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(54) Title: AMORPHOUS LUMACAFTOR AND ITS SOLID DISPERSION

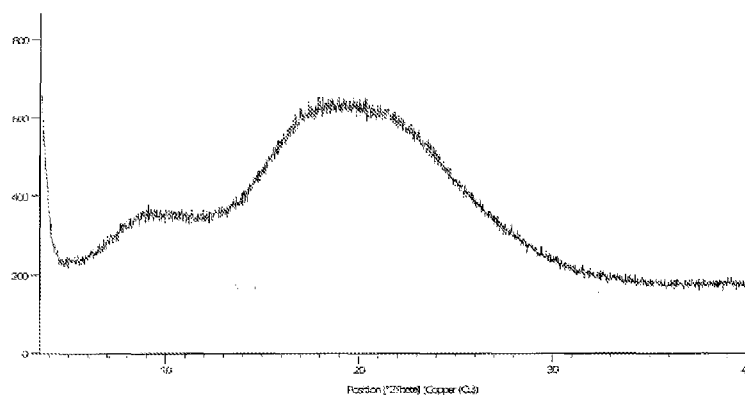


Figure 1: XRPD of amorphous lumacافتor

(57) Abstract: The present invention provides a novel amorphous form of lumacافتor and its preparation by various methods. The patent invention also relates to novel lumacافتor hydrobromide crystalline form A and process for its preparation. The present invention relates to amorphous lumacافتor premixed with an excipient and process for the preparation of the premix.



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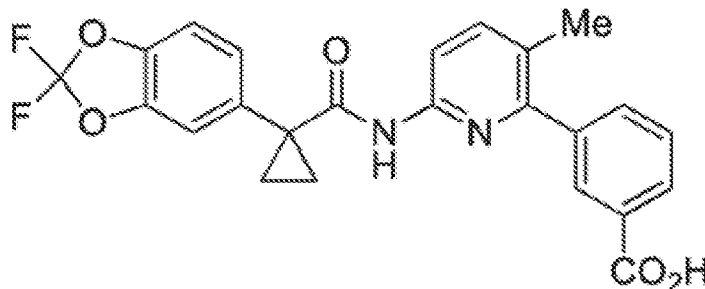
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AMORPHOUS LUMACAFTOR AND ITS SOLID DISPERSION**Field of the Invention:**

The present invention relates to novel amorphous form of lumacaftor and various methods for its preparation. The present invention also relates to lumacaftor hydrobromide crystalline form A and process for its preparation. The present invention also relates to the amorphous lumacaftor premixed with an excipient and process for the preparation of the premix.

Background of the Invention:

The present invention is related to lumacaftor which is a drug for the treatment of cystic fibrosis. The drug is designed to be effective in patients that have the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR), the defective protein that causes the disease.



(I)

Lumacaftor (I) chemically known as 3-[6-([1-(2,2-difluoro-1,3-benzodioxol-5-yl)cyclopropyl]carbonyl)amino)-3-methylpyridin-2-yl]benzoic acid is disclosed in the PCT application WO 2007/056341. The patent US 8,507,534, US 8,461,342 and US 8,124,781 discloses polymorphic forms and processes for preparation of lumacaftor.

The present invention is directed to amorphous form of lumacaftor. It is known that the amorphous forms in a number of drugs exhibit different dissolution characteristics and in some cases different bioavailability patterns compared to crystalline forms. The thermodynamically stable forms are always preferred for the formulation because of their stability. For some therapeutic indications one bioavailability pattern may be favored over

another. Therefore, there is a need to develop an amorphous form of lumacaftor which has improved characteristics. The inventors of the present invention provide here efficient and simple processes to obtain amorphous lumacaftor.

- 5 The present invention is also directed to amorphous form of lumacaftor which is prepared via hydrobromide salt of lumacaftor.

The amorphous solid dispersions of an active pharmaceutical ingredient (API) can provide further prospective opportunities to improve the performance profile of a pharmaceutical composition comprising the said API. Therefore, development of
10 processes to prepare amorphous solid dispersion of an API is of importance. The present invention provides a process for the preparation of amorphous lumacaftor and lumacaftor solid dispersion premixed with an excipient.

15 **Summary of the invention:**

The present invention provides amorphous form of lumacaftor. It further provides various methods for its preparation, such as:

Method 1: dissolving the lumacaftor in suitable solvent followed by drying,

Method 2: dispersing lumacaftor in a solvent followed by base-acid treatment, and

- 20 Method 3: melting lumacaftor followed by cooling.

