

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property

Organization

International Bureau

(43) International Publication Date

18 June 2020 (18.06.2020)



(10) International Publication Number

WO 2020/121326 A1

(51) International Patent Classification:

C07D 231/12 (2006.01) A61K 9/00 (2006.01)

C07C 217/74 (2006.01)

(21) International Application Number:

PCT/IN2019/050904

(22) International Filing Date:

11 December 2019 (11.12.2019)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

201841047151 13 December 2018 (13.12.2018) IN

(71) Applicant: MYLAN LABORATORIES LIMITED

[IN/IN]; Plot No 564/A/22, Road No 92, Jubilee Hills, Hyderabad 500033 (IN).

(72) Inventors: JETTI, Ramakoteswara Rao; Mylan Labora-

tories LTD, Plot No 564/A/22, Road No 92, Jubilee Hills, Hyderabad 500033 (IN). GOLIVI, Ramamohana Rao; Mylan Laboratories LTD, Plot No 564/A/22, Road No 92, Jubilee Hills, Hyderabad 500033 (IN). JAYACHANDRA, Sureshbabu; Mylan Laboratories LTD, Plot No 564/A/22, Road No 92, Jubilee Hills, Hyderabad 500033 (IN).

(74) Agent: HASAN, Afzal et al.; HASAN AND SINGH, Flat

No. 04, Sree Nilayam Apartment, Plot No. 12, Camelot Layout (Near Chirec Public School), Kondapur, Hyderabad 500084 (IN).

(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, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, 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, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- 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))
- of inventorship (Rule 4.17(iv))

Published:

- with international search report (Art. 21(3))
- in black and white; the international application as filed contained color or greyscale and is available for download from PATENTSCOPE

(54) Title: AMORPHOUS (RAC)-TRAMADOL.HCL-CELECOXIB (1:1)

(57) Abstract: The present invention provides an amorphous form of (rac)-tramadol.HCl-celecoxib (1:1) and a solid dispersion and processes for the preparation of the same.

WO 2020/121326 A1

**AMORPHOUS (RAC)-TRAMADOL.HCl-CELECOXIB (1:1)****CROSS-REFERENCE TO RELATED APPLICATION(S)**

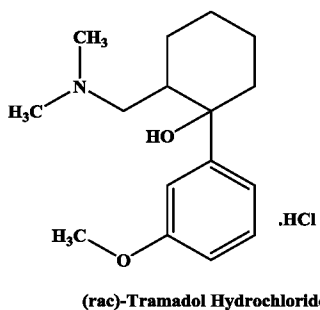
This application claims the priority to and benefit of Indian Patent Application No. IN201841047151 filed on December 13, 2018; the disclosures of which are incorporated herein by reference.

**FIELD OF THE INVENTION**

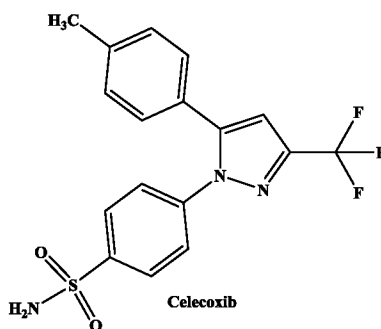
The present invention provides amorphous form of (rac)-tramadol HCl-celecoxib (1:1) and its solid dispersion.

**BACKGROUND OF THE INVENTION**

Tramadol, 2-[(dimethylamino)-methyl]-1-(3-methoxyphenyl) cyclohexanol, is widely used as an analgesic in its physiologically acceptable salt forms. (rac)-Tramadol.HCl of the present invention has the following structure.



Celecoxib, 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzene sulfonamide, has the following structure.



A co-crystal comprising (rac)-tramadol.HCl and celecoxib is reported in US8598152 and US9012440.

**OBJECT AND SUMMARY OF THE INVENTION**

The principal object of the present invention is to provide an amorphous form of (rac)-tramadol.HCl-celecoxib (1:1)

5 In one aspect, the present invention provides an amorphous form of (rac)-tramadol.HCl-celecoxib (1:1)

In another aspect, the present invention provides an amorphous solid dispersion of (rac)-tramadol.HCl-celecoxib (1:1).

