



(51) International Patent Classification:

C07D 403/12 (2006.01) A61P 13/02 (2006.01)

C07C 65/10 (2006.01) A61K 31/55 (2006.01)

A61P 13/00 (2006.01)

(21) International Application Number:

PCT/US2020/014929

(22) International Filing Date:

24 January 2020 (24.01.2020)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/796,151 24 January 2019 (24.01.2019) US

62/807,285 19 February 2019 (19.02.2019) US

62/820,314 19 March 2019 (19.03.2019) US

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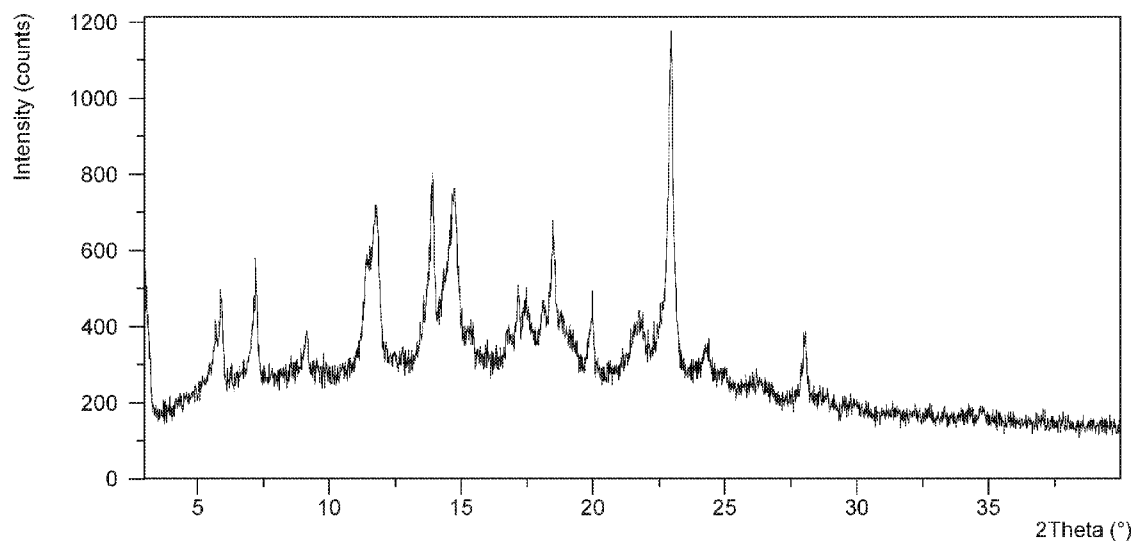
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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM,

(54) Title: SOLID STATE FORMS OF FEDOVAPAGON-SALICYCLIC ACID CO-CRYSTAL

Figure 1: A powder X-ray diffraction pattern of a co-crystal of Fedovapagon and salicylic acid form alpha



(57) Abstract: The present disclosure relates to co-crystals of Fedovapagon, processes for preparation thereof as well as a pharmaceutical composition including the same.

TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,
KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

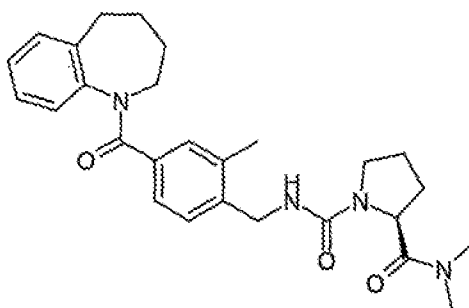
SOLID STATE FORMS OF FEDOVAPAGON-SALICYCLIC ACID CO-CRYSTAL

TECHNICAL FIELD

[0001] The present disclosure relates to co-crystals of Fedovapagon, processes for preparation thereof as well as a pharmaceutical composition including the same.

BACKGROUND

[0002] Fedovapagon has the chemical name (2S)-2-N,2-N-dimethyl-1-N-[[2-methyl-4-(2,3,4,5-tetrahydro-1-benzazepine-1-carbonyl)phenyl]methyl]pyrrolidine-1,2-dicarboxamide. Fedovapagon has the following chemical structure:



[0003] Fedovapagon is a Vasopressin V2 receptor agonists indicated for the treatment of Nocturia.

[0004] Fedovapagon is disclosed in U.S. Patent No 7,074,781 (counterpart of WO 0149682).

[0005] Crystalline forms of Fedovapagon are disclosed in WO 2011/121308 and WO 2012/131389.

[0006] Polymorphism, the occurrence of different crystal forms, is a property of some molecules and molecular complexes. A single compound, like Fedovapagon or salt thereof, may give rise to a variety of polymorphs having distinct crystal structures and physical properties like melting point, thermal behaviors (e.g. measured by thermogravimetric analysis – "TGA", or differential scanning calorimetry – "DSC"), powder X-ray diffraction (PXRD) pattern, infrared absorption fingerprint, Raman absorption fingerprint, and solid state (^{13}C -) NMR spectrum. One or more of these techniques may be used to distinguish different polymorphic forms of a compound.

[0007] Different salts and solid state forms (including solvated forms and co-crystals) of an active pharmaceutical ingredient may possess different properties. Such variations in the properties of different salts and solid state forms, co-crystals and solvates may provide a basis for

improving formulation, for example, by facilitating better processing or handling characteristics, improving the dissolution profile, or improving stability (polymorph as well as chemical stability) and shelf-life. These variations in the properties of different salts and solid state forms may also provide improvements to the final dosage form, for instance, if they serve to improve bioavailability. Different salts and solid state forms, co-crystals and solvates of an active pharmaceutical ingredient may also give rise to a variety of polymorphs or crystalline forms, which may in turn provide additional opportunities to use variations in the properties and characteristics of a solid active pharmaceutical ingredient for providing an improved product.

[0008] Discovering new salts, solid state forms, co-crystals and solvates of a pharmaceutical product can provide materials having desirable processing properties, such as ease of handling, ease of processing, storage stability, and ease of purification or as desirable intermediate crystal forms that facilitate conversion to other salts or polymorphic forms. New salts, polymorphic forms, co-crystals and solvates of a pharmaceutically useful compound can also provide an opportunity to improve the performance characteristics of a pharmaceutical product (dissolution profile, bioavailability, etc.). It enlarges the repertoire of materials that a formulation scientist has available for formulation optimization, for example by providing a product with different properties, e.g., a different crystal habit, higher crystallinity or polymorphic stability which may offer better processing or handling characteristics, improved dissolution profile, or improved shelf-life.

SUMMARY

[0009] The present disclosure relates to co-crystals of Fedovapagon, in particular to co-crystal forms of Fedovapagon and salicylic acid, to processes for preparation thereof, and to pharmaceutical compositions including these co-crystals or combinations thereof.

[0010] The present disclosure encompasses process for preparation of co-crystal forms of Fedovapagon including reacting Fedovapagon with a co-former in a molar ratio of between about 1:1 to about 1:2, in embodiments in a molar ratio of about 1:1.

[0011] The present disclosure also provides uses of the co-crystals of Fedovapagon for preparing other solid state forms of Fedovapagon, other co-crystals and/or salts of Fedovapagon and solid state forms thereof.

[0012] In another embodiment, the present disclosure encompasses the herein described co-crystals of Fedovapagon for use in the preparation of pharmaceutical compositions and/or formulations, in embodiments for the treatment of Nocturia.

[0013] Another embodiment the present disclosure encompasses the use of the herein described co-crystals of Fedovapagon for the preparation of pharmaceutical compositions and/or formulations.

[0014] The present disclosure further provides pharmaceutical compositions including co-crystals of Fedovapagon.

[0015] In yet another embodiment, the present disclosure encompasses pharmaceutical formulations including any one or a combination of the co-crystals of Fedovapagon and at least one pharmaceutically acceptable excipient. The pharmaceutical composition or formulation includes oral dosage forms, e.g. tablet or capsule.

[0016] The present disclosure encompasses processes to prepare said pharmaceutical formulations of co-crystals of Fedovapagon and solid state forms thereof, including combining any one or a combination of the co-crystals of Fedovapagon according to the present disclosure with at least one pharmaceutically acceptable excipient.

[0017] The co-crystals of Fedovapagon, as well as the pharmaceutical compositions or formulations of co-crystals of Fedovapagon according to the present disclosure, can be used as medicaments, in embodiments for the treatment of Nocturia.

[0018] The present disclosure also provides methods of treating Nocturia by administering a therapeutically effective amount of any one or a combination of the co-crystals of Fedovapagon according to the present disclosure, or at least one of the above pharmaceutical compositions or formulations, to a subject suffering from Nocturia, or otherwise in need of the treatment.

[0019] The present disclosure also provides uses of co-crystals of Fedovapagon of the present disclosure, or at least one of the above pharmaceutical compositions or formulations for the manufacture of a medicament for treating Nocturia.

BRIEF DESCRIPTION OF THE FIGURES

[0020] Figure 1 shows a powder X-ray diffraction pattern ("powder XRD" or "PXRD") of a co-crystal of Fedovapagon and salicylic acid form alpha.

[0021] Figure 2 shows a PXRD of a co-crystal of Fedovapagon and salicylic acid form beta.

[0022] Figure 3 shows a PXRD of a co-crystal of Fedovapagon and salicylic acid form gamma (prepared according to Example 3).

[0023] Figure 4 shows a PXRD of a co-crystal of Fedovapagon and salicylic acid form gamma (prepared according to Example 8).

[0024] Figure 5 shows a ^{13}C solid state NMR of a co-crystal of Fedovapagon and salicylic acid form beta.

[0025] Figure 6 shows a DSC thermogram of a co-crystal of Fedovapagon and salicylic acid form beta prepared according to Example 2.

[0026] Figure 7 shows a TGA thermogram of a co-crystal of Fedovapagon and salicylic acid form beta prepared according to Example 2.

[0027] Figure 8 shows a DSC thermogram of a co-crystal of Fedovapagon and salicylic acid form gamma prepared according to Example 8.

[0028] Figure 9 shows a TGA thermogram of a co-crystal of Fedovapagon and salicylic acid form gamma prepared according to Example 8.

DETAILED DESCRIPTION

[0029] The present disclosure relates to co-crystals of Fedovapagon and a co-crystal former, to processes for preparation thereof, and to pharmaceutical compositions including these co-crystals of Fedovapagon or combinations thereof.

[0030] The co-crystals of Fedovapagon and solid state forms thereof according to the present disclosure may have advantageous properties selected from at least one of: chemical or polymorphic purity, flowability, solubility, dissolution rate, bioavailability, morphology or crystal habit, stability such as chemical stability as well as thermal and mechanical stability with respect to polymorphic conversion, stability towards dehydration and/or storage stability, a lower degree of hygroscopicity, low content of residual solvents and advantageous processing and handling characteristics such as compressibility, or bulk density.