The present invention also relates to preparation of amorphous lumacaftor via lumacaftor hydrobromide salt. The present invention also relates to the amorphous lumacaftor premixed with an excipient and process for the preparation of the premix.

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The present invention further relates to a process for preparation of lumacaftor by crystallization from organic solvents.

Description of the drawings:

- 30 Figure 1: X-ray powder diffractogram (XRPD) for amorphous lumacaftor obtained by the processes of the present invention.

Figure 2: X-ray powder diffractogram (XRPD) of novel crystalline form A of lumacaftor hydrobromide obtained by the processes of the present invention.

Figure 3: X-ray powder diffractogram (XRPD) for amorphous lumacaftor premixed with syloid 244FP.

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Detailed description of the invention:

An embodiment of the present patent application provides an amorphous form of lumacaftor.

10 In an embodiment of the present invention provides process for preparation of lumacaftor comprising:

- a) dissolving lumacaftor in a suitable solvent and
- b) isolating lumacaftor from reaction mixture thereof.

15 The term “suitable solvent” in the method described above includes alcohols like methanol, ethanol, n-propanol, isopropanol, ketones like acetone, 2-butanone, methyl isobutyl ketone; esters like ethyl acetate and isopropyl acetate; ethers such as tetrahydrofuran, ethyl ether, methyl t-butyl ether, di-isopropyl ether; chlorinated hydrocarbons such as dichloromethane, ethylene dichloride and chloroform, and mixtures
20 thereof; the most preferred solvent is tetrahydrofuran.

The isolation techniques involve the use of spray drying, lyophilization etc. followed by vacuum drying of the material.

25 In yet another embodiment, the present invention provides process for preparation of lumacaftor comprising:

- a) dispersing lumacaftor in water;
- b) adding base to the dispersion;
- c) treating the mixture with acid and
- 30 d) isolating lumacaftor.

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The method described above includes dispersing lumacaftor in water followed by addition of a base to obtain clear solution followed by treatment with acid to obtain a solid that is filtered and dried.

- 5 The bases used in above method are selected from a group comprising of inorganic bases of hydroxides as sodium hydroxide, potassium hydroxide, lithium hydroxide, carbonates such as sodium carbonate, potassium carbonate, sodium bicarbonate, organic bases such as triethyl amine, diisopropyl amine, DBU etc.
- 10 The acid used in above method is selected from a group comprising of mineral acids such as hydrochloric acid, sulphuric acid, nitric acid, boric acid, phosphoric acid, hydrobromic acid, hydrofluoric acid, per chloric acid, hydro iodic acid etc.

In another embodiment is provided a process for preparation of lumacaftor comprising:

- 15 a) heating lumacaftor up to 200-250°C,
 b) cooling the mass to 10-50°C,
 c) isolating lumacaftor.

- 20 The above method uses a melt crystallization technique for preparation of amorphous lumacaftor.

Any physical form of lumacaftor such as crystalline, amorphous or their mixtures can be utilized as an input in these methods.

- 25 The amorphous form of lumacaftor obtained by the process of the present invention is characterized by XRPD (X-ray powder diffraction pattern) pattern as shown in figure 1.

The amorphous form of lumacaftor described herein is further identified by DSC with peak at 203.78°C.

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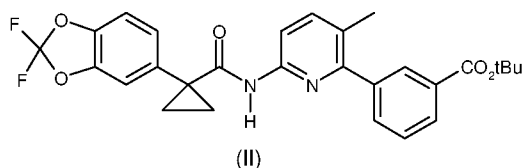
The amorphous form of lumacaftor obtained by the process of the present invention is further characterized by IR peaks at 701.7, 907.6, 1031.9, 1155.5, 1238.4, 1373.7, 1413.9, 1463.9, 1508.1, 1497.2, 1691.2, 1723.7, 2929.4, 3071.7 and 3406.4 cm⁻¹.

- 5 The effective amount of stable amorphous form of lumacaftor can be used to prepare pharmaceutical composition in association with one or more non-toxic pharmaceutically acceptable carriers and /or diluents thereof.