In one more aspect, the present invention provides a process for the preparation of an amorphous form of (rac)-tramadol.HCl-celecoxib (1:1) comprising the steps of:

- 10       a) dissolving (rac)-tramadol.HCl and celecoxib in an organic solvent or mixtures thereof;  
         b) removing the solvent to isolate amorphous (rac)-tramadol.HCl-celecoxib (1:1).

In one more aspect, the present invention provides a process for the preparation of an amorphous form of (rac)-tramadol.HCl-celecoxib (1:1) comprising the steps of:

- 15       a) dissolving a 1:1 co-crystal of (rac)-tramadol.HCl-celecoxib in an organic solvent or mixtures thereof;  
         b) removing the solvent to isolate the amorphous form of (rac)-tramadol.HCl-celecoxib (1:1).

In another aspect, the present invention provides a process for the preparation of an amorphous solid dispersion of (rac)-tramadol.HCl-celecoxib (1:1) comprising the steps of:

- 20       a) dissolving (rac)-tramadol.HCl and celecoxib and a pharmaceutically acceptable excipient in a suitable solvent or mixtures thereof, and  
         b) removing the solvent to isolate the amorphous solid dispersion of (rac)-tramadol.HCl-celecoxib (1:1).

25 In another aspect, the present invention provides a process for the preparation of an amorphous solid dispersion of (rac)-tramadol.HCl-celecoxib (1:1) comprising the steps of:

- a) dissolving (rac)-tramadol HCl and celecoxib in a suitable solvent or mixtures thereof,  
         b) adding a pharmaceutically acceptable excipient, and  
         c) removing the solvent to isolate the amorphous solid dispersion of (rac)-tramadol.HCl-celecoxib (1:1).

## BRIEF DESCRIPTION OF THE DRAWINGS

Further aspects of the present disclosure together with additional features contributing there to and advantages accruing there from will be apparent from the following description of embodiments of the disclosure which are shown in the accompanying figures wherein:

5 Figure 1: PXRD pattern of amorphous (rac)-tramadol.HCl-celecoxib (1:1) of Example 1.

Figure 2: PXRD pattern of amorphous (rac)- tramadol.HCl-celecoxib (1:1) of Example 2.

Figure 3: PXRD pattern of amorphous solid dispersion of (rac)- tramadol.HCl-celecoxib (1:1) of Example 3.

10 Figure 4: PXRD pattern of amorphous solid dispersion of (rac)- tramadol.HCl-celecoxib (1:1) of Example 4.

Figure 5: PXRD pattern of amorphous solid dispersion of (rac)- tramadol.HCl-celecoxib (1:1) of Example 5.

Figure 6: Modulated DSC thermogram of (rac)- tramadol.HCl-celecoxib amorphous form.

15 Figure 7: Comparison of FTIR spectra of the amorphous form and co-crystal/crystalline form of (rac)- tramadol.HCl-celecoxib (1:1).

Figure 8: Comparison of  $^{13}\text{C}$  SSNMR data of an 1:1 admixture of (rac)-tramadol.HCl (A) and celecoxib (B), a 1:1 complex of (rac)- tramadol.HCl-celecoxib amorphous form, a 1:1 co-crystal of (rac)- tramadol.HCl-celecoxib crystalline form, (rac)-tramadol.HCl (A) and celecoxib (B).

20 Figure 9: Variable temperature PXRD data of (rac)- tramadol.HCl-celecoxib amorphous form.

Figure 10: PXRD overlay of amorphous form storage at  $5\pm 3^\circ\text{C}$  (top) sample after 6 months, (middle) after 2 months, and (bottom) the initial sample.

## DETAILED DESCRIPTION OF THE INVENTION

25 The principal object of the present invention is to provide an amorphous form of (rac)-tramadol.HCl-celecoxib (1:1)

### Instrumentation Details:

The PXRD measurements were carried out using PANalytical X'Pert PRO powder diffractometer equipped with goniometer of  $\theta/\theta$  configuration and X'Celerator detector. The Cu-anode X-ray tube was operated at 40kV and 30mA. The experiments were conducted over the  $2\theta$  range of  $2.0^\circ$ - $50.0^\circ$ ,  $0.030^\circ$  step size and 50 seconds step time.

5 **FT-IR:**

The FT-IR data was recorded using Perkin Elmer Spectrum One instrument in the range of  $400$ - $4000\text{ cm}^{-1}$  by using KBr pellets.

