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- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

(54) Title: PHARMACEUTICAL COMPOSITION COMPRISING IVACAFTOR

(57) Abstract: The present invention relates to an immediate release tablet composition comprising free particles of ivacaftor a pH dependent polymer and surfactant extragranularly and intragranularly.



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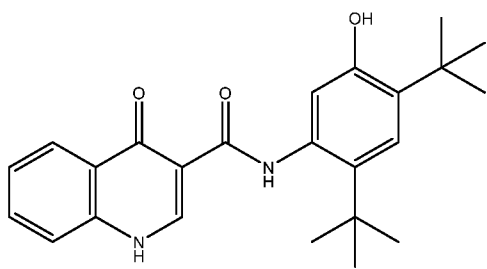
PHARMACEUTICAL COMPOSITION COMPRISING IVACAFTOR

FIELD OF THE INVENTION

The present invention relates to pharmaceutical formulation comprising particles of a free drug of ivacaftor.

BACKGROUND OF THE PRESENT INVENTION

Ivacaftor or *N*-(2,4-ditert-butyl-5-hydroxyphenyl)-4-oxo-1*H*-quinoline-3-carboxamide of the formula 1:



is a potentiator of the CFTR(cystic fibrosis transmembrane conductance regulator) protein and has demonstrated clinical activity against cystic fibrosis.

Ivacaftor is marketed by Vertex under the brand name Kalydeco[®] and it has been disclosed in WO2006002421.

Pharmaceutical compositions comprising ivacaftor have been disclosed as well; WO2007079139 disclosed amorphous solid dispersion with 50wt% ivacaftor and 50wt% of a polymer. This kind of system increases greatly the solubility of the drug substance and subsequently its bioavailability may be promoted. In WO2010019239 these amorphous solid dispersions were improved reducing the quantity of polymer till about 20wt% and increasing the quantity of ivacaftor till 80wt% resulting in a high load smaller tablet of ivacaftor.

The common purpose of the use of solid dispersions in pharmaceutical delivery systems is to increase the solubility of very poor soluble active ingredients and stabilize the amorphous form of the drug substance once the latter is molecularly dispersed in the polymer matrix. There are different

ways to produce solid dispersions. Hot-melt extrusion and spray-drying are the most common technologies to obtain this kind of delivery systems.

Hot-melt extrusion is a manufacturing process where polymeric materials are heated above their glass-transition temperature and mechanically mixed with active compounds, in order to disperse the drug substance molecularly into the polymeric net. The main drawbacks of this technology are:

- The active compounds should not get degraded at high temperature;
- The melting point of the active substance should be lower enough to get dispersed molecularly;
- Similarly, glass-transition temperatures of the polymers must be low enough to have a feasible manufacturing process, but sufficiently high to stabilize the solid dispersion;
- Equipment required to perform hot-melt extrusion is a high costly technology.

Spray-drying consists in two main steps: i) complete dissolution of the drug substance and a dilution material (e.g. a polymer) in a solvent or mixture of solvents and ii) fast spray-drying of the previous solution in order to collect the solid material.

Spray-drying technology shows numerous inconveniences:

- The use of organic solvents to dissolve the active ingredient is normally required since the latter usually shows very poor solubility in aqueous media; the drying process is not able to remove completely the residual solvent in the drug product, requiring a second drying process to assure safety, with acceptable levels of the organic solvent;
- The fact of dissolving the drug substance and the excipients in a solvent may lead to chemical reactions, which may also be triggered during the drying step due to the high drying air temperature;
- The resulting product after spray-drying usually exhibits small particle size and very low bulk density, resulting in very poor flow. This particular feature of the spray-dried material can be transferred to the final blend properties, making the tableting step very challenging. Consequently, an intermediate dry granulation process of this material may be required to improve the flow properties;

- Spray-drying manufacturing requires high costly technology and wide, large space to fit the bulky equipment pieces;
- Spray-drying process is a time consuming process, conditioned by the amount of solvent required to dissolve all the components and by the maximum spraying speed to have a feasible process.

Hence, it would be desirable to have a tablet composition comprising ivacaftor that is stable, easy to produce on commercial scale and that exhibits adequate dissolution and is bioequivalent to Kalydeco[®].

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the flow chart of the process of dry granulation applied to prepare the tablets of Example 1.