- Another embodiment of the present invention is related to crystalline form A of lumacaftor hydrobromide. The crystalline form A of lumacaftor hydrobromide obtained by the process of the present invention is characterized by XRPD pattern as shown in figure 2. The crystalline form A of lumacaftor hydrobromide shows characteristic peaks in XRPD at 8.98 and 18.69 $\pm$ 0.2 degree 2 θ . The crystalline form of lumacaftor hydrobromide is further characterized by peaks in XRPD at 10.08, 10.46, 14.25, 17.26, 15 17.40, 18.02, 18.53, 20.68, 25.76, 29.98 $\pm$ 0.2 degree 2 θ .

The crystalline form A of lumacaftor hydrobromide described herein is further identified by DSC with peak at 220.83°C.

- 20 Yet another embodiment of the present invention is to provide a process for the preparation of crystalline form A of lumacaftor hydrobromide which comprises hydrolysis of 3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)cyclopropanecarboxamido)-3-methylpyridine-2-yl)-t-butylbenzoate (II).



3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)
cyclopropanecarboxamido)-3-methyl
pyridine-2-yl)-t-butylbenzoate

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The quantity of acetonitrile used for preparation of lumacaftor hydrobromide is 5-30 times, preferably 10-15 times. The quantity of hydrobromic acid used is 5-30 times, preferably 10-20 times. The temperature at which the reaction is carried is 10-50°C.

- 5 The effective amount of crystalline lumacaftor hydrobromide can be used to prepare any physical form of lumacaftor such as crystalline, amorphous or their mixtures.

Further embodiment of the present patent application provides a process for the preparation of and lumacaftor premixed with and one or more excipient comprising the steps of:

- 10 a) dissolving lumacaftor base in organic solvent,
b) adding one or more excipient and
c) isolating solid dispersion of amorphous lumacaftor from the reaction mixture thereof.

15

The lumacaftor can be obtained as per methods known in literature.

The organic solvent in step (a) is selected from benzene, toluene, xylene, hexane, heptane, cyclohexane, cycloheptane, methanol, ethanol, n-butanol, t-butanol, acetone, 2-butanone, methyl isobutyl ketone, ethyl acetate, isopropyl acetate, ethyl ether, methyl t-butyl ether, di-isopropyl ether; dichloromethane, ethylene dichloride, dimethyl formamide, dimethyl sulfoxide, tetrahydrofuran, acetonitrile, isopropyl nitrile and chloroform, methanol, ethanol, propanol and mixtures thereof; the most preferred organic solvent is mixture of dichloromethane and methanol.

25

The excipients used in step (b) include, but not limited to mannitol, lactose, fructose, sorbitol, xylitol, maltodextrin, dextrans, lactitol, inositol, trehalose, maltose, raffinose, .alpha.-, .beta.- and .gamma.-cyclodextrins, gum arabic, sodium alginate, propylene glycol alginate, agar, gelatin, tragacanth, xanthan gum, starch, lectins, urea, chitosan, chitosan glutamate, hydroxypropyl beta.-cyclodextrin chitosan, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), methylcellulose (MC), cellulose acetate phthalate (CAP), hydroxypropylmethylcellulose phthalate