**Modulated Differential Scanning Calorimetry (MDSC)**

10 The glass transition temperature ( $T_g$ ) of the amorphous of (rac)-tramadol.HCl-celecoxib was measured on TA Q2000 of TA instruments with modulated DSC software. The sample was heated from  $30$  to  $250^\circ\text{C}$  at a heating rate of  $5.0^\circ\text{C}/\text{min}$  with modulation amplitude  $\pm 1.0^\circ\text{C}$ , modulation period 60sec and nitrogen purging at a flow rate of  $50\text{ml}/\text{min}$ . Standard aluminum pans covered by lids with one pin hole were utilized.

**Solid State NMR:**

15 The solid-state  $^{13}\text{C}$  cross polarization/ magic angle spinning (CP-MAS) nuclear magnetic resonance spectrum of amorphous form of (rac)-tramadol.HCl-celecoxib was recorded on Bruker 500 MHz Avance III HD NMR spectrometer at 500MHz operated at 125 MHz for carbon 13. The chemical shifts were reported on scale in ppm. Cross polarization technique is used to enhance carbon 13 sensitivity by transferring proton magnetization to carbon.

20 **Variable temperature Powder X-ray Diffraction (VTPXRD):**

The thermal stability of polymorph of the present disclosure is characterized by variable temperature on Bruker D8 Discover powder X-ray diffractometer equipped with a goniometer of  $\theta/2\theta$  configuration and LynxEye detector with Anton Paar CHC plus Chamber. Primary Optics  $0.3^\circ$  opening;  $2.5^\circ$  Soller slit on the primary and secondary optics; nickel filter in  
25 primary optics; secondary optics opening 4mm. The Cu-anode X-ray tube was operated at 40kV and 40mA. The experiments were conducted over the  $2\theta$  range of  $2.0^\circ$ - $50.0^\circ$ ,  $0.03^\circ$  step size and 0.2 seconds step time. Variable temperature powder X-ray diffraction data was measured in the temperature range of  $30^\circ\text{C}$ - $180^\circ\text{C}$  and re-cooled to  $30^\circ\text{C}$ .

In one embodiment, present invention provides amorphous form of (rac)-tramadol.HCl-celecoxib (1:1).

In another embodiment, the present invention provides an amorphous form of (rac)-tramadol.HCl-celecoxib (1:1) characterized by a PXRD pattern substantially as depicted in  
5 Figure 1 and Figure 2.

In one more embodiment the present invention provides a process for the preparation of an amorphous form of (rac)-tramadol.HCl-celecoxib (1:1) comprising the steps of:

- a) dissolving (rac)-tramadol.HCl and celecoxib in an organic solvent or mixtures thereof;  
and
- 10 b) removing the solvent to isolate the amorphous form of (rac)-tramadol.HCl-celecoxib (1:1)

In one embodiment of the present invention, (rac)-tramadol HCl and celecoxib are dissolved in an organic solvent or mixtures thereof which is capable of dissolving (rac)-tramadol.HCl and celecoxib.

- 15 The organic solvents of the above embodiment are selected from chlorinated solvents, polar protic solvents, or polar aprotic solvents. The chlorinated solvents may include but are not limited to dichloromethane, and chloroform. The polar protic solvents may include but are not limited to methanol, ethanol, propanol, butanol, 2-butanol, isopropanol, 3-methyl-1-butanol, 2-methyl-1-propanol, and 1-pentanol. The polar aprotic solvents may include but are not limited  
20 to tetrahydrofuran, dioxane, dimethyl sulfoxide, acetonitrile, dimethyl formamide and N-methyl pyrrolidone. The solvents may be mixtures thereof.

Next, the solvent is removed from the resulting clear solution to isolate an amorphous form of (rac)-tramadol.HCl-celecoxib (1:1). The solvent removal can be carried out by processes known in the art such as evaporation, distillation, spray drying, lyophilization, or agitated thin  
25 film drying, preferably spray drying.

In another embodiment, the present invention provides a process for the preparation of an amorphous form of (rac)-tramadol.HCl-celecoxib (1:1) comprising the steps of:

- a) dissolving a 1:1 co-crystal of (rac)-tramadol.HCl-celecoxib in an organic solvent or mixtures thereof;

b) removing the solvent to isolate the amorphous (rac)-tramadol.HCl-celecoxib (1:1).