[0031] A crystal form may be referred to herein as being characterized by graphical data "as depicted in" a Figure. Such data include, for example, powder X-ray diffractograms and solid state NMR spectra. As is well-known in the art, the graphical data potentially provides additional technical information to further define the respective solid state form (a so-called "fingerprint") which can not necessarily be described by reference to numerical values or peak positions alone. In any event, the skilled person will understand that such graphical

representations of data may be subject to small variations, *e.g.*, in peak relative intensities and peak positions due to factors such as variations in instrument response and variations in sample concentration and purity, which are well known to the skilled person. Nonetheless, the skilled person would readily be capable of comparing the graphical data in the Figures herein with graphical data generated for an unknown crystal form and confirm whether the two sets of graphical data are characterizing the same crystal form or two different crystal forms. A crystal form of Fedovapagon referred to herein as being characterized by graphical data "as depicted in" a Figure will thus be understood to include any crystal forms of the Fedovapagon, characterized with the graphical data having such small variations, as are well known to the skilled person, in comparison with the Figure.

[0032] A solid state form (or polymorph) may be referred to herein as polymorphically pure or substantially free of any other solid state (or polymorphic) forms. As used herein in this context, the expression "substantially free of any other forms" will be understood to mean that the solid state form contains about 20% or less, about 10% or less, about 5% or less, about 2% or less, about 1% or less, or about 0% of any other forms of the subject compound as measured, for example, by PXRD. Thus, co-crystal of Fedovapagon or solid state forms thereof described herein as substantially free of any other solid state forms would be understood to contain greater than about 80% (w/w), greater than about 90% (w/w), greater than about 95% (w/w), greater than about 98% (w/w), greater than about 99% (w/w), or about 100% (w/w) of the subject co-crystal of Fedovapagon and solid state forms thereof. Accordingly, in some embodiments of the disclosure, the described co-crystal of Fedovapagon and solid state forms thereof may contain from about 1% to about 20% (w/w), from about 5% to about 20% (w/w), or from about 5% to about 10% (w/w) of one or more other solid state forms of the same Fedovapagon.

[0033] "Co-Crystal" or "Co-crystal" as used herein is defined as a crystalline material including two or more molecules in the same crystalline lattice and associated by non-ionic and non-covalent bonds. In some embodiments, the co-crystal includes two molecules which are in natural state.

[0034] "Co-crystal former" or "crystal former" as used herein is defined as a molecule that forms a co-crystal with Fedovapagon, for example salicylic acid.

[0035] The modifier "about" should be considered as disclosing the range defined by the absolute values of the two endpoints. For example, the expression "from about 2 to about 4" also

discloses the range "from 2 to 4." When used to modify a single number, the term "about" may refer to plus or minus 10% of the indicated number and includes the indicated number. For example, "about 10%" may indicate a range of 9% to 11%, and "about 1" means from 0.9-1.1.

[0036] As used herein, unless stated otherwise, PXRD peaks reported herein are preferably measured using $\text{CuK}\alpha$ radiation, $\lambda = 1.5418\text{\AA}$.

[0037] As used herein, unless stated otherwise, ^{13}C NMR reported herein are measured at 125 MHz at a magic angle spinning frequency $\omega/2\pi = 18\text{ kHz}$, preferably at a temperature of $293^\circ\text{K} \pm 3^\circ\text{K}$.

[0038] As used herein, the term "isolated" in reference to solid state forms of a co-crystal with Fedovapagon of the present disclosure corresponds to solid state forms of a co-crystal with Fedovapagon that are physically separated from the reaction mixture in which it is formed.

[0039] A thing, *e.g.*, a reaction mixture, may be characterized herein as being at, or allowed to come to "room temperature", often abbreviated "RT." This means that the temperature of the thing is close to, or the same as, that of the space, *e.g.*, the room or fume hood, in which the thing is located. Typically, room temperature is from about 20°C to about 30°C , or about 22°C to about 27°C , or about 25°C . A process or step may be referred to herein as being carried out "overnight." This refers to a time interval, *e.g.*, for the process or step, that spans the time during the night, when that process or step may not be actively observed. This time interval is from about 8 to about 20 hours, or about 10 to about 18 hours, typically about 16 hours.

[0040] As used herein, the expression "wet crystalline form" refers to a polymorph that was not dried using any conventional techniques to remove residual solvent. Examples for such conventional techniques can be, but not limited to, evaporation, vacuum drying, oven drying, drying under nitrogen flow, etc.

[0041] As used herein, the expression "dry crystalline form" refers to a polymorph that was dried using any conventional techniques to remove residual solvent. Examples of such conventional techniques can be, but are not limited to, evaporation, vacuum drying, oven drying, drying under nitrogen flow, etc.

[0042] The term "solvate", as used herein and unless indicated otherwise, refers to a crystal form that incorporates a solvent in the crystal structure. When the solvent is water, the solvate is often referred to as a "hydrate." The solvent in a solvate may be present in either a stoichiometric or in a non-stoichiometric amount.

[0043] The amount of solvent employed in a chemical process, e.g., a reaction or a crystallization, may be referred to herein as a number of "volumes" or "vol" or "V." For example, a material may be referred to as being suspended in 10 volumes (or 10 vol or 10V) of a solvent. In this context, this expression would be understood to mean milliliters of the solvent per gram of the material being suspended, such that suspending 5 grams of a material in 10 volumes of a solvent means that the solvent is used in an amount of 10 milliliters of the solvent per gram of the material that is being suspended or, in this example, 50 mL of the solvent. In another context, the term "v/v" may be used to indicate the number of volumes of a solvent that are added to a liquid mixture based on the volume of that mixture. For example, adding methyl tert-butyl ether (MTBE) (1.5 v/v) to a 100 ml reaction mixture would indicate that 150 mL of MTBE was added.

[0044] As used herein, the term "reduced pressure" refers to a pressure of about 10 mbar to about 50 mbar.

[0045] The present disclosure includes co-crystals of Fedovapagon and salicylic acid (Fedovapagon: salicylic acid).

[0046] The present disclosure further includes a co-crystal of Fedovapagon and salicylic acid designated as Form alpha. Form alpha of Fedovapagon: salicylic acid co-crystal can be characterized by data selected from one or more of the following: a PXRD pattern having peaks at 5.9, 7.2, 14.7, 18.5 and 23.0 degrees 2-theta $\pm$ 0.2 degrees 2-theta; a PXRD pattern as depicted in Figure 1; or combinations of these data.

[0047] Form alpha of Fedovapagon: salicylic acid co-crystal may be further characterized by the PXRD pattern having peaks at 5.9, 7.2, 14.7, 18.5 and 23.0 degrees 2-theta $\pm$ 0.2 degrees 2-theta, and also having one, two, three, four or five additional peaks at 9.2, 11.8, 13.9, 20.0 and 28.0 degrees 2-theta $\pm$ 0.2 degrees 2-theta.

[0048] Form alpha of Fedovapagon: salicylic acid co-crystal may be characterized by each of the above characteristics alone/or by all possible combinations, e.g., by PXRD pattern having peaks at 5.9, 7.2, 14.7, 18.5 and 23.0 degrees 2-theta $\pm$ 0.2 degrees 2-theta and a PXRD pattern as depicted in Figure 1.

[0049] Form alpha of Fedovapagon: salicylic acid co-crystal may be alternatively characterized by the PXRD pattern having peaks at 5.9, 7.2, 9.2, 11.8, 13.9, 14.7, 18.5, 20.0, 23.0 and 28.0 degrees 2-theta $\pm$ 0.2 degrees 2-theta.

[0050] Form alpha of Fedovapagon: salicylic acid co-crystal according to any of the above embodiments may be in a molar ratio between about 1:1.5 and 1.5:1, or between about 1:1.25 and 1.25:1, in some embodiments in a molar ratio of about 1:1.

[0051] The present disclosure further includes a co-crystal of Fedovapagon and salicylic acid designated as Form beta. Form beta of Fedovapagon: salicylic acid co-crystal can be characterized by data selected from one or more of the following: a PXRD pattern having peaks at 8.7, 10.2, 16.0, 20.6 and 23.2 degrees 2-theta $\pm$ 0.2 degrees 2-theta; a PXRD pattern as depicted in Figure 2; a ^{13}C solid state NMR having peaks at the range of 100-200 ppm at 172.6, 162.2, 127.8, 125.0, 116.7 ppm $\pm$ 0.2 ppm; a solid state ^{13}C NMR spectrum having the following chemical shift absolute differences from a reference peak at 57.6 ± 0.2 ppm $\pm$ 2 ppm of 115.0, 104.6, 70.2, 67.4, 59.1 ± 0.1 ppm respectively; or by a ^{13}C solid state NMR spectrum substantially as depicted in Figure 5; or combinations of these data.

[0052] Form beta of Fedovapagon: salicylic acid co-crystal may be further characterized by the PXRD pattern having peaks at 8.7, 10.2, 16.0, 20.6 and 23.2 degrees 2-theta $\pm$ 0.2 degrees 2-theta, and also having one, two, three, four or five additional peaks at 5.1, 8.0, 19.4, 25.7 and 30.3 degrees 2-theta $\pm$ 0.2 degrees 2-theta.

[0053] Form beta of Fedovapagon: salicylic acid co-crystal may be alternatively characterized by the PXRD pattern having peaks at 5.1, 8.0, 8.7, 10.2, 16.0, 19.4, 20.6, 23.2 and 25.7 degrees 2-theta $\pm$ 0.2 degrees 2-theta.

[0054] Form beta of Fedovapagon: salicylic acid co-crystal according to any of the embodiments described herein may be anhydrous form. In embodiments, Form beta has a weight loss of about 0.28% (w/w) at temperature of up to about 125°C, as measured by TGA.

[0055] Form beta of Fedovapagon: salicylic acid co-crystal may be characterized by each of the above characteristics alone/or by all possible combinations, e.g., by a PXRD pattern having peaks at 8.7, 10.2, 16.0, 20.6 and 23.2 degrees 2-theta $\pm$ 0.2 degrees 2-theta and a PXRD pattern as depicted in Figure 2.

[0056] Form beta of Fedovapagon: salicylic acid co-crystal according to any of the above embodiments may be in a molar ratio between about 1:1.5 and 1.5:1, or between about 1:1.25 and 1.25:1, in some embodiments in a molar ratio of about 1:1.

[0057] Form beta of Fedovapagon: salicylic acid co-crystal may have advantageous properties, as described above. In embodiments, form beta is non-hygroscopic form and it is

polymorphically stable at various conditions for periods of time from at least 7 days to at least 30 days. For example, it is polymorphically stable and it is non-hygroscopic at room temperature and relative humidity ("RH") of 20%-100% or room conditions humidity, for a period of at least 30 days. It is also stable at RH of 75% and 100% at temperature of about 40°C, for a period of at least 7 days. In addition, form beta is polymorphically stable at high temperature, for example for about 1 hour heating to temperature of about 60°C, or about 80°C or about 100°C.

[0058] The present disclosure further includes a co-crystal of Fedovapagon and salicylic acid designated as Form gamma. Form gamma of Fedovapagon: salicylic acid co-crystal can be characterized by data selected from one or more of the following: a PXRD pattern having peaks at 11.0, 17.2, 18.5, 19.2 and 23.0 degrees 2-theta $\pm$ 0.2 degrees 2-theta; a PXRD pattern having peaks at 7.2, 17.2, 18.5, 19.2 and 23.0 degrees 2-theta $\pm$ 0.2 degrees 2-theta; a PXRD pattern as depicted in Figure 3 or Figure 4; or combinations of these data.