30

(HPMC-P), hydroxypropyl methylcellulose acetate succinate (HPMC-AS), carboxymethylethylcellulose (CMEC), carboxymethyl cellulose, sodium carboxymethyl cellulose, cellulose acetate butyrate, hydroxyethyl cellulose, ethyl cellulose, co-(lactic/glycolic)copolymers, poly(orthoester), polyvinyl chloride, polyvinyl acetate, ethylene vinyl acetate, carbopols, silicon elastomers, polyacrylic polymers, polyvinylacetal diethylaminoacetate, aminoalkyl methacrylate copolymer E, aminoalkyl methacryl copolymer RS, methacrylic acid copolymer L, methacrylic acid copolymer LD, methacrylic acid copolymer S, and carboxylvinyl polymer, polyvinylpyrrolidones (homopolymers or copolymers of N-vinyl pyrrolidone), polyethyleneglycols of various molecular weights, polyethylene-/polypropylene-/polyethylene-oxide block copolymers, polymethacrylates, polyvinylalcohol (PVA) and co-polymers thereof with PVP or with other polymers, polyacrylates, hypromellose phthalates, polyhydric alcohols, polyethylene glycols, polyethylene oxides, polyoxyethylene derivatives, organic amines such as alkyl amines (primary, secondary, and tertiary), aromatic amines, alicyclic amines, cyclic amines, aralkyl amines, hydroxylamine or its derivatives, hydrazine or its derivatives, and guanidine or its derivatives; diluents such as starches and derivative thereof, e.g. dextrin, pullulan, corn starch and potato starch pregelatinized starches; lactose, sucrose, glucose, reduced maltose, mannitol, sorbitol, xylitol, trehalose, powdered cellulose, microcrystalline cellulose, dicalcium phosphate, tricalcium phosphate, crystalline cellulose/carmellose sodium, hydroxypropyl cellulose, magnesium aluminometasilicate, silica excipients like silicon dioxide, syloid, light anhydrous silicic acid or the like; binders such as acacia, guar gum, tragacanth, gelatin, polyvinylpyrrolidones, hydroxypropyl celluloses, hydroxypropyl methylcelluloses, pregelatinized starches or the like; disintegrants such as hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose, croscarmellose sodium, a starch, methylcellulose, sodium alginate, sodium carboxymethyl starch, carmellose calcium, carmellose sodium, crystalline cellulose and crystalline cellulose/carmellose sodium, sodium starch glycolate, pregelatinized starches, crospovidones, colloidal silicon dioxide or the like; lubricants such as stearic acid, magnesium stearate, talc, light anhydrous silicic acid, calcium stearate, zinc stearate, magnesium oxide, sodium lauryl sulfate, sodium stearyl fumarate, magnesium aluminometasilicate or the like; flavoring agents such as sucrose, aspartame, mannitol, dextran, saccharin, menthol, citric acid, tartaric acid, malic acid, ascorbic acid,

sweet hydrangea leaves, fennel, ethanol, fructose, xylitol, glycyrrhizinic acid, purified sucrose, L-glutamine, cyclodextrin, peppermint, methyl salicylate or the like; surfactants such as sodium lauryl sulfate, polysolvate 80, sucrose fatty acid ester, polyoxyl 40 stearate, polyoxyethylene 60 hydrogenated castor oil, sorbitan monostearate, sorbitan
5 monopalmitate or the like; complex forming agents such as various grades of cyclodextrins and resins; release rate controlling agents such as hydroxypropyl celluloses, hydroxymethyl celluloses, hydroxypropyl methylcelluloses, ethylcelluloses, methylcelluloses, various grades of methyl methacrylates, waxes or the like. Other pharmaceutically acceptable carriers that can be used include, but are not limited to, film
10 formers, plasticizers, colorants, viscosity enhancers, preservatives, antioxidants, or the like.

In the preferred embodiment the excipient includes povidone like PVP K-30, copovidones like Kolidon VH-64, silica excipients like silicon dioxide, syloid FP silica, colloidal
15 silica, preferably syloid FP silica. The syloid FP silica excipients are micronized synthetic amorphous silica gels of high purity which are widely formulated into many pharmaceutical products. Syloid FP silica is available in various types such as 244FP, 63FP, 27FP.

20 The steps (a) to (c) can be carried out at 10-100°C, preferably 10-50°C; most preferably 25-40 °C.

Isolation of lumacaftor premixed with excipient can be achieved by various methods such as concentration, removal of solvent by evaporation, distillation, crash cooling, flash
25 evaporation, rotational drying, spray drying, thin film drying, freeze drying, and lyophilization.

The amorphous lumacaftor premixed with excipient obtained by the process of the present invention is characterized by XRPD (X-ray powder diffraction pattern) as shown
30 in figure 3.

The amorphous lumacaftor premixed with excipient of the present invention may be formulated as solid oral dosage forms such as powders, granules, pellets, tablets and capsules, suppositories, sachets, troches or lozenges, liquid oral dosage forms such as syrups, suspensions, dispersions, emulsions, injectables.

5

Another embodiment of the present invention is related to process for the preparation of lumacaftor by crystallization using a suitable organic solvent.

The organic solvent is selected from esters such as ethyl acetate, methyl acetate, tertiary butyl acetate, isopropyl acetate etc. The most preferred solvent is ethyl acetate.

10

The quantity of ethyl acetate used for crystallization of lumacaftor is 5-30 times, preferably 10-20 times. The temperature at which the reaction is carried is 40-100°C.

The effective amount of lumacaftor can be used to prepare any physical form of lumacaftor such as crystalline, amorphous or their mixtures.

15

The lumacaftor used as input can be obtained as per methods known in literature.