In one embodiment of the present invention, the 1:1 co-crystal of (rac)-tramadol HCl and celecoxib is dissolved in an organic solvent or mixtures thereof which is capable of dissolving 1:1 co-crystal of (rac)-tramadol.HCl-celecoxib.

5 The organic solvents of the above embodiment are selected from chlorinated solvents, polar protic solvents and polar aprotic solvents. The chlorinated solvents may include but are not limited to dichloromethane, and chloroform. The polar protic solvents may include, but are not limited to methanol, ethanol, propanol, butanol, 2-butanol, isopropanol, 3-methyl-1-butanol, 2-methyl-1-propanol, and 1-pentanol. The polar aprotic solvents may include but are  
10 not limited to tetrahydrofuran, dioxane, dimethyl sulfoxide, acetonitrile, dimethyl formamide and N-methyl pyrrolidone. The solvents may be mixtures thereof.

Next, the solvent is removed from the resulting clear solution of (rac)-tramadol.HCl and celecoxib to isolate amorphous (rac)-tramadol.HCl-celecoxib (1:1). The removal of solvent can be carried out by processes known in the art such as evaporation, distillation, spray drying,  
15 lyophilization, or agitated thin film drying, preferably spray drying.

The present invention provides amorphous (rac)-tramadol HCl-celecoxib (1:1) and a pharmaceutical excipient.

In an embodiment, the present invention provides an amorphous solid dispersion of (rac)-tramadol.HCl-celecoxib (1:1).

20 In another embodiment, the pharmaceutical excipient may include diluents, lubricants, binders, glidants, stabilizers, surface active agents, anti-adherents, opacifiers, solvents, colorants, lubricants, pigments, anti-foam agents, and polishing agents. In some embodiments, microcrystalline cellulose, polysorbate, mannitol, and hydroxypropyl methylcellulose are found to be particularly useful excipients. Within the context of the present invention, the  
25 excipient or combinations of excipients may be included in the formulation.

Examples of useful pharmaceutical excipients within the context of the present invention include starches, lactose, mannitol (for example, Pearlitol™ SD200), cellulose and cellulose derivatives, and confectioner's sugar. Different forms of lactose may be useful in the context of the present invention, for example, lactose monohydrate, lactose DT (direct tableting), and

lactose anhydrous. Different forms of starches may be used in the context of the present invention, for example, maize starch, potato starch, rice starch, wheat starch, pre-gelatinized starch, starch 1500, starch 1500 LM grade, and fully pre-gelatinized starch. Examples of suitable cellulose compounds for use in the context of the present invention include crystalline celluloses, such as Ceolus™ KG-801, and a variety of Avicel™ celluloses (for example, PH-101, PH-102, PH-301, PH-302, PH-F20, PHI-12, PH-114, and PH-112). Powdered celluloses may be used as well. Other useful cellulose derivatives include hydroxypropylcellulose (HPC examples include Klucel™ LF and Klucel™ EXF), low-substituted hydroxypropylcelluloses (L-HPCS examples include LH-11, LH-21, LH-31, LH-22, LH-32, LH-20, LH-30, LH-32 and LH-33), hydroxypropylmethylcellulose (also called hypromellose or HPMC, one example is Methocel™). Other suitable binders/disintegrants include polyvinylpyrrolidones (also called povidone; examples include PVP-K25, PVP-K29, PVP-K30, and PVP-K90), copovidone (for example, Plasdone™ S-630). Other suitable excipients include powdered acacia, gelatin, guar gum, sodium starch glycolate, colloidal silicon dioxide, carbomers (for example, Carbopol™), methylcelluloses, polymethacrylates, carmellose calcium, carboxymethyl starch sodium, croscarmellose sodium, and crospovidones (for example, cross-linked povidone, Kollidon™ CL Polyplasdone™ XL, XI-10, and INF-10). Further examples of suitable excipients include sorbitan esters (for example, Span™), polyhydroxyethylenically-treated sorbitan esters (for example, Tween™), aliphatic alcohols and polyethylene glycol (PEG) ethers, phenol and PEG ethers, quaternary ammonium salts (e.g., cetyltrimethylammonium bromide), amine salts (for example, octadecylamine HCl), stearates (for example, glyceryl monostearates, polyoxyethylene monostearates, ethylene glycol stearates, propylene glycol stearates, diethylene glycol stearates, glycerol stearates, sodium stearate, potassium stearate, ammonium stearate, calcium stearate, sodium stearate, triethanolamine stearate, zinc stearate, and magnesium stearate), sodium lauryl sulfate, magnesium lauryl sulfate, calcium and sodium soaps, sodium dioctylsulfosuccinate, sodium dodecylbenzenesulfonate, palmitic acid, talc, carnauba wax, silicate, silicon dioxide, hydrogenated vegetable oils and fats, stearic acid, and combinations thereof. Phospholipids (e.g., diacylphosphatidylglycerols, diacylphosphatidylcholines, and diacylphosphatidic acids, the precursors and derivatives thereof, such as soybean lecithin and egg yolk) may also be used. Examples of suitable pigments include titanium oxide, silicon dioxide, iron oxides, zinc oxide, and combinations thereof. Suitable plasticizers include, as examples, castor oil, diacetylated monoglycerides, dibutyl sebacate, diethyl phthalate, glycerin, polyethylene glycol, propylene glycol, triacetin, and triethyl citrate. Suitable basic inorganic salts of sodium, potassium, magnesium, and