DETAILED DESCRIPTION OF THE PRESENT INVENTION

The present invention relates to an immediate release pharmaceutical composition, advantageously a tablet, of ivacaftor comprising an ivacaftor granulate. The term “immediate release” as used throughout the disclosure and claims are, in accordance with common understanding, those dosage forms that allow drugs to be released directly in the gastrointestinal fluids, with no intention of delaying drug dissolution or absorption. According to the European Pharmacopoeia, in most cases the acceptance criteria for immediate-release dosage forms are that at least 80 per cent of the active substance is released within a specified time, typically 45 minutes or less.

Ivacaftor of formula (1) above is a known compound, which is commercially available or may be produced by procedures known in the art.

One embodiment of the present invention relates to a tablet composition comprising granules and one or more extragranular pharmaceutical excipients, wherein the granules comprise all based on the total weight of the composition:

- a) Amorphous ivacaftor in an amount from 15 to 40% by weight, wherein said compound is provided as particles of a free drug;

- b) pH dependent polymer in an amount from 5 to 10% by weight;
 - c) surfactant in an amount from 0.1 to 0.4% by weight;
- and wherein the extragranular excipients comprise surfactant in an amount of from 0.1% to 1%, preferably from 0.3% to 0.7% by weight based on the total weight of the composition, wherein free drug refers to solid particles not intimately embedded in a polymeric co-precipitate.

These tablets compositions of ivacaftor are suitable for oral administration of ivacaftor to humans comprising up to 150 mg of the active substance in a single dose.

In one embodiment, the present invention relates to a granulate of amorphous ivacaftor provided as particles of a free drug. The term free drug refers to solid particles consisting of ivacaftor as opposed to the compound intimately embedded in a polymeric coprecipitate. The granulate comprises amorphous ivacaftor in an amount from 15 to 40%, preferably 20 to 35%, even more preferably 25 to 30% by weight based on the total weight of the composition.

Kalydeco® is marketed as an amorphous solid dispersion: The drug substance is practically insoluble in water and in buffers of pH 1.0 – 7.0. Amorphous ivacaftor dissolves more quickly than the crystalline forms but is less thermodynamically stable, so it converts to the crystalline form over time. In the past this problem was avoided formulating ivacaftor as a solid dispersion, wherein the amorphous form is stable, the preferred way to formulate the commercial solid dispersions is spray drying and this method is used to produce Kalydeco. However, the commercial process of spray drying has numerous disadvantages as explained above.

It was surprisingly found by the present inventors that a tablet composition comprising granules with amorphous ivacaftor, pH dependent polymer and surfactant intragranularly and extragranularly keeps the amorphous form stable without the need of a solid dispersion.

The granulate of the present invention comprises 5 to 10% by weight of a pH dependent polymer, preferably 6 to 8% by weight based on the total weight of the composition.

A pH dependent polymer is a polymer which responds to the changes in the pH of the surrounding medium by varying their solubility. Examples of these pH dependent polymers are: Hypromellose Acetate Succinate (HPMCAS), cellulose acetate phthalate, polymethacrylates, such as

methacrylic acid-ethyl acrylate copolymer (1:1), methacrylic acid-methyl acrylate copolymer (1:1) and methacrylic acid-methyl acrylate copolymer (1:2), hydroxypropyl methylcellulose phthalate, poly vinyl acetate phthalate.

In a preferred embodiment HPMCAS is used as a pH dependent polymer.

The granulate of the present invention comprises surfactant.

Surfactants are compounds that lower the surface tension (or interfacial tension) between two liquids, between a gas and a liquid, or between a liquid and a solid. Surfactants may act as wetting agents. Wetting agent is a surfactant that, when dissolved in water, lowers the advancing contact angle, aids in displacing an air phase at the surface, and replaces it with a liquid phase. A preferred surfactant to be used according to the present invention is sodium lauryl sulphate, polysorbate 80, poloxamer, most preferably sodium lauryl sulphate. Surfactants are preferably used intragranularly in an amount of from 0.03% to 3%, more preferably 0.05 % to 2%, most preferably 0.1% to 0.4% by weight based on the total weight of the composition.

Further, the granulate of the present invention can comprise other pharmaceutical acceptable excipients, chosen from, for example, diluents, binders, disintegrants, lubricants and glidants.

Diluents are fillers which are used to increase the bulk volume of a tablet or capsule. By combining a diluent with the active pharmaceutical ingredient, the final product is given adequate weight and size to assist in production and handling. Binders hold the excipients that are present in a tablet together. Binders ensure that tablets and granules can be formed having the desired or required mechanical strength.

The granulate of the present invention preferably contains at least one diluent.