The powder X-ray diffraction spectrum is measured using Philips (PAN analytical X'pert pro) diffractogram (copper anti cathode) and expressed in terms of inter planar distance d , Bragg's angle 2θ , intensity (expressed as a percentage of the most intense peak). The scanning parameters include: measurement range 3-40 degrees two theta; measurement temperature 25°C; continuous scan.

20

DSC was recorded on Perkin Elmer Diamond DSC at 10°C per minute.

25

The rotavapor used for concentration is Buchi-R-215 with 100-150 revolutions per minute.

The present invention is illustrated by the following representative example and are not intended to limit the scope of the invention.

30

Example 1: Preparation of amorphous lumacaftor

Lumacaftor (4gm) was dissolved in tetrahydrofuran (40 ml). The reaction mixture was heated to 62°C and filtered. The reaction mixture was concentrated under reduced pressure. The resulting amorphous lumacaftor was dried in oven under reduced pressure.

5 Yield: 3.7 gm

Example 2: Preparation of amorphous lumacaftor

Lumacaftor (2 gm) was added to water (100 ml). To the mixture was added 0.1 N sodium hydroxide (100 ml) till the reaction mixture became clear. The solution was filtered. To
10 the filtered solution was added 0.1 N hydrochloric acid (80 ml) till the solid precipitated. The obtained solid was filtered and dried in oven under reduced pressure.

Yield: 2 gm.

Example 3: Preparation of amorphous lumacaftor

15 Lumacaftor (3 gm) was taken into a sublimation apparatus. The tube of the apparatus was heated at 210°C for 4 hours till the solid melted. The obtained molten liquid was cooled to 30°C in two hours. The solid was removed by scratching.

Yield: 2.9 gm.

Example 4: Preparation of crystalline form A of lumacaftor Hydrobromide .

3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)cyclopropanecarboxamido)-3-methylpyridine-2-yl)-t-butylbenzoate (10 gm) was charged to acetonitrile (100 ml). To the reaction mixture aqueous hydrobromic acid (47%) (15 ml) was charged and the reaction was stirred. The reaction mixture was stirred at room temperature for two hours
25 and filtered. The solid was washed with acetonitrile. The resulting solid was dried under reduced pressure.

Yield: 5.3 gm

Example 5: Preparation of Lumacaftor from lumacaftor Hydrobromide salt.

30 Water (750 ml) was charged to crystalline lumacaftor hydrobromide (75 gm). To the reaction mixture was added 1N NaOH (160 ml) at 28°C till pH is 8. The obtained solid is filtered and washed with water. The resulting solid was dried under reduced pressure.

Yield: 54.3 gm

Example 6: Preparation of amorphous lumacaftor

Lumacaftor (20 gm) was added to methanol (800 ml) at 25°C. To the reaction mixture
5 dichloromethane (40ml) was added. The reaction mixture was heated at 60°C till a clear
solution was obtained. The reaction mixture was filtered and the solution was spray dried.
Yield: 10.2 gm

Example 7: Preparation of lumacaftor premix with povidone K-30

10 Lumacaftor (15 gm) was added to methanol (30 ml). To the reaction mixture
dichloromethane (120 ml) was added. The reaction mixture was heated to 37°C till clear
solution was obtained. The reaction mixture was cooled to 25°C and povidone K-30
(3.75 gm) was added. The reaction mixture was stirred to obtain a clear solution. The
solution was filtered and washed with dichloromethane (7.5 ml). The filtrate was spray
15 dried.
Yield : 17.39 gm

Example 8: Preparation of lumacaftor premix with Kolidon VH-64

Lumacaftor (15 gm) was added to methanol (30 ml). To the reaction mixture
20 dichloromethane (120 ml) was added. The reaction mixture was heated to 37°C till clear
solution was obtained. The reaction mixture was cooled to 25°C and Kolidon VH-64
(3.75 gm) was added. The reaction mixture was stirred to obtain a clear solution. The
solution was filtered and washed with dichloromethane (7.5 ml). The filtrate was spray
dried.
25 Yield : 16.4 gm

Example 9: Preparation of lumacaftor premix with Syloid 244 FP

Lumacaftor (15 gm) was added to dichloromethane (120 ml). To the reaction mixture
methanol (30 ml) was added. The reaction mixture was heated to 37°C till clear solution
30 was obtained. The reaction mixture was cooled to 25°C and syloid 244FP (3.75 gm) was
added. The reaction mixture was stirred to obtain a clear solution. The filtrate was spray
dried.

