESH [IN]; ISSA CHAYAPATHY [IN]; MALIK) 24 June 2004 (2004-06-24) the whole document	1-12

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/PL2008/000026

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2005084648 A	15-09-2005	NONE	
WO 2005079751 A	01-09-2005	EP 1711168 A2	18-10-2006
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WO 2004052345 A	24-06-2004	AU 2003302881 A1	30-06-2004
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