Suitable examples of diluents to be used in accordance with the present invention include starch, pregelatinized starch, microcrystalline cellulose(MCC), and calcium phosphate. Lactose, sorbitol, mannitol and sucrose are also suitable water-soluble diluents. Diluents are preferably used intragranularly in an amount of from 10% to 50%, more preferably 20% to 40%, even more preferably from 27% to 37% by weight based on the total weight of the composition.

In a preferred embodiment of the present invention microcrystalline cellulose is used as intragranularly diluent.

Disintegrants are added to a tablet composition extragranularly to promote the breakup of the tablet into smaller fragments and intragranularly to promote the breakup of the granules that contain ivacaftor. The granulate of the present invention preferably contains at least one disintegrant.

Suitable examples of disintegrants to be used in accordance with the present invention include crospovidone, sodium starch glycolate, croscarmellose sodium, and mixtures of any of the foregoing. A preferred disintegrant is croscarmellose sodium.

In a preferred embodiment disintegrants are used intragranularly in an amount of from 1% to 10%, preferably 2% to 6%, by weight based on the total weight of the composition.

Glidants enhance product flow by reducing interparticulate friction. A suitable example is colloidal silicon dioxide, starch or talc.

The granulate of the present invention may contain a glidant. Colloidal anhydrous silica is a preferred glidant to be used. Its small particle size and large specific surface area gives it desirable flow characteristics that are exploited to improve the flow properties of dry powders in a number of processes such as tableting and capsule filling. Colloidal anhydrous silica is preferably used intragranularly in an amount of from 0.1% to 5%, preferably 0.3 % to 3%, more preferably 0.4% to 0.8% by weight based on the total weight of the composition.

The granulate of the present invention may contain a lubricant. Lubricants are generally used in order to reduce sliding friction. In particular, to decrease friction at the interface between a tablet's surface and the die wall during ejection, and reduce wear on punches and dies. Suitable lubricants to be used in accordance with the present invention include magnesium stearate, calcium stearate, stearic acid, glyceryl behenate, hydrogenated vegetable oil, and glycerine fumarate. A preferred lubricant is magnesium stearate.

Lubricants preferably are used in a total amount of from 0.05% to 5%, preferably 0.1% to 2%, even more preferably 0.4% to 1.5% by weight based on the total weight of the composition. Lubricants can be used intragranularly, extragranularly or both.

In the tablet composition, the extragranular excipients comprise at least one surfactant. The surfactant may be the same or different than that as used in the granulate composition.

A preferred surfactant to be used according to the present invention is sodium lauryl sulphate, polysorbate 80, poloxamer, most preferably sodium lauryl sulphate. Surfactants are preferably used extragranularly in an amount of from 0.1% to 1%, more preferably from 0.3% to 0.7% even more preferably from 0.4% to 0.6% by weight based on the total weight of the composition.

The combination of intragranular pH dependent polymer and surfactant intragranular and extragranular results in a bioequivalent product to Kalydeco® with excellent stability properties.

Other suitable extragranular pharmaceutical excipients in a tablet composition include, without limitation: disintegrants, diluents, lubricants. The disintegrant, diluents and lubricants may be the same or different than that as used in the granulate composition. In a preferred embodiment diluents are used extragranularly in an amount of from 10% to 50%, preferably 12% to 40% even more preferably 15% to 30%, by weight based on the total weight of the composition. A preferred diluent to be used is MCC, lactose monohydrate or mixtures thereof.

In a preferred embodiment disintegrants are used extragranularly in an amount of from 1% to 10%, preferably 2% to 6%, by weight based on the total weight of the composition. A preferred disintegrant to be used is croscarmellose sodium.

In a preferred embodiment lubricant are used extragranularly in a total amount of from 0.05% to 5%, preferably 0.1% to 2%, even more preferably 0.4% to 1.5% by weight based on the total weight of the composition. A preferred lubricant to be used is magnesium stearate.

In a preferred embodiment, the tablet composition of the present invention contains the following ingredients, based on the total weight of the composition:

Granules comprising intragranularly:

- a) Amorphous ivacaftor wherein said compound is provided as particles of a free drug, in an amount of from 15% to 40% by weight based on the total weight of the composition;
- b) pH dependent polymer, preferably HPMCAS in an amount of from 5% to 10% by weight based on the total weight of the composition;
- c) Surfactant, preferably sodium lauryl sulphate in an amount of from 0.1% to 0.4% by weight based on the total weight of the composition;

- d) Disintegrant, preferably croscarmellose sodium in an amount of 1% to 10%, preferably from 2% to 6% by weight based on the total weight of the composition;
- e) Diluent(s), preferably MCC in an amount of from 10% to 50% by weight based on the total weight of the composition.