Yield : 16.8 gm

Example 10: Preparation of lumacaftor

Lumacaftor (10 gm) was charged to ethyl acetate (120 ml). The reaction mixture was
5 heated to 80 °C till a clear solution was obtained. The reaction mass was cooled to 30°C
and the solid was stirred. The solid was further cooled to 0-5°C and filtered and dried.
The solid was washed with chilled ethyl acetate. The resulting solid was dried under
reduced pressure.

Yield: 8.0 gm

CLAIMS

- 1) Amorphous lumacaftor
- 5 2) Amorphous lumacaftor according to claim 1 characterized by XRD pattern substantially as illustrated by figure 1.
- 3) A process for preparation of amorphous form of lumacaftor according to claim 1 comprising;
10 a) dissolving lumacaftor in a suitable solvent and
 b) isolating lumacaftor from the reaction mixture thereof.
- 4) A process according to claim 3 wherein solvents used are selected from group comprising of alcohols like methanol, ethanol, n-propanol, isopropanol, ketones
15 like acetone, 2-butanone, methyl isobutyl ketone; esters like ethyl acetate and isopropyl acetate; ethers such as tetrahydrofuran, ethyl ether, methyl t-butyl ether, di-isopropyl ether; chlorinated hydrocarbons such as dichloromethane, ethylene dichloride and chloroform, and mixtures thereof.
- 20 5) A process according to claim 4 wherein the preferred solvent is tetrahydrofuran.
- 6) A process according to claim 3, isolation techniques involve the use of spray drying, lyophilization followed by vacuum drying.
- 25 7) The process according to claim 6 wherein the preferred technique of drying is vacuum drying.
- 8) A process for preparation of amorphous form of lumacaftor according to claim 1 comprising;
30 a) dispersing lumacaftor in water;
 b) adding base to the dispersion;
 c) treating the mixture with acid and

d) isolating lumacaftor.

9) The process according to claim 8, wherein base used is selected from a group comprising of inorganic bases of hydroxides as sodium hydroxide, potassium hydroxide, lithium hydroxide, carbonates such as sodium carbonate, potassium carbonate, sodium bicarbonate, organic bases such as triethyl amine, diisopropyl amine, DBU.

10) The process according to claim 9 wherein the preferred base is sodium hydroxide.

11) The process according to claim 8, wherein acid used is selected from a group comprising of mineral acids such as hydrochloric acid, sulphuric acid, nitric acid, boric acid, phosphoric acid, hydrobromic acid, hydrofluoric acid, per chloric acid, hydro iodic acid.

12) The process according to claim 11 wherein the preferred acid is hydrochloric acid.

13) A process for preparation of amorphous form of lumacaftor according to claim 1 comprising;

- a) heating lumacaftor up to 200-250°C,
- b) cooling the mass to 10-50°C,
- c) isolating lumacaftor.

14) Crystalline form A of lumacaftor hydrobromide.

15) Crystalline form A of lumacaftor hydrobromide according to claim 14 characterized by XRD pattern substantially as illustrated by figure 2.

16) A process for preparation of crystalline form A of lumacaftor hydrobromide according to claim 14 which comprises hydrolysis of 3-(6-(1-(2,2-difluorobenzo[d][1,3]dioxol-5-yl)cyclopropanecarboxamido)-3-methylpyridine-2-yl)-t-butylbenzoate (II) in the presence of acetonitrile and hydrobromic acid.

- 17) An amorphous solid dispersion of lumacaftor and one or more pharmaceutically acceptable carriers.
- 5 18) An amorphous solid dispersion of lumacaftor according to claim 17 characterized by XRD pattern substantially as illustrated by figure 3.
- 10 19) The amorphous solid dispersion according to claim 17 wherein the pharmaceutically acceptable carriers include povidone like PVP K-30, copovidones like Kolidon VH-64, silica excipients like silicon dioxide, syloid FP silica, colloidal silica.
- 15 20) The process for the preparation of amorphous solid dispersion of lumacaftor according to claim 17 comprising the steps of:
- a) dissolving lumacaftor base in organic solvent,
 - b) adding one or more excipient and
 - c) isolating solid dispersion of amorphous lumacaftor from the reaction mixture thereof.
- 20 21) The process for the preparation of lumacaftor by crystallization using a suitable solvent.
- 25 22) The process according to claim 21 wherein organic solvent is selected from esters such as ethyl acetate, methyl acetate, tertiary butyl acetate, isopropyl acetate.
- 23) The process according to claim 22 wherein the preferred solvent is ethyl acetate.