[0059] Form gamma of Fedovapagon: salicylic acid co-crystal may be further characterized by the PXRD pattern having peaks at 11.0, 17.2, 18.5, 19.2 and 23.0 degrees 2-theta $\pm$ 0.2 degrees 2-theta or a PXRD pattern having peaks at 7.2, 17.2, 18.5, 19.2 and 23.0 degrees 2-theta $\pm$ 0.2 degrees 2-theta, and also having one, two, three, four or five additional peaks at 14.7, 11.8, 15.4, 28.8 and 34.7 degrees 2-theta $\pm$ 0.2 degrees 2-theta. Thus, form gamma of Fedovapagon:salicylic acid co-crystal may be further characterized by the PXRD pattern having peaks at 11.0, 17.2, 18.5, 19.2 and 23.0 degrees 2-theta $\pm$ 0.2 degrees 2-theta and also having one, two, three, four or five additional peaks at 14.7, 11.8, 15.4, 28.8 and 34.7 degrees 2-theta $\pm$ 0.2 degrees 2-theta. Alternatively, Form gamma of form gamma of Fedovapagon:salicylic acid co-crystal may be further characterized by the PXRD pattern having peaks at 7.2, 17.2, 18.5, 19.2 and 23.0 degrees 2-theta $\pm$ 0.2 degrees 2-theta, and also having one, two, three, four or five additional peaks at 14.7, 11.8, 15.4, 28.8 and 34.7 degrees 2-theta $\pm$ 0.2 degrees 2-theta.

[0060] Form gamma of Fedovapagon: salicylic acid co-crystal may be alternatively characterized by the PXRD pattern having peaks at 11.0, 11.8, 14.7, 15.4, 17.2, 18.5, 19.2, 23.0, 28.8 and 34.7 degrees 2-theta $\pm$ 0.2 degrees 2-theta.

[0061] Form gamma of Fedovapagon: salicylic acid co-crystal may be optionally characterized by the PXRD pattern having peaks at 7.2, 11.8, 14.7, 15.4, 17.2, 18.5, 19.2 and 23.0, 28.8 and 34.7 degrees 2-theta $\pm$ 0.2 degrees 2-theta.

[0062] Form gamma of Fedovapagon: salicylic acid co-crystal according to any of the embodiments described herein may be anhydrous form. In embodiments, Form gamma has a weight loss of about 0.42% (w/w) at temperature of up to about 100°C, as measured by TGA.

[0063] Form gamma of Fedovapagon: salicylic acid co-crystal may be characterized by each of the above characteristics alone/or by all possible combinations, e.g., by a PXRD pattern having peaks at 11.0, 17.2, 18.5, 19.2 and 23.0 degrees 2-theta $\pm$ 0.2 degrees 2-theta or a PXRD pattern having peaks at 7.2, 17.2, 18.5, 19.2 and 23.0 degrees 2-theta $\pm$ 0.2 degrees 2-theta and a PXRD pattern as depicted in Figure 3 or Figure 4.

[0064] Form gamma of Fedovapagon: salicylic acid co-crystal according to any of the above embodiments may be in a molar ratio between about 1:2.5 and 1.5:2, i.e. 1:1.33 to 1:2.5; or between about 1:2.25 and 1.25:2, 1:1.6 to 1:2.5. In some embodiments in a molar ratio of about 1:2.

[0065] Form gamma of Fedovapagon: salicylic acid co-crystal may have advantageous properties, as described above. In embodiments, form gamma is non-hygroscopic and it is polymorphically stable at various conditions for periods of time from at least 7 days to at least 30 days. For example, it is polymorphically stable and it is non-hygroscopic at room temperature and relative humidity ("RH") of 20%-100% or room conditions humidity, for a period of at least 30 days. It is also stable at RH of 75% and 100% at temperature of about 40°C, for a period of at least 7 days. In addition, form gamma is polymorphically stable at high temperature, for example for about 1 hour heating to temperature of about 60°C, or about 80°C. Form gamma is also stable under mechanic pressure and upon grinding.

[0066] The present disclosure also provides the use of the co-crystals of Fedovapagon and solid state forms thereof of the present disclosure for preparing different solid state forms of Fedovapagon, salts and co-crystals of Fedovapagon and solid state forms thereof.

[0067] The present disclosure further encompasses processes for preparing the co-crystals of Fedovapagon of the present disclosure. The disclosure further includes processes for preparing different co-crystals and solid state forms of Fedovapagon or salts of Fedovapagon and solid state forms thereof. The process includes preparing at least one of the co-crystals of Fedovapagon of the present disclosure, and converting it to different solid state forms of Fedovapagon, or different co-crystals or salts of Fedovapagon and solid state forms thereof. The conversion to Fedovapagon salt can be done, for example, by a process including reacting at

least one of the obtained co-crystals of Fedovapagon with an appropriate acid to obtain Fedovapagon acid addition salt.

[0068] In another embodiment the present disclosure encompasses the above described co-crystals of Fedovapagon for use in the preparation of pharmaceutical compositions and/or formulations, in embodiments for the treatment of Nocturia.

[0069] In another embodiment the present disclosure encompasses the use of the above described co-crystals of Fedovapagon for the preparation of pharmaceutical compositions and/or formulations.

[0070] The present disclosure further provides pharmaceutical compositions including the co-crystals of Fedovapagon of the present disclosure.

[0071] In yet another embodiment, the present disclosure encompasses pharmaceutical formulations including co-crystals of Fedovapagon of the present disclosure, and at least one pharmaceutically acceptable excipient.

[0072] Pharmaceutical formulations of the present invention contain any one or a combination of the co-crystals of Fedovapagon of the present disclosure. In addition to the active ingredient, the pharmaceutical formulations of the present disclosure can contain one or more excipients. Excipients are added to the formulation for a variety of purposes.

[0073] Diluents increase the bulk of a solid pharmaceutical composition, and can make a pharmaceutical dosage form containing the composition easier for the patient and caregiver to handle. Diluents for solid compositions include, for example, microcrystalline cellulose (e.g. Avicel®), microfine cellulose, lactose, starch, pregelatinized starch, calcium carbonate, calcium sulfate, sugar, dextrans, dextrin, dextrose, dibasic calcium phosphate dihydrate, tribasic calcium phosphate, kaolin, magnesium carbonate, magnesium oxide, maltodextrin, mannitol, polymethacrylates (e.g. Eudragit®), potassium chloride, powdered cellulose, sodium chloride, sorbitol, and talc.

[0074] Solid pharmaceutical compositions that are compacted into a dosage form, such as a tablet, can include excipients whose functions include helping to bind the active ingredient and other excipients together after compression. Binders for solid pharmaceutical compositions include acacia, alginic acid, carbomer (e.g. carbopol), carboxymethylcellulose sodium, dextrin, ethyl cellulose, gelatin, guar gum, hydrogenated vegetable oil, hydroxyethyl cellulose, hydroxypropyl cellulose (e.g. Klucel®), hydroxypropyl methyl cellulose (e.g. Methocel®),

liquid glucose, magnesium aluminum silicate, maltodextrin, methylcellulose, polymethacrylates, povidone (e.g. Kollidon®, Plasdone®), pregelatinized starch, sodium alginate, and starch.

[0075] The dissolution rate of a compacted solid pharmaceutical composition in the patient's stomach can be increased by the addition of a disintegrant to the composition. Disintegrants include alginic acid, carboxymethylcellulose calcium, carboxymethylcellulose sodium (e.g. Ac-Di-Sol®, Primellose®), colloidal silicon dioxide, croscarmellose sodium, crospovidone (e.g. Kollidon®, Polyplasdone®), guar gum, magnesium aluminum silicate, methyl cellulose, microcrystalline cellulose, polacrillin potassium, powdered cellulose, pregelatinized starch, sodium alginate, sodium starch glycolate (e.g. Explotab®), and starch.

[0076] Glidants can be added to improve the flowability of a non-compacted solid composition and to improve the accuracy of dosing. Excipients that can function as glidants include colloidal silicon dioxide, magnesium trisilicate, powdered cellulose, starch, talc, and tribasic calcium phosphate.

[0077] When a dosage form such as a tablet is made by the compaction of a powdered composition, the composition is subjected to pressure from a punch and dye. Some excipients and active ingredients have a tendency to adhere to the surfaces of the punch and dye, which can cause the product to have pitting and other surface irregularities. A lubricant can be added to the composition to reduce adhesion and ease the release of the product from the dye. Lubricants include magnesium stearate, calcium stearate, glyceryl monostearate, glyceryl palmitostearate, hydrogenated castor oil, hydrogenated vegetable oil, mineral oil, polyethylene glycol, sodium benzoate, sodium lauryl sulfate, sodium stearyl fumarate, stearic acid, talc, and zinc stearate.

[0078] Flavoring agents and flavor enhancers make the dosage form more palatable to the patient. Common flavoring agents and flavor enhancers for pharmaceutical products that can be included in the composition of the present invention include maltol, vanillin, ethyl vanillin, menthol, citric acid, fumaric acid, ethyl maltol, and tartaric acid.

[0079] Solid and liquid compositions can also be dyed using any pharmaceutically acceptable colorant to improve their appearance and/or facilitate patient identification of the product and unit dosage level.

[0080] In liquid pharmaceutical compositions of the present disclosure, the active ingredient and any other solid excipients may be dissolved or suspended in a liquid carrier such as water, vegetable oil, alcohol, polyethylene glycol, propylene glycol, or glycerin.

[0081] Liquid pharmaceutical compositions can contain emulsifying agents to disperse uniformly throughout the composition an active ingredient or other excipient that is not soluble in the liquid carrier. Emulsifying agents that can be useful in liquid compositions of the present invention include, for example, gelatin, egg yolk, casein, cholesterol, acacia, tragacanth, chondrus, pectin, methyl cellulose, carbomer, cetostearyl alcohol, and cetyl alcohol.

[0082] Liquid pharmaceutical compositions of the present disclosure can also contain a viscosity enhancing agent to improve the mouth-feel of the product and/or coat the lining of the gastrointestinal tract. Such agents include acacia, alginic acid bentonite, carbomer, carboxymethylcellulose calcium or sodium, cetostearyl alcohol, methyl cellulose, ethylcellulose, gelatin guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, maltodextrin, polyvinyl alcohol, povidone, propylene carbonate, propylene glycol alginate, sodium alginate, sodium starch glycolate, starch tragacanth, and xanthan gum.

[0083] Sweetening agents such as sorbitol, saccharin, sodium saccharin, sucrose, aspartame, fructose, mannitol, and invert sugar can be added to improve the taste.

[0084] Preservatives and chelating agents such as alcohol, sodium benzoate, butylated hydroxyl toluene, butylated hydroxyanisole, and ethylenediamine tetraacetic acid can be added at levels safe for ingestion to improve storage stability.

[0085] According to the present disclosure, a liquid composition can also contain a buffer such as gluconic acid, lactic acid, citric acid, or acetic acid, sodium gluconate, sodium lactate, sodium citrate, or sodium acetate. Selection of excipients and the amounts used can be readily determined by the formulation scientist based upon experience and consideration of standard procedures and reference works in the field.