calcium (e.g., sodium carbonate, sodium hydrogen carbonate, sodium hydroxide, potassium carbonate, calcium carbonate, magnesium carbonate, dibasic calcium phosphate, tribasic calcium phosphate, potassium hydrogen carbonate, potassium hydroxide, heavy magnesium carbonate, magnesium,  $[Mg_6Al(OH)_{16} \cdot CO_3 \cdot 4H_2O]$ , aluminum hydroxide-magnesium, and  
5  $[2.5MgO \cdot Al_2O_3 \cdot H_2O]$  may be include in the formulation as well.

Many of the excipients listed above can act in a multitude of functional roles (e.g., starches can act both as a disintegrants and a binder depending on the formulation) to dictate the final properties of the desired product. One of skill in the art will readily recognize these various functional aspects of each excipient and be able to incorporate, without undue experimentation,  
10 an excipient or combinations of excipients to achieve the desired final product.

In some embodiments, Plasdane S-630, Povidone-K30, silicon dioxide and mixtures thereof have been found to particularly useful excipients for preparing a premix of (rac)-tramadol.HCl-celecoxib (1:1).

In another aspect, the present invention provides a process for the preparation of amorphous  
15 solid dispersion of (rac)-tramadol.HCl - celecoxib (1:1) comprising the steps of:

- a) dissolving (rac)-tramadol.HCl, celecoxib and a pharmaceutically acceptable excipient in a suitable solvent or mixtures thereof, and
- b) removing the solvent to isolate the amorphous solid dispersion of (rac)-tramadol.HCl-celecoxib (1:1).

20 In one embodiment of the present invention, (rac)-tramadol HCl and celecoxib and a pharmaceutically acceptable excipient are dissolved in a suitable solvent or mixtures thereof which is capable of dissolving (rac)-tramadol.HCl and celecoxib and the pharmaceutically acceptable excipient.

Within the context of the invention, the pharmaceutically acceptable excipient is as disclosed  
25 in the above embodiments.

The suitable solvents of the above embodiment is selected from chlorinated solvents, polar protic solvents and polar aprotic solvents. The chlorinated solvents may include but are not limited to dichloromethane, and chloroform. The polar protic solvents may include, but are not limited to methanol, ethanol, propanol, butanol, 2-butanol, isopropanol, 3-methyl-1-

butanol, 2-methyl-1-propanol, and 1-pentanol. The polar aprotic solvents may include but are not limited to tetrahydrofuran, dioxane, dimethyl sulfoxide, acetonitrile, dimethyl formamide and N-methyl pyrrolidone. The solvents may be mixtures thereof.

5 Next, the solvent is removed from the resulting clear solution to isolate the amorphous solid dispersion of (rac)-tramadol .HCl-celecoxib (1:1) with the pharmaceutically acceptable excipient. The removal solvent can be carried out by processes known in the art such as evaporation, distillation, spray drying, lyophilization, or agitated thin film drying, preferably distillation.