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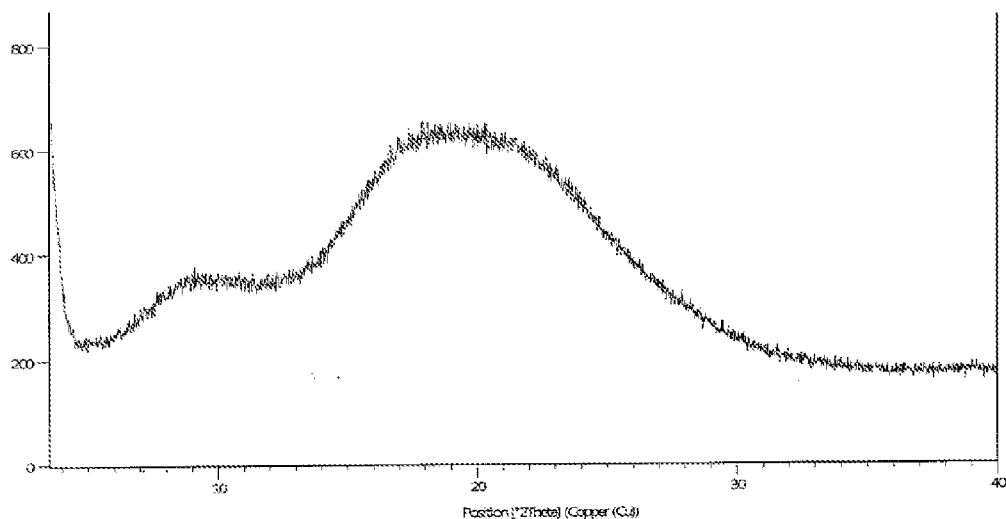


Figure 1: XRPD of amorphous lumacaftor

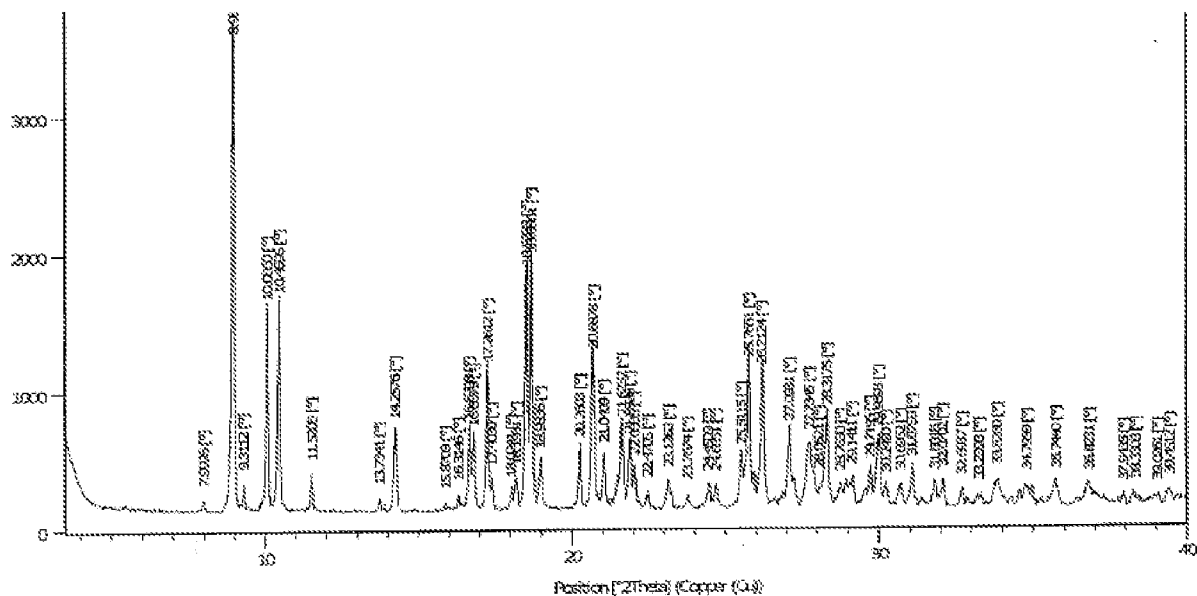


Figure 2: X-ray powder diffractogram (XRPD) of novel crystalline form A of lumacaftor hydrobromide.