[0086] The solid compositions of the present disclosure include powders, granulates, aggregates, and compacted compositions. The dosages include dosages suitable for oral, buccal, rectal, parenteral (including subcutaneous, intramuscular, and intravenous), inhalant, and ophthalmic administration. Although the most suitable administration in any given case will depend on the nature and severity of the condition being treated, the most preferred route of the present disclosure is oral. The dosages can be conveniently presented in unit dosage form and prepared by any of the methods well-known in the pharmaceutical arts.

[0087] Dosage forms include solid dosage forms like tablets, powders, capsules, suppositories, sachets, troches, and lozenges, as well as liquid syrups, suspensions, and elixirs.

[0088] The dosage form of the present disclosure can be a capsule containing the composition, such as a powdered or granulated solid composition of the invention, within either a hard or soft shell. The shell can be made from gelatin and optionally contain a plasticizer such as glycerin and sorbitol, and an opacifying agent or colorant.

[0089] The active ingredient and excipients can be formulated into compositions and dosage forms according to methods known in the art.

[0090] A composition for tableting or capsule filling can be prepared by wet granulation. In wet granulation, some or all of the active ingredients and excipients in powder form are blended and then further mixed in the presence of a liquid, typically water, that causes the powders to clump into granules. The granulate is screened and/or milled, dried, and then screened and/or milled to the desired particle size. The granulate can then be tableted, or other excipients can be added prior to tableting, such as a glidant and/or a lubricant.

[0091] A tableting composition can be prepared conventionally by dry blending. For example, the blended composition of the actives and excipients can be compacted into a slug or a sheet and then comminuted into compacted granules. The compacted granules can subsequently be compressed into a tablet.

[0092] As an alternative to dry granulation, a blended composition can be compressed directly into a compacted dosage form using direct compression techniques. Direct compression produces a more uniform tablet without granules. Excipients that are particularly well suited for direct compression tableting include microcrystalline cellulose, spray dried lactose, dicalcium phosphate dihydrate, and colloidal silica. The proper use of these and other excipients in direct compression tableting is known to those in the art with experience and skill in particular formulation challenges of direct compression tableting.

[0093] A capsule filling of the present invention can comprise any of the aforementioned blends and granulates that were described with reference to tableting, but they are not subjected to a final tableting step.

[0094] In embodiments, a pharmaceutical formulation of Fedovapagon and Fedovapagon co-crystals is formulated for administration to a mammal, such as a human. Fedovapagon and Fedovapagon co-crystals, such as Fedovapagon salicylic acid can be formulated, for example, as a viscous liquid solution or suspension, such as a clear solution, for injection. The formulation can contain one or more solvents. A suitable solvent can be selected by considering the solvent's

physical and chemical stability at various pH levels, viscosity (which would allow for syringeability), fluidity, boiling point, miscibility, and purity. Suitable solvents include alcohol USP, benzyl alcohol NF, benzyl benzoate USP, and Castor oil USP. Additional substances can be added to the formulation such as buffers, solubilizers, and antioxidants, among others. Ansel et al., *Pharmaceutical Dosage Forms and Drug Delivery Systems*, 7th ed.

[0095] The present disclosure encompasses a process to prepare said formulations of co-crystals of Fedovapagon and solid state forms thereof by combining the co-crystal prepared according to the present disclosure and at least one pharmaceutically acceptable excipient.

[0096] Co-crystals of Fedovapagon as defined herein, as well as the pharmaceutical compositions or formulations of Fedovapagon and Fedovapagon co-crystals, such as Fedovapagon salicylic acid can be used as medicaments, in embodiments for the treatment of Nocturia.

[0097] The present disclosure also provides a method of treating of Nocturia, by administering a therapeutically effective amount of Fedovapagon co-crystal prepared according to the present disclosure, or at least one of the above pharmaceutical compositions or formulations, to a subject suffering from Nocturia, or otherwise in need of the treatment.

[0098] The present disclosure also provides the use of co-crystals of Fedovapagon, or at least one of the above pharmaceutical compositions or formulations for the manufacture of a medicament for treating Nocturia.

[0099] Having described the co-crystals of Fedovapagon with reference to certain exemplary embodiments, other embodiments will become apparent to one skilled in the art from consideration of the specification. The disclosure is further illustrated by reference to the following examples describing in detail the preparation of the composition and methods of use of the disclosure. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the scope of the disclosure.

Analytical Methods

Powder X-ray diffraction pattern ("PXRD") method:

[00100] Sample after being powdered in a mortar and pestle is applied directly on a silicon plate holder. The X-ray powder diffraction pattern was measured with Philips X'Pert PRO X-ray powder diffractometer, equipped with Cu irradiation source = 1.54184 Å (Ångström), X'Celerator (2.022° 2θ) detector. Scanning parameters: angle range: 3-40 deg., step size 0.0167,

time per step 37 seconds, continuous scan. The described peak positions were determined without using silicon powder as an internal standard in an admixture with the sample measured.

¹³C solid state Nuclear Magnetic Resonance ("ss-NMR" or ¹³C solid state NMR) method:

[00101] Solid state NMR spectra were measured at 11.7 T using a Bruker Avance III HD 500 US/WB NMR spectrometer (Karlsruhe, Germany, 2013). The ¹³C CP/MAS NMR spectra employing cross-polarization were acquired using the standard pulse scheme at spinning frequency of 18 kHz. The recycle delay was 8 s and the cross-polarization contact time was 2 ms. The strength of spin-locking fields B₁(¹³C) expressed in frequency units $\omega_{1/2\pi} = \gamma B_1$ was 64 kHz. The ¹³C NMR scale was referenced to α -glycine (176.03 ppm). Frictional heating of the spinning samples was offset by active cooling, and the temperature calibration was performed with Pb(NO₃)₂. The NMR spectrometer was completely calibrated and all experimental parameters were carefully optimized prior the investigation. Magic angle was set using KBr during standard optimization procedure and homogeneity of magnetic field was optimized using adamantane sample (resulting line-width at half-height $\Delta\nu_{1/2}$ was less than 3.5 Hz at 250 ms of acquisition time).

Differential scanning calorimetry ("DSC") method:

[00102] Equipment: TA Instruments Discovery DSC

Scanning parameters:

Heating range: 25-300 °C

Heating rate: 10 C°/min.

Sample was placed in hermetically closed aluminum pan with one hole on the crucible.

Purging with 50 ml/min N₂ flow.

Thermo-Gravimetric analysis (TGA) method:

[00103] Equipment: TA Instruments Discovery TGA

Scanning parameters:

Heating range: 25-300 °C

Heating rate: 10 C°/min.

Sample was placed in open aluminum pan.

Purging with 50 ml/min N₂ flow.

[00104] Equipment: Mettler TGA

Scanning parameters:

Heating range: 25-300 °C

Heating rate: 10 C°/min.

Sample placed in open aluminum pan

Purging with 30 ml/min N₂ flow.

Examples

[00105] Fedovapagon can be prepared according to any procedure known in the art, for example the procedures described in WO 0149682, WO 2011/121308 and/or WO 2012/131389. Amorphous Fedovapagon can be prepared by any known method for preparing amorphous material, such as lyophilization, spray dry, fast evaporation, etc.

Example 1: Preparation of co-crystal of Fedovapagon and salicylic acid form alpha

[00106] A suspension of Fedovapagon (amorphous form, 462.6 mg, 1.0 mmol), salicylic acid (138.1 mg, 1.0 mmol) and heptane (10 mL) was stirred in a closed 25 mL round bottom flask at 200 rpm for 6 hours at room temperature. The solid was isolated by vacuum filtration (554 mg) and it was dried at room temperature for 18 hours. The obtained solid was analyzed by PXRD, Fedovapagon salicylic acid co-crystal form alpha was obtained. PXRD pattern is given in Figure 1.

Example 2: Preparation of Fedovapagon and salicylic acid cocrystal form beta

[00107] A suspension of Fedovapagon (120 mg, 0.25 mmol, amorphous form), salicylic acid (35.2 mg, 0.25 mmol) and heptane (0.5 mL) was stirred in a closed clear glass vial at 350 rpm for three days at room temperature. The solid was isolated by vacuum filtration (112.0 mg), and dried on funnel for 15 minutes. The obtained solid was analyzed by PXRD, Fedovapagon salicylic acid co-crystal form beta was obtained. PXRD pattern is given in Figure 2; a DSC thermogram is shown in Figure 6; a TGA thermogram is shown in Figure 7.

Example 3: Preparation of Fedovapagon and salicylic acid cocrystal form gamma

[00108] A suspension of Fedovapagon (115 mg, 0.24 mmol, amorphous form), salicylic acid (67.4 mg, 0.48 mmol) and heptane (2.5 mL) was stirred in a closed clear glass vial at 350 rpm for three days at room temperature. The solid was isolated by vacuum filtration (150.9 mg), and

dried on funnel for 15 minutes. The obtained solid was analyzed by PXRD, Fedovapagon salicylic acid co-crystal form gamma was obtained. PXRD pattern is given in Figure 3.

Example 4: Preparation of Fedovapagon and salicylic acid cocrystal form beta

[00109] A suspension of Fedovapagon (1 gram, 0.002 mol amorphous form), salicylic acid (0.278 grams, 0.002 mol) and heptane (4 mL) was stirred in a closed clear glass vial at 300 rpm for 5 days at room temperature. After 5 days a solid was isolated by vacuum filtration and was dried on a funnel under vacuum at room temperature for 1 hour. The obtained solid was analyzed by PXRD. Fedovapagon salicylic acid co-crystal form beta was obtained (Isolated: 1.097 grams).

Example 5: Preparation of Fedovapagon and salicylic acid cocrystal form beta

[00110] Fedovapagon (1.10 grams, 0.002 mol, amorphous form) and salicylic acid (0.61 grams, 0.004 mol) were weighed out into a clear glass vial (20 mL). Isopropyl acetate (8 mL) was added to the vial at room temperature and Fedovapagon and salicylic acid were dissolved. The obtained solution was filtered (0.2 μ m Watman PTFE filter). The vial was washed twice with isopropyl acetate (1mL). The filtrate and residual fluid (used for washing) were collected and maintained at room temperature, the fluid was slowly evaporated in air. The obtained solid was analyzed by PXRD. Fedovapagon salicylic acid co-crystal (1:1) form beta was obtained (Isolated: 852 mg).

Example 6: Preparation of Fedovapagon and salicylic acid cocrystal form beta

[00111] Fedovapagon (1.10 grams, 0.002 mol, amorphous form) and salicylic acid (0.30 grams, 0.002 mol) were weighed out into a clear glass vial (20 mL). Isopropyl acetate (8 mL) was added at room temperature and Fedovapagon and salicylic acid were dissolved. The obtained solution was filtered (0.2 μ m Watman PTFE filter). The vial was washed twice time with isopropyl acetate (1mL). The filtrate and residual fluid (used for washing) were collected and maintained at room temperature and the fluid was slowly evaporated in air. Crystallization started within one hour. After one day the crystals were separated by vacuum filtration, washed with isopropyl acetate (2 x 1.5 mL) and dried on a funnel under vacuum and at room temperature for 1 hour. The obtained solid was analyzed by PXRD. Fedovapagon salicylic acid co-crystal form beta was obtained (Isolated: 542 mg).