10 In another aspect, the present invention provides a process for the preparation of an amorphous solid dispersion of (rac)-tramadol.HCl - celecoxib (1:1) comprising the steps of:

- a) dissolving (rac)-tramadol.HCl, celecoxib in a suitable solvent or mixtures thereof,
- b) adding a pharmaceutically acceptable excipient, and
- c) removing the solvent to isolate amorphous solid dispersion of (rac)-tramadol.HCl-celecoxib (1:1).

15 In one embodiment of the present invention, (rac)-tramadol HCl and celecoxib dissolved in a suitable solvent or mixtures thereof which is capable of dissolving (rac)-tramadol.HCl and celecoxib.

20 The suitable solvents of the above embodiment is selected from chlorinated solvents, polar protic solvents and polar aprotic solvents. The chlorinated solvents may include but are not limited to dichloromethane, and chloroform. The polar protic solvents may include, but are not limited to methanol, ethanol, propanol, butanol, 2-butanol, isopropanol, 3-methyl-1-butanol, 2-methyl-1-propanol, and 1-pentanol. The polar aprotic solvents may include but are not limited to tetrahydrofuran, dioxane, dimethyl sulfoxide, acetonitrile, dimethyl formamide and N-methyl pyrrolidone. The solvents may be mixtures thereof.

25 In another embodiment, the pharmaceutically acceptable excipient is added to the (rac)-tramadol HCl and celecoxib mixture.

With in the context of the invention, the pharmaceutically acceptable excipient is as disclosed in the above embodiments.

Next, the solvent was removed from the resulting clear solution to isolate the amorphous solid dispersion of (rac)-tramadol.HCl-celecoxib (1:1) with the pharmaceutically acceptable excipient. The removal solvent can be carried out by processes known in the art, such as evaporation, distillation, spray drying, lyophilization, or agitated thin film drying, preferably distillation.

#### DSC:

The MDSC data of amorphous form of (rac)-tramadol.HCl-celecoxib shows a glass transition temperature (T<sub>g</sub>) of 59.8 °C above which a recrystallization exothermic event is observed at about 120 °C which converts the material to a crystalline form that finally melts at about 167 °C. Figure 6 shows the modulated DSC thermogram of (rac)-tramadol.HCl-celecoxib amorphous Form.

#### IR spectrum:

Comparison of the FTIR spectra of co-crystal/crystalline form of US8598152 and amorphous (rac)-tramadol.HCl-celecoxib (1:1) of present invention. The Figure 7 shows comparative FTIR spectra.

#### Solid state NMR:

The solid-state NMR spectra of the amorphous complex is similar to the US8598152 co-crystal/crystalline form (except the broadening) pointing out that the complex integrity is intact in the amorphous complex (Figure 8). Also, <sup>13</sup>C SSNMR spectra of an 1:1 admixture of (rac)-tramadol.HCl and celecoxib is comparable to individual spectra of (rac)-tramadol.HCl and celecoxib with no change in chemical shifts corresponding to functional groups such as -CH<sub>3</sub>, -OCH<sub>3</sub>, aromatic-carbons and N-methyl groups, etc., further confirming the amorphous form as a molecular complex but not a physical mixture of individual APIs. Figure 8 shows a comparison of <sup>13</sup>C SSNMR data of a 1:1 admixture of (rac)-tramadol.HCl (A) and celecoxib (B), 1:1 complex of (rac)-tramadol.HCl-celecoxib amorphous form, 1:1 co-crystal of (rac)-tramadol.HCl-celecoxib crystalline form, (rac)-tramadol.HCl (A) and celecoxib (B).

#### Variable temperature (VT) PXRD data:

Variable temperature PXRD data of (rac)-tramadol.HCl-celecoxib amorphous form was studied from 30 °C to 180 °C followed by cooling to 30 °C. The amorphous form is stable up

to 120°C and above this temperature it converts to crystalline form which melts at about 180 °C and then converts to amorphous which upon re-cooling remains amorphous. Figure 9 shows the variable temperature PXRD data of the (rac)-tramadol.HCl-celecoxib amorphous form.