Extragranular excipients comprising:

- a) Surfactant, preferably sodium lauryl sulphate in an amount of from 0.1% to 1% by weight based on the total weight of the composition;
 - b) Disintegrant, preferably croscarmellose sodium in an amount of from 1% to 10%, preferably from 2% to 6% by weight based on the total weight of the composition;
 - c) Diluent(s), preferably MCC, lactose or mixture of both in an amount of from 12% to 40% by weight based on the total weight of the composition;
 - d) Lubricant, preferably magnesium stearate in an amount of from 0.1% to 2% by weight based on the total weight of the composition;
- wherein free drug refers to solid particles not intimately embedded in a polymeric co-precipitate.

The tablet compositions described herein can be made using conventional methods and equipment well-known in the art. In a preferred embodiment the composition is prepared by granulation process. Granulation can be performed by a wet or dry process, wherein wet granulation using water or organic solvents or mixtures thereof as granulation liquid and dry granulation can be performed by processes known as slugging and/or roller compaction. Dry granulation is the preferred method of preparation.

The present invention further relates to a tablet composition as described hereinabove, prepared by a dry-granulation process, which process comprises:

- a) Mixing amorphous ivacaftor in an amount from 15% to 40% by weight wherein said compound is provided as particles of a free drug, a pH dependent polymer in an amount from 5% to 10% by weight and a surfactant in an amount from 0.1% to 0.4% by weight, and optionally one or more pharmaceutically acceptable excipients to form a mixture to form a granulate;

- b) Further mixing the obtained granulate with one or more further pharmaceutically acceptable excipients to form a further mixture, wherein the extragranular excipients comprises surfactant 0.1% to 1% by weight;
- c) Compressing the mixture obtained in step (b) into a tablet; and optionally;
- d) Coating the tablet.

All weight referred to the total tablet weight.

The granules of the present invention typically have a particle size distribution D_{50} of from 100 to 400 μm , preferably from 200 to 300 μm and D_{90} from 400 to 600 μm , preferably from 450 to 550 μm .

In a preferred embodiment the tablet of the invention above described has ivacaftor with a small particle size, preferably of D_{50} less than 20 microns, more preferably between 5-15 μm and/or D_{90} less than 90 μm preferably less than 70 μm , even more preferably between 1-50 μm , even more preferably between 1-40 μm most preferably between 10 and 40 μm . Granulates made from ivacaftor of higher particle size may negatively affect dissolution and or the hardness of final tablets. Accordingly, starting ivacaftor should be first milled and screened to the desirable particle size, if necessary, prior to charging in the granulator.

The tablet compositions of the present invention show an in vitro dissolution profile wherein at least 80% of ivacaftor is released within thirty minutes when the composition is subjected to a dissolution study in 900 ml 0.7% SLS in 50 mM sodium phosphate buffer, pH 6.8 using a USP apparatus II at 65 rpm at 37°C. The tablet composition in accordance with the present invention is bioequivalent in vitro and in vivo to the commercially available ivacaftor tablets.

The present invention is illustrated by the following Examples.

Example 1: Pharmaceutical composition comprising ivacaftor

The tablets comprising ivacaftor were prepared by dry granulation process and have the composition as given in table 1.

Table 1

	Ivacaftor tablet composition	
Component	mg/tablet	%
<i>Intragranular components</i>		
Amorphous ivacaftor	150	27.27
HPMC-AS grade HMP	36.60	6.65%
Sodium lauryl sulfate	0.94	0.17%
Microcrystalline cellulose	192.71	35.04%
Croscarmellose sodium	16.5	3.00%
Colloidal silicon dioxide	2.75	0.50%
Magnesium stearate	2.75	0.50%
<i>Extragranular components</i>		
Sodium lauryl sulfate	2.75	0.50%
Lactose monohydrate	62.60	11.38%
Microcrystalline cellulose	63.16	11.48%
Croscarmellose sodium	16.50	3.00%
Magnesium stearate	2.75	0.50%
Total core tablet weight	550	100.0

Example 2:

68.18 grams of ivacaftor, 16.64 grams of hydroxypropyl methylcellulose acetate succinate (AQOAT AS-HF[®] grade), 0.43 grams of sodium lauryl sulfate, 87.6 grams of microcrystalline cellulose, 7.50 grams of croscarmellose sodium, 1.25 grams of colloidal silicon dioxide were accurately weighed and sieved through 0.8 mm mesh for deagglomeration. Afterwards, the components were placed in a container and mixed at 72 rpm for 10 minutes using a diffusion blender obtaining a blend (1). 1.25 grams of magnesium stearate was accurately weighed and sieved through 0.5 mm mesh for deagglomeration. Then the blend (1) was mixed with the magnesium stearate at 72

rpm for 3 minutes using a diffusion blender to obtain a homogenous blend (2). The blend (2) was compressed to obtain slugs of approximately 1000 mg. The slugs were then crushed and sieved through 0.8 mm mesh obtaining homogenous granules (3).