Example 7: Preparation of Fedovapagon and salicylic acid cocrystal form beta

[00112] Fedovapagon (498.0 mg, 0.001 mol, amorphous form) and salicylic acid (152.0 mg, 0.001 mol) were weighed out into a round bottom flask (10 ml) and isopropyl acetate (1.0 ml)

was added at room temperature. Fedovapagon and salicylic acid were dissolved by mixing on magnetic stirrer (400 rpm, in open flask). Crystallization occurred after 15 minutes of mixing at room temperature. The obtained solid was isolated by vacuum filtration and analyzed by PXRD. Fedovapagon salicylic acid co-crystal form beta was obtained (Isolated: 550 mg).

Example 8: Preparation of Fedovapagon and salicylic acid cocrystal form gamma

[00113] A suspension of Fedovapagon (0.96 grams, 0.002 mol, amorphous form), salicylic acid (0.53 grams, 0.004 mol) and heptane (20 mL) was stirred in an Erlenmeyer flask (50 mL) at 250 rpm for one day at room temperature. The obtained solid material was separated by vacuum filtration, washed with heptane (3 x 1.5 mL) and was dried on a funnel under vacuum and at room temperature for 1 hour. The obtained solid was analyzed by PXRD. Fedovapagon salicylic acid co-crystal form gamma was obtained (Isolated: 1.37 g). PXRD pattern is given in Figure 4; a DSC thermogram is shown in Figure 8; a TGA thermogram is shown in Figure 9.

Example 9: Preparation of Fedovapagon and salicylic acid cocrystal form gamma

[00114] Fedovapagon (506.5 mg, 0.001 mol, amorphous form) and salicylic acid (304.5 mg, 0.002 mol) were weighed out into a round bottom flask (25 ml) and isopropyl acetate (1.0 ml) was added at room temperature. Fedovapagon and salicylic acid were dissolved by mixing on a magnetic stirrer (400 rpm, in open flask). Crystallization occurred after 15 minutes of mixing at room temperature. The obtained solid was isolated by vacuum filtration and analyzed by XRPD. Fedovapagon salicylic acid co-crystal form gamma was obtained (Isolated: 640 mg).

Claims:

1. Fedovapagon: salicylic acid co-crystal.
2. A Fedovapagon: salicylic acid co-crystal according to Claim 1, designated form beta, having data selected from one or more of the following:
 - a. a PXRD pattern having peaks at 8.7, 10.2, 16.0, 20.6 and 23.2 degrees 2-theta $\pm$ 0.2 degrees 2-theta;
 - b. a PXRD pattern as depicted in Figure 2;
 - c. a ^{13}C solid state NMR having peaks at at the range of 100-200 ppm at 172.6, 162.2, 127.8, 125.0, 116.7 ppm $\pm$ 0.2 ppm;
 - d. a solid state ^{13}C NMR spectrum having the following chemical shift absolute differences from a reference peak at 57.6 ± 0.2 ppm ppm $\pm$ 2 ppm of 115.0, 104.6, 70.2, 67.4, 59.1 ± 0.1 ppm respectively;
 - e. a ^{13}C solid state NMR spectrum substantially as depicted in Figure 5; and
 - f. combinations of these data.
3. A Fedovapagon: salicylic acid co-crystal form beta according to Claim 1 or Claim 2, characterized by the PXRD pattern having peaks at 8.7, 10.2, 16.0, 20.6 and 23.2 degrees 2-theta $\pm$ 0.2 degrees 2-theta, and also having one, two, three, four or five additional peaks at 5.1, 8.0, 19.4, 25.7 and 30.3 degrees 2-theta $\pm$ 0.2 degrees 2-theta.
4. Fedovapagon: salicylic acid co-crystal form beta according any of Claims 1 to 3, which is an anhydrous form.
5. A Fedovapagon: salicylic acid co-crystal according to any one of Claims 1-4, wherein the molar ratio of Fedovapagon and salicylic acid is between about 1:1.5 and 1.5:1.
6. A Fedovapagon: salicylic acid co-crystal according to any one of Claims 1-5, wherein the molar ratio of Fedovapagon and salicylic acid is between about 1:1.25 and 1.25:1.
7. A Fedovapagon: salicylic acid co-crystal according to any one of Claims 1-6, wherein the molar ratio of Fedovapagon and salicylic acid is about 1:1.

8. A Fedovapagon: salicylic acid co-crystal according to Claim 1, designated form gamma, having data selected from one or more of the following:
 - a. a PXRD pattern having peaks at 11.0, 17.2, 18.5, 19.2 and 23.0 degrees 2-theta $\pm$ 0.2 degrees 2-theta, and optionally a PXRD pattern as depicted in Figure 3;
 - b. a PXRD pattern having peaks at 7.2, 17.2, 18.5, 19.2 and 23.0 degrees 2-theta $\pm$ 0.2 degrees 2-theta, and optionally a PXRD pattern as depicted in Figure 4.
9. A Fedovapagon: salicylic acid co-crystal form gamma according to Claim 8, characterized by the PXRD pattern having peaks at 11.0, 17.2, 18.5, 19.2 and 23.0 degrees 2-theta $\pm$ 0.2 degrees 2-theta or a PXRD pattern having peaks at 7.2, 17.2, 18.5, 19.2 and 23.0 degrees 2-theta $\pm$ 0.2 degrees 2-theta, and also having one, two, three, four or five additional peaks at 14.7, 11.8, 15.4, 28.8 and 34.7 degrees 2-theta $\pm$ 0.2 degrees 2-theta.
10. Fedovapagon: salicylic acid co-crystal form gamma according Claim 8 or Claim 9, which is an anhydrous form.
11. A Fedovapagon: salicylic acid co-crystal according to any one of Claims 8-10, wherein the molar ratio of Fedovapagon and salicylic acid is between about 1:1.33 to 1:2.5.
12. A Fedovapagon: salicylic acid co-crystal according to any one of Claims 8-11, wherein the molar ratio of Fedovapagon and salicylic acid is between about 1:1.6 to 1:2.5.
13. A Fedovapagon: salicylic acid co-crystal according to any one of Claims 8-12, wherein the molar ratio of Fedovapagon and salicylic acid is about 1:2.
14. A Fedovapagon: salicylic acid co-crystal according to any preceding claim, which contains: no more than about 20%, no more than about 10%, no more than about 5%, no more than about 2%, no more than about 1% or about 0% of any other Fedovapagon: salicylic acid co-crystal form.
15. A Fedovapagon: salicylic acid co-crystal according to any preceding claim, which contains: no more than about 20%, no more than about 10%, no more than about 5%, no more than about 2%, no more than about 1% or about 0% of any other crystalline form of Fedovapagon.

16. A pharmaceutical composition comprising any one or a combination of Fedovapagon: salicylic acid co-crystal form according to any of Claims 1-15.
17. Use of any one or a combination of Fedovapagon: salicylic acid co-crystal form according to any one of Claims 1 to 15 for the preparation of a pharmaceutical composition and/or oral formulation, preferably wherein the pharmaceutical formulation is an oral formulation.
18. A pharmaceutical formulation comprising any one or a combination of Fedovapagon: salicylic acid co-crystal form according to any of Claims 1-15, or a pharmaceutical composition of Claim 16, and at least one pharmaceutically acceptable excipient.
19. A process for preparing the pharmaceutical formulation according to Claim 18, comprising combining any one or a combination of Fedovapagon: salicylic acid co-crystal form according to any one of Claims 1-15 or a pharmaceutical composition of Claim 16, with at least one pharmaceutically acceptable excipient.
20. Fedovapagon: salicylic acid co-crystal form according to any one of Claims 2-6 or Claims 8-12 or Claims 14-15, a pharmaceutical composition according to Claim 16, or a pharmaceutical formulation according to Claim 18, for use as a medicament.
21. Fedovapagon: salicylic acid co-crystal form according to any of Claims 1-15, a pharmaceutical composition according to Claim 16, or a pharmaceutical formulation according to Claim 18, for use in the treatment of Nocturia.
22. A method of treating Nocturia, comprising administering a therapeutically effective amount of Fedovapagon: salicylic acid co-crystal form according to any of Claims 1-15, or a pharmaceutical composition according to Claim 16, or a pharmaceutical formulation according to Claim 18 to a subject in need of the treatment.
23. Fedovapagon: salicylic acid co-crystal form according to any of Claims 1-15, a pharmaceutical composition according to Claim 16, or a pharmaceutical formulation according to Claim 18, for the manufacture of a medicament for treatment of Nocturia.
24. Use of Fedovapagon: salicylic acid co-crystal form according to any of Claims 1-15, in the preparation of another solid state form of Fedovapagon, or salts and co-crystals of Fedovapagon and solid state forms thereof.

Figure 1: A powder X-ray diffraction pattern of a co-crystal of Fedovapagon and salicylic acid form alpha

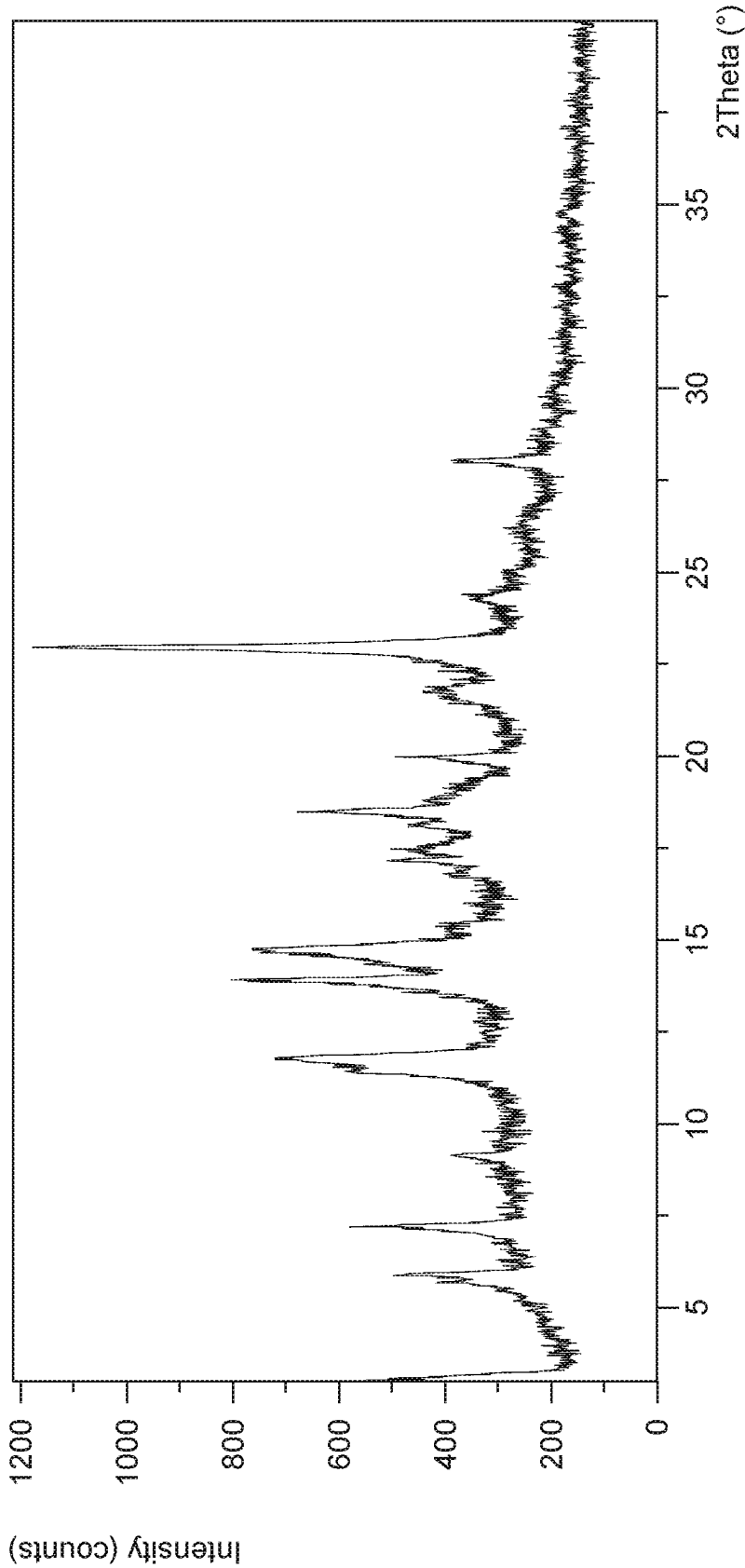


Figure 2: A powder X-Ray diffraction pattern of a co-crystal of Fedovapagon and salicylic acid form beta