#### Indicative stability:

- 5 In another embodiment, the physical stability of 1:1 co-crystal of (rac)-tramadol.HCl-celecoxib amorphous form was determined by storing the samples at 40°C and 75% relative humidity (RH), 25°C and 60% relative humidity (RH) and 5±3°C for six months and the samples were analyzed by PXRD. The results are shown in below Table 1. The 1:1 co-crystal of (rac)-tramadol.HCl-celecoxib amorphous form was found to be physically stable at 5±3°C up to six  
10 months.

**Table 1**

| Stability Condition | Duration | PXRD      |
|---------------------|----------|-----------|
| 5±3°C               | Initial  | Amorphous |
|                     | 2 months | Stable    |
|                     | 6 months | Stable    |

The Figure 10 shows the PXRD overlay of amorphous form storage at 5±3°C. (top) sample after 6months, (middle) after 2 months and (bottom) the initial sample.

#### 15 Solubility:

The solubility of a drugs play a major role in in formulating them. Drugs having a low solubility are a major problem encountered with formulation development. Any drug to be absorbed must be present in the form of solution at the site of absorption. The amorphous solid dispersion of (rac)-tramadol.HCl-celecoxib as described herein has enhanced solubility as shown in table 2.

- 20 The solubility of amorphous and crystalline form of 1:1 co-crystal of (rac)-tramadol.HCl - celecoxib were determined in water and different aqueous buffers of different pH at 37 °C. The results are shown in the following Table 2. The 1:1 co-crystal of (rac)-tramadol.HCl-celecoxib amorphous form shows about a 4-5 fold increase in buffer and aqueous solubility in comparison with the crystalline form.

Table 2

| S.No | Buffer pH (USP) | Solubility at 37°C (mg/mL)                     |                |
|------|-----------------|------------------------------------------------|----------------|
|      |                 | 1:1 Co-crystal of (rac)-tramadol.HCl celecoxib |                |
|      |                 | Crystalline form reported in US8598152         | Amorphous form |
| 1.   | pH 1.2          | 0.26                                           | 1.23           |
| 2.   | pH 4.5          | 0.23                                           | 1.17           |
| 3.   | pH 6.0          | 0.24                                           | 1.18           |
| 4.   | pH 6.8          | 0.24                                           | 1.06           |
| 5.   | pH 8.0          | 0.24                                           | 1.08           |
| 6.   | Water           | 0.25                                           | 1.17           |

In view of the above description and the examples below, one of ordinary skill in the art will be able to practice the invention as claimed without undue experimentation. The foregoing will be better understood with reference to the following examples that detail certain procedures for the preparation of molecules according to the present invention. All references made to these examples are for the purposes of illustration. The following examples should not be considered exhaustive, but merely illustrative of only a few of the many aspects and embodiments contemplated by the present disclosure.

#### 10 Examples:

**Example 1:** Five grams of (rac)-tramadol.HCl and 6.36 g of celecoxib were dissolved in 25 mL of methanol at 20-30°C. The resulting clear solution was filtered through Hyflo filter aid to remove any undissolved particulate and the solution was subjected to spray-drying in a laboratory spray-dryer (model: Buchi B-290) with a feed rate of solution at 5ml/min and an inlet temperature at 75°C with 100% aspiration to yield an amorphous form of (rac)-tramadol.HCl-celecoxib (1:1).

Yield: 9.1 g

**Example 2:** Twenty grams of a 1:1 co-crystal of tramadol.HCl-celecoxib were dissolved in 100 mL of methanol at 20-30 °C. The resulting clear solution was filtered through Hyflo filter aid to remove any undissolved particulate and the solution was subjected to spray-drying in a laboratory spray-dryer (model: Buchi B-290) with a feed rate of solution 5ml/min and an inlet temperature at 75°C with 100% aspiration to yield the amorphous form of (rac)-tramadol.HCl-celecoxib (1:1).

Yield: 17.1 g

**Example 3:** 0.5 gram of (rac)-Tramadol.HCl, 0.636 g of celecoxib and 1.136 g of plasdone S-630 were dissolved in 6 mL of methanol at 25±5°C. The resulting clear solution was filtered through Hyflo filter aid to remove any undissolved particulates, the filter aid washed with methanol, and the solvent was then distilled off under vacuum at 50 °C to yield a 1:1:1 amorphous solid dispersion of (rac)-tramadol.HCl-celecoxib with plasdone S-630.