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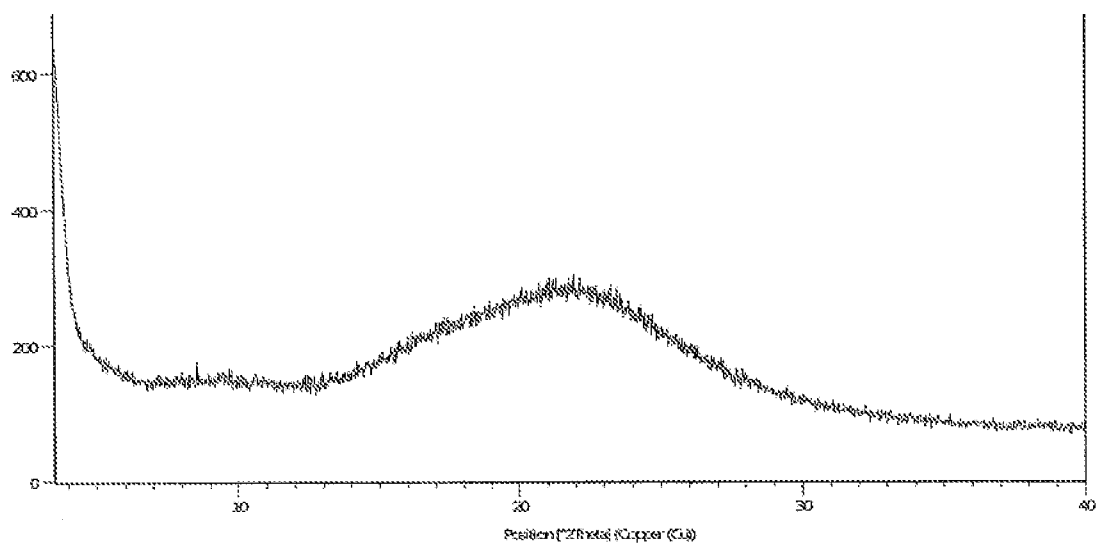


Figure 3: X-ray powder diffractogram (XRPD) for amorphous lumacaftor premixed with syloid 244FP.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2017/050679

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D405/12
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)
C07D

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, BIOSIS, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2009/073757 A1 (VERTEX PHARMA [US]; KESHAVARZ-SHOKRI ALI [US]; ZHANG BEILI [US]; KRAWI) 11 June 2009 (2009-06-11) paragraphs [0013], [0015] - [0017], [0140] - [0148]; claims 2, 32	1-13, 17-20
Y	WO 2011/127290 A2 (VERTEX PHARMA [US]; KESHAVARZ-SHOKRI ALI [US]; ZHANG BEILI [US]; KRAWI) 13 October 2011 (2011-10-13) paragraph [0212] - paragraph [0213]; claims 24, 47	1-13, 17-20

☒ 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

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

3 April 2017

Date of mailing of the international search report

19/06/2017

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
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Stroeter, Thomas

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2017/050679

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BERNSTEIN J: "Polymorphism of pharmaceuticals", POLYMORPHISM IN MOLECULAR CRYSTALS, 2002, pages 253-255, XP002308143, Chapter 7.7: lines 4-7 of the 4th paragraph on page 253; 1st paragraph on page 254 as well as 2nd paragraph, lines 1-5 -----	1-13, 17-20
Y	HANCOCK B C ET AL: "CHARACTERISTICS AND SIGNIFICANCE OF THE AMORPHOUS STATE IN PHARMACEUTICAL SYSTEMS", JOURNAL OF PHARMACEUTICAL SCIENCES, AMERICAN PHARMACEUTICAL ASSOCIATION, WASHINGTON, US, vol. 86, no. 1, 1 January 1997 (1997-01-01), pages 1-12, XP000929450, ISSN: 0022-3549, DOI: 10.1021/JS9601896 "The amorphous state may also be introduced..."; page 8, left-hand column, line 12, paragraph 2 - line 18 -----	1-13, 17-20

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2017/050679

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-13, 17-20

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-13, 17-20

Amorphous form of lumacaftor and amorphous solid dispersions of lumacaftor and processes for the preparation thereof

2. claims: 14-16

Crystalline form A of lumacaftor hydrobromide and a process for the preparation thereof

3. claims: 21-23

A process for the preparation of lumacaftor by crystallisation

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2017/050679

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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