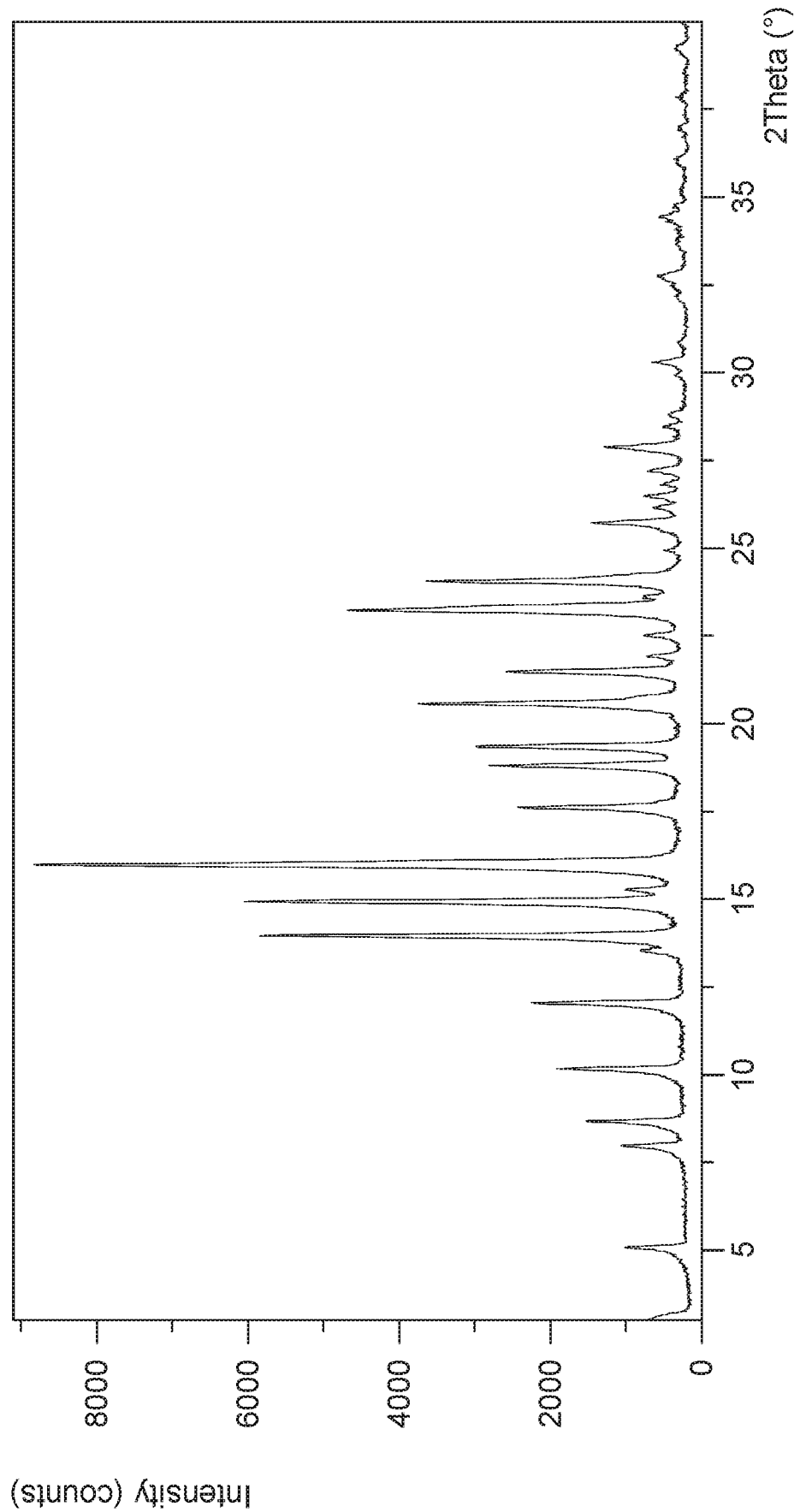


Figure 3: A PXRD of a co-crystal of Fedovapagon and salicylic acid form gamma (prepared according to example 3)

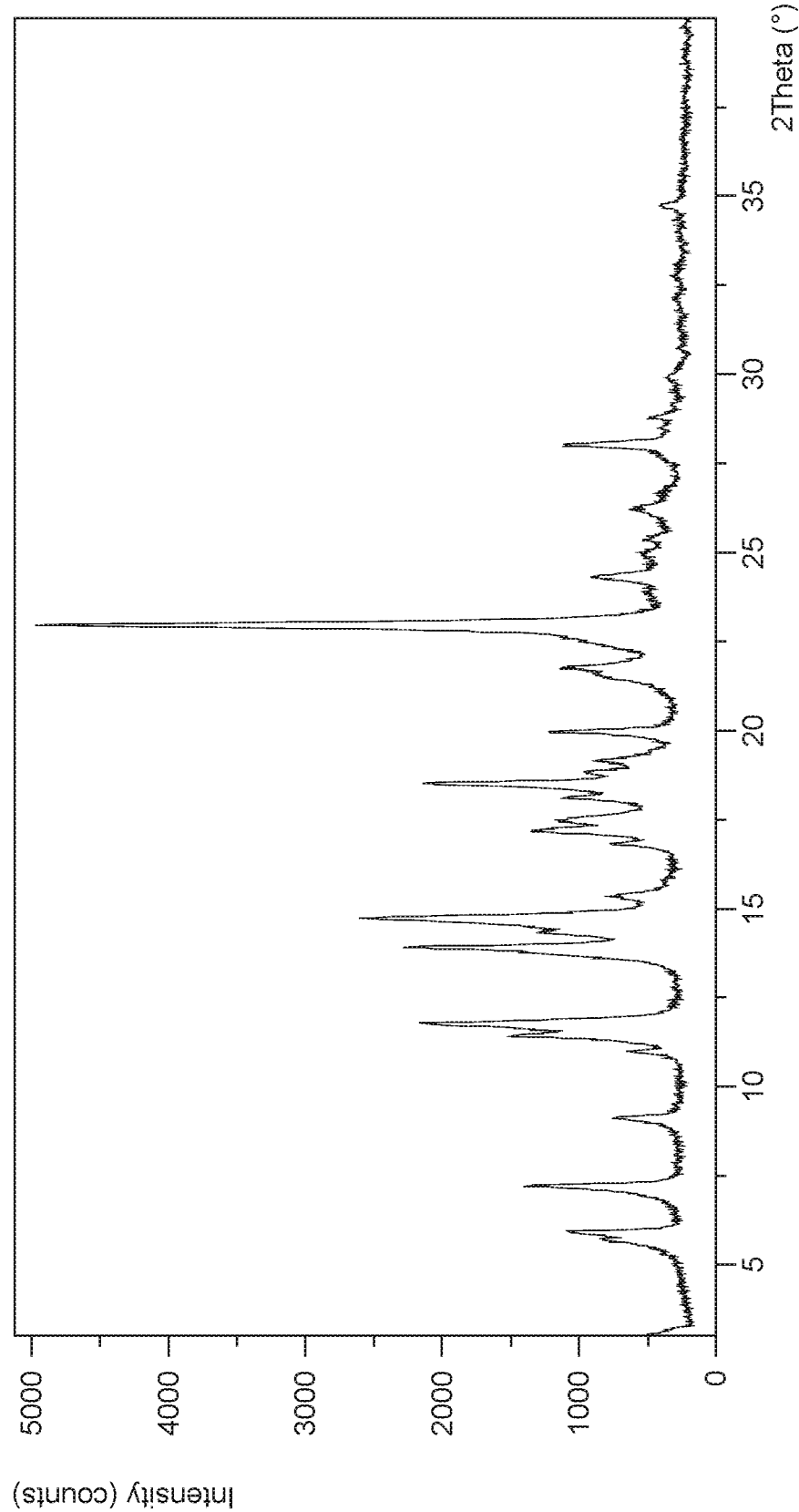
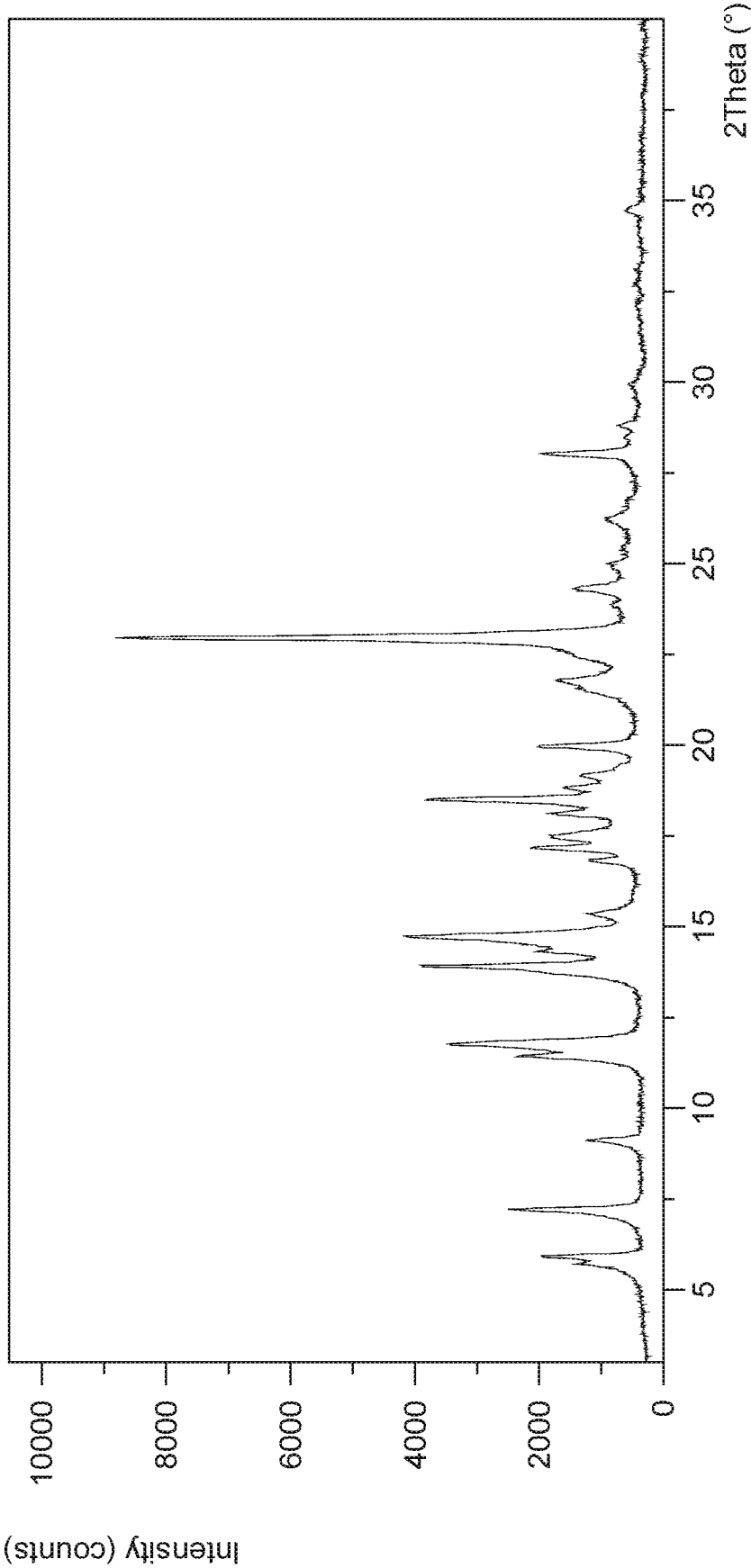