28.45 grams of lactose monohydrate, 28.71 grams of microcrystalline cellulose, 1.25 grams of sodium lauryl sulfate and 7.50 grams of croscarmellose sodium were accurately weighed and sieved through 0.8 mm mesh for deagglomeration. The components were placed in a container together with the granules (3) and mixed at 72 rpm for 10 minutes using a diffusion blender resulting in a homogenous blend (4). 1.25 grams of magnesium stearate were accurately weighed and sieved through 0.5 mm mesh for deagglomeration. Afterwards the magnesium stearate was mixed with the previous blend (4) at 72 rpm for 3 minutes using a diffusion blender resulting in a homogenous blend (5). Finally, this blend was compressed obtaining 550 mg, 16 mm x 8 mm oblong tablets (6).

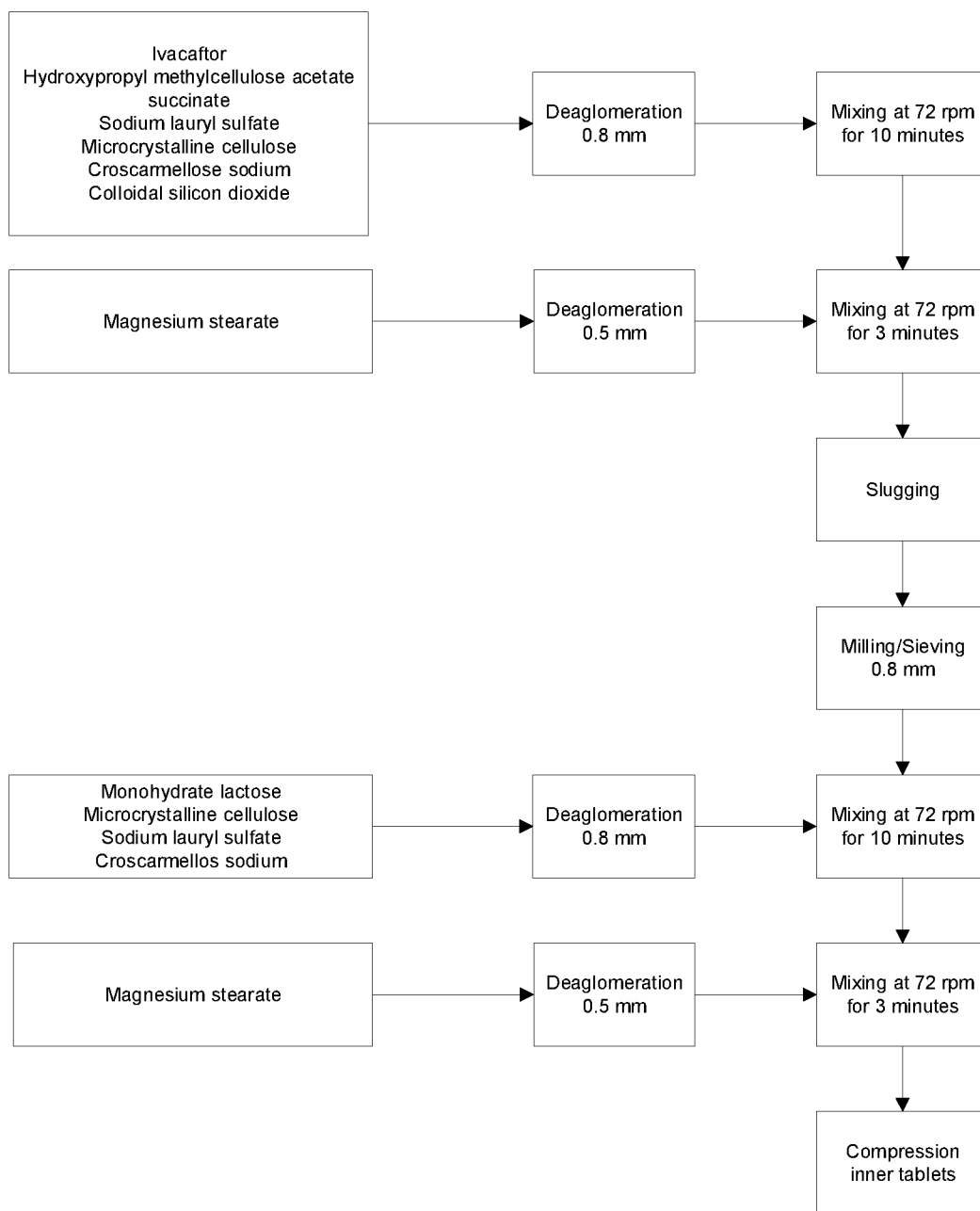
CLAIMS

1. A tablet composition comprising granules and one or more extragranular pharmaceutical excipients, wherein the granules comprise all based on the total weight of the composition:
 - a) Amorphous ivacaftor in an amount from 15% to 40% by weight, wherein said compound is provided as particles of a free drug
 - b) pH dependent polymer in an amount from 5% to 10% by weight of;
 - c) Surfactant in an amount from 0.1% to 0.4% by weight;and wherein the extragranular excipients comprise surfactant in an amount of from 0.1% to 1%, preferably from 0.3% to 0.7% by weight based on the total weight of the composition, wherein free drug refers to solid particles not intimately embedded in a polymeric co-precipitate.
2. A tablet composition according to claim 1 wherein the surfactant is sodium lauryl sulphate.
3. A tablet composition according to any one of the claims 1 to 2 wherein the pH dependent polymer is HPMCAS.
4. A tablet composition according to any one of the claims 1 to 3 wherein the granule further comprises diluent in an amount of from 10% to 50% by weight based on the total weight of the composition.
5. A tablet composition according to claim 4 wherein the diluent is MCC.
6. A tablet composition according to any one of the claims 1 to 5 wherein the granule further comprises disintegrant intragranularly in an amount of from 1% to 10% by weight based on the total weight of the composition.
7. A tablet composition according to claim 6 wherein the disintegrant is crosscarmellose sodium.
8. A tablet composition according to any one of claims 1 to 7, wherein the extragranular excipients further comprises disintegrant(s) in an amount from 1% to 10% by weight based on the total weight of the composition.