Figure 4: A PXRD of a co-crystal of Fedovapagon and salicylic acid form gamma (prepared according to example 8)



A ^{13}C solid state NMR of a co-crystal of Fedovapagon and salicylic acid form beta

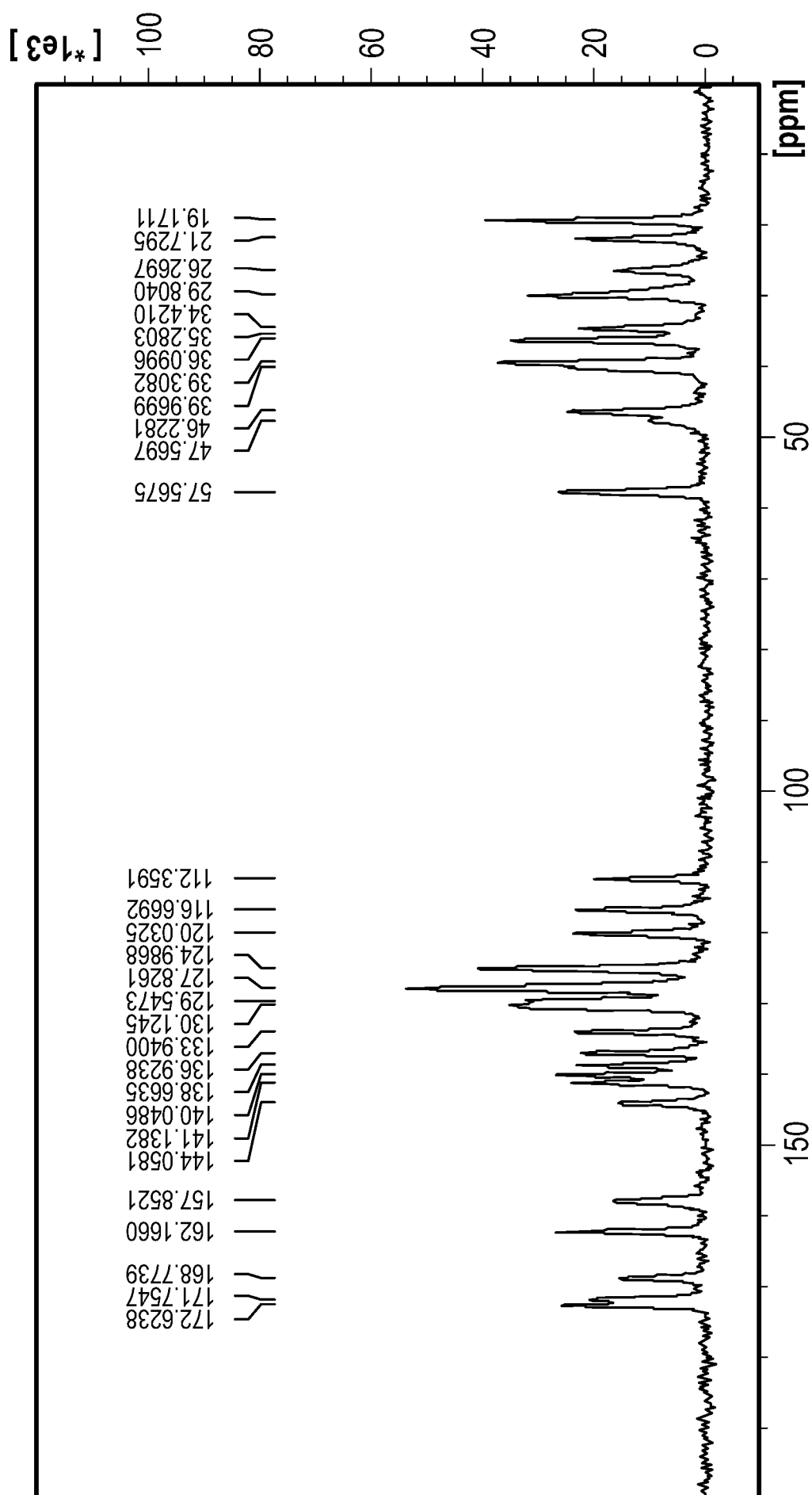


FIG. 5

A DSC thermogram of a co-crystal of Fedovapagon and salicylic acid form beta prepared according to Example 2

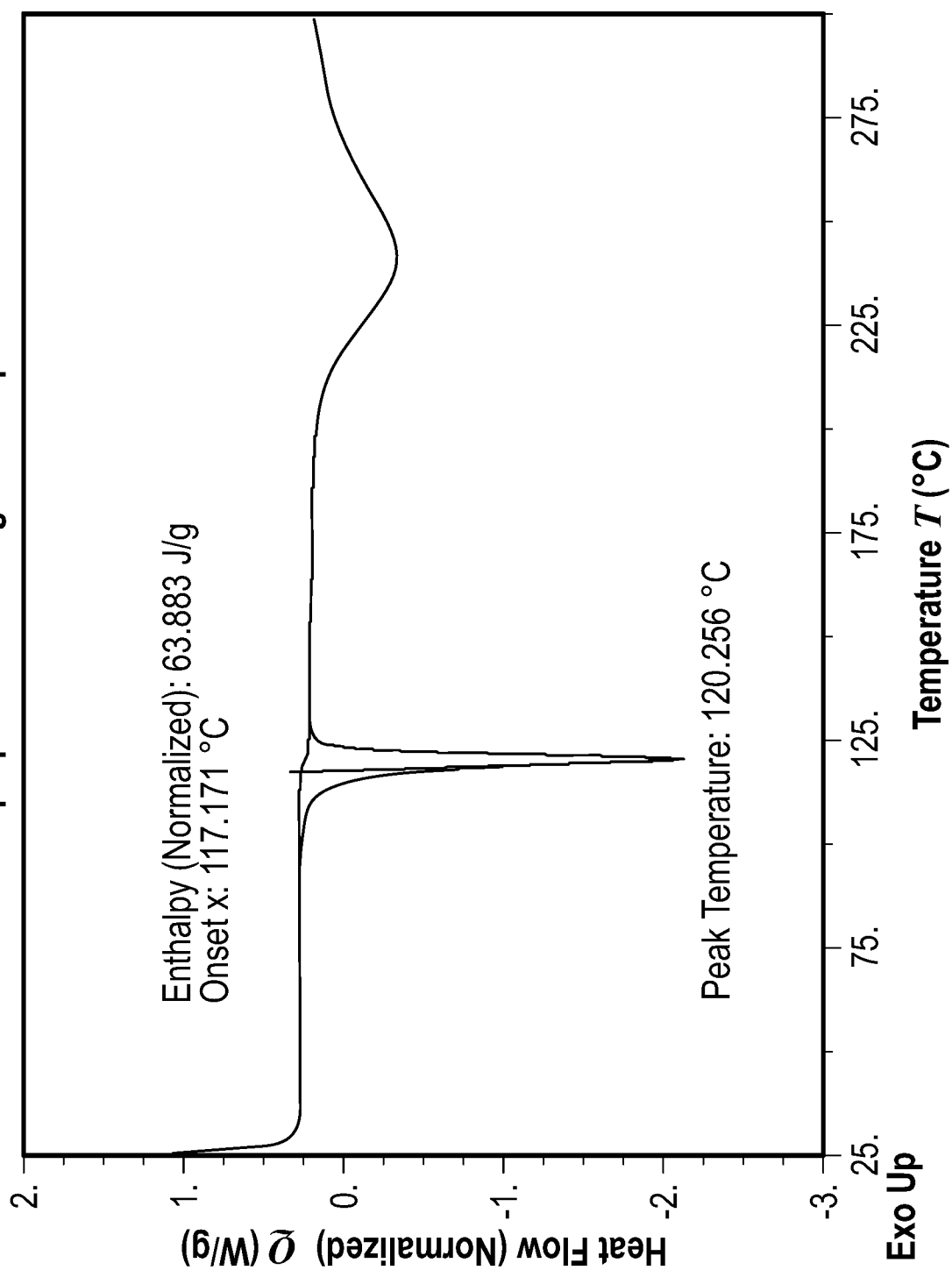


FIG. 6

A TGA thermogram of a co-crystal of Fedovapagon and salicylic acid form beta prepared according to Example 2

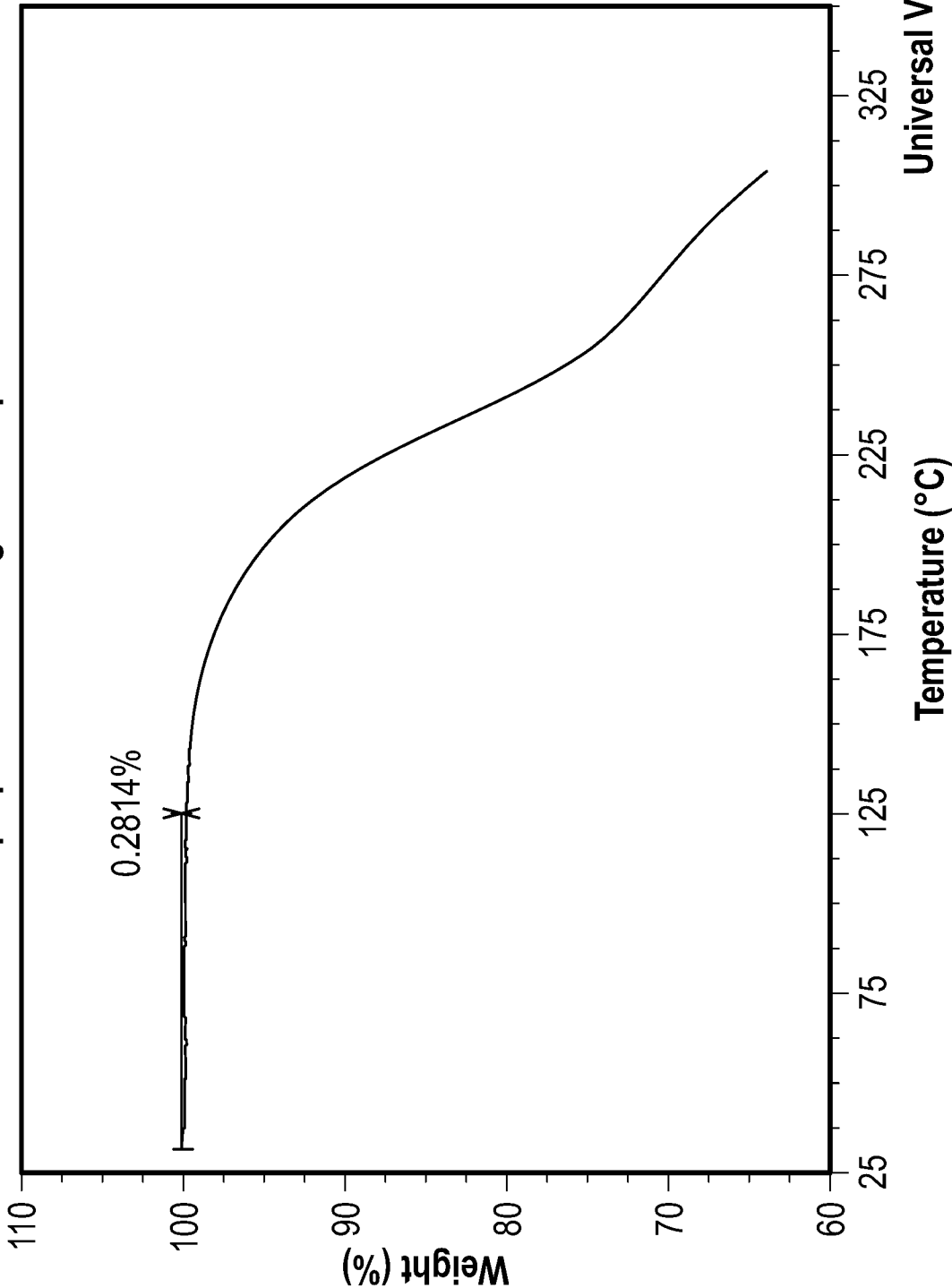


FIG. 7

A DSC thermogram of a co-crystal of Fedovapagon and salicylic acid form gamma prepared according to Example 8

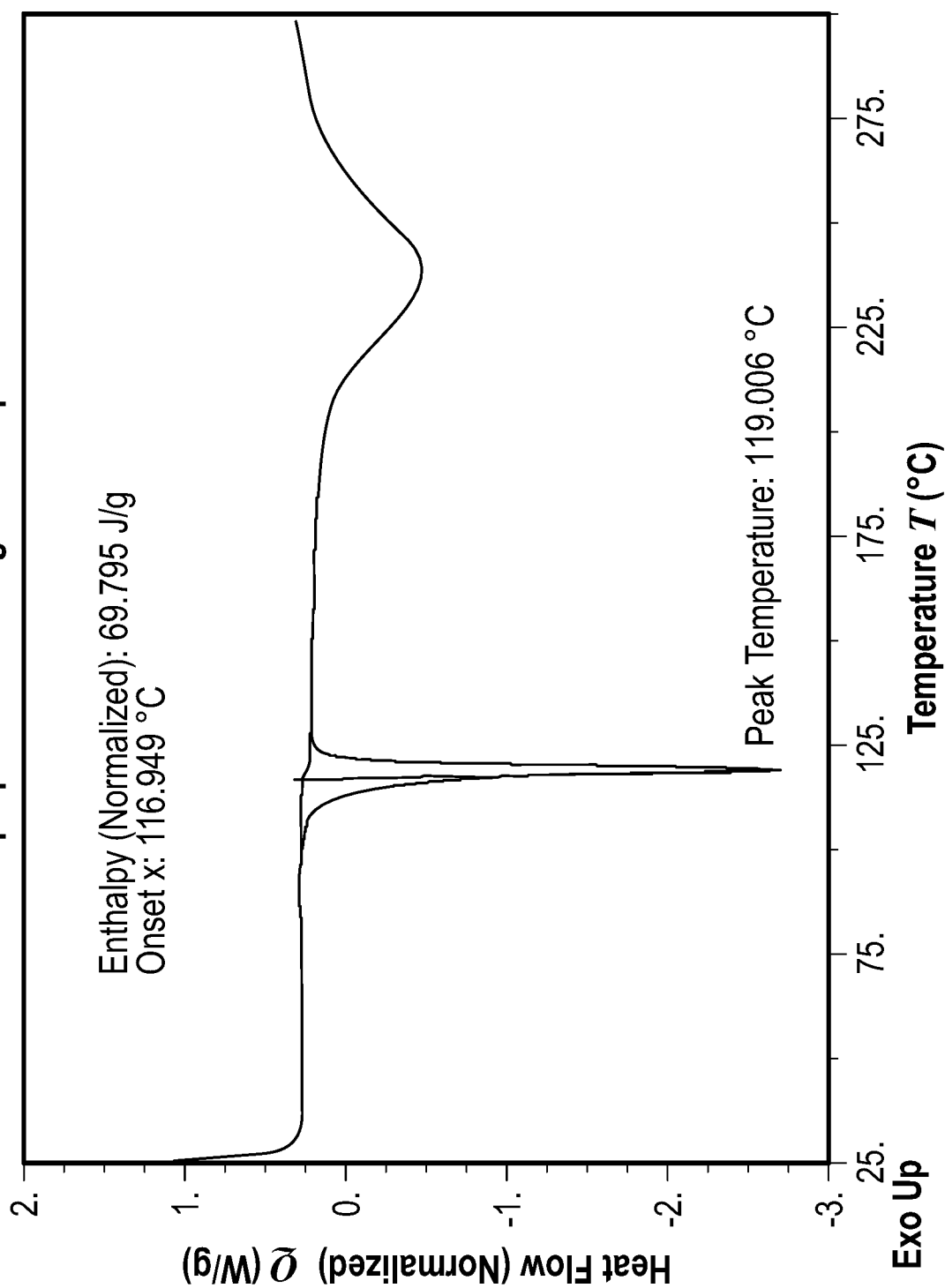


FIG. 8

A TGA thermogram of a co-crystal of Fedovapagon and salicylic acid form gamma prepared according to Example 8

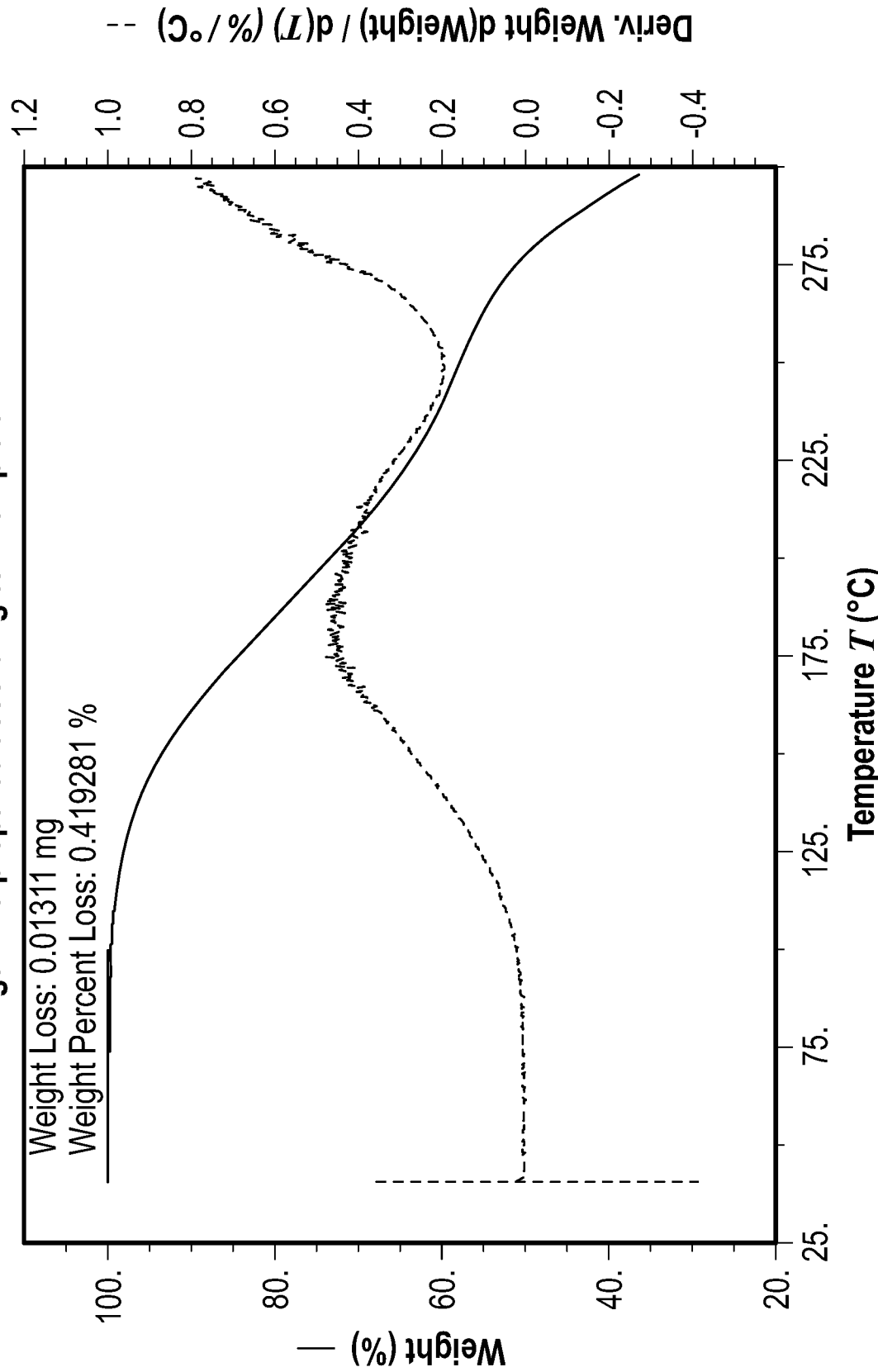


FIG. 9

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2020/014929

A. CLASSIFICATION OF SUBJECT MATTER INV. C07D403/12 C07C65/10 A61P13/00 A61P13/02 A61K31/55 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, WPI Data, CHEM ABS Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/00626 A1 (FERRING BV [NL]; ASHWORTH DOREEN MARY [GB] ET AL.) 3 January 2002 (2002-01-03) the whole document	1-24
X	WO 2011/121308 A1 (VANTIA LTD [GB]; KJELLSTROEM JOHAN HENRIK [DK] ET AL.) 6 October 2011 (2011-10-06) cited in the application the whole document ----- -/--	1-24
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
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Date of the actual completion of the international search 7 April 2020		Date of mailing of the international search report 20/04/2020
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