9. A tablet composition according to any one of claims 1 to 8 wherein the extragranular excipients further comprises one or more diluents in an amount from 12% to 40% by weight based on the total weight of the composition.

10. A tablet composition according to claim 9 wherein the diluent is lactose, MCC or a mixture of both.
11. A tablet composition according to any one of claims 1 to 10, wherein the extragranular excipients further comprises a lubricant in a total amount of from 0.1% to 2% by weight based on the total weight of the composition.
12. A tablet composition according to any one of claims 1 to 11, wherein the particle size d₉₀ is less than 90 µm.
13. A tablet composition according to any one of claims 1 to 12 prepared by a dry-granulation process, which process comprises:
 - a) Mixing amorphous ivacaftor in an amount from 15% to 40% by weight wherein said compound is provided as particles of a free drug, a pH dependent polymer in an amount from 5% to 10% by weight and a surfactant in an amount from 0.1% to 0.4% by weight, and optionally one or more pharmaceutically acceptable excipients to form a mixture to form a granulate;
 - b) Further mixing the obtained granulate with one or more further pharmaceutically acceptable excipients to form a further mixture, wherein the extragranular excipients comprises surfactant 0.1% to 1% by weight;
 - c) Compressing the mixture obtained in step (b) into a tablet; and optionally
 - d) Coating the tablet.

DRAWINGS

Figure 1



INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2021/069774

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/20 A61K31/00
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 practicable, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2012/027247 A2 (VERTEX PHARMA [US]; ALARGOVA ROSSITZA GUEORGUEVA [US] ET AL.) 1 March 2012 (2012-03-01) paragraph [0351] - paragraph [0371]; table 15	1-13
A	----- US 2011/064811 A1 (HURTER PATRICIA [US] ET AL) 17 March 2011 (2011-03-17) cited in the application paragraph [0239] - paragraph [0257]; table 4 -----	1-13



Further documents are listed in the continuation of Box C.



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

26 October 2021

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Name and mailing address of the ISA/

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Authorized officer

Frelichowska, J

INTERNATIONAL SEARCH REPORT

Information on patent family members

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