Yield: 1.81g

**Example 4:** 0.5 gram of (rac)-Tramadol.HCl, 0.636 g of celecoxib and 1.136 g of povidone-K30 were dissolved in 6 mL of methanol at 25±5 °C. The resulting clear solution was filtered through Hyflo filter aid to remove any undissolved particulates, the filter aid was washed with methanol, and the solvent was then distilled off under vacuum at 50°C to yield a 1:1:1 amorphous solid dispersion of (rac)-tramadol.HCl-celecoxib with povidone K-30.

Yield: 1.7g

**Example 5:** 0.5 gram of (rac)-Tramadol.HCl and 0.636 g of celecoxib were dissolved in 3 mL of methanol at 25±5°C. The resulting clear solution was filtered through Hyflo filter aid to remove any undissolved particulates, and the filter aid was washed with methanol. To the resulting clear solution was added 1.136 g of silicon dioxide (Aeroperl 300) and the solvent was distilled off under vacuum at 50°C to yield 1:1:1 amorphous solid dispersion of (rac)-tramadol.HCl-celecoxib with silicon dioxide.

Yield: 1.5g

**We claim:**

1. An amorphous form of (rac)-tramadol.HCl-celecoxib (1:1).
2. An amorphous form of (rac)-tramadol.HCl-celecoxib (1:1) characterized by a PXRD pattern substantially as depicted in Figure 1 and Figure 2.
3. A process for the preparation of an amorphous form of (rac)-tramadol.HCl-celecoxib (1:1) comprising the steps of:
  - a) dissolving (rac)-tramadol.HCl and celecoxib in an organic solvent or mixtures thereof; and
  - b) removing the solvent to isolate the amorphous form of (rac)-tramadol.HCl-celecoxib (1:1)
4. A process for the preparation of an amorphous form of (rac)-tramadol.HCl-celecoxib (1:1) comprising the steps of:
  - a) dissolving a 1:1 co-crystal of (rac)-tramadol.HCl-celecoxib in an organic solvent or mixtures thereof;
  - b) removing the solvent to isolate amorphous (rac)-tramadol.HCl-celecoxib (1:1).
5. The process as claimed in claim 3 and 4, wherein the organic solvent or mixtures thereof is selected from the solvent which is capable of dissolving (rac)-tramadol HCl and celecoxib.
6. The process as claimed in claim 5, wherein the organic solvent is selected from dichloromethane, chloroform, methanol, ethanol, propanol, butanol, 2-butanol, isopropanol, 3-methyl-1-butanol, 2-methyl-1-propanol, 1-pentanol, tetrahydrofuran, dioxane, dimethyl sulfoxide, acetonitrile, dimethyl formamide, N-methyl pyrrolidone, and mixtures thereof.
7. The process as claimed in claim 3 and 4, wherein the solvent is removed by evaporation, distillation, spray drying, lyophilization, or agitated thin film drying.

8. An amorphous solid dispersion of (rac)-tramadol.HCl-celecoxib (1:1) with at least one pharmaceutically acceptable excipient.
9. The amorphous solid dispersion as claimed in claim 8, wherein the pharmaceutically acceptable excipient is selected from diluents, lubricants, binders, glidants, stabilizers, surface active agents, anti-adherents, opacifiers, solvents, colorants, pigments, anti-foam agents, polishing agents, starches, lactose, mannitol, cellulose derivatives, confectioner's sugar, binders, powdered acacia, gelatin, guar gum, sodium starch glycolate, colloidal silicon dioxide, carbomers, methylcelluloses, polymethacrylates, carmellose calcium, carboxymethyl starch sodium, croscarmellose sodium, crospovidones, stearates, phospholipids, sorbitan esters, aliphatic alcohols, and polyethylene glycol ethers.
10. The pharmaceutical excipient as claimed in claim 8, wherein the pharmaceutically acceptable excipient is selected from a 60:40 linear random copolymer of N-vinyl-2-pyrrolidone, polyvinylpyrrolidone, and silicon dioxide.
11. A process for the preparation of an amorphous solid dispersion of (rac)-tramadol.HCl and celecoxib (1:1) comprising the steps of:
  - a) dissolving (rac)-tramadol.HCl, celecoxib and a pharmaceutically acceptable excipient in a suitable solvent or mixtures thereof, and
  - b) removing the solvent to isolate the amorphous solid dispersion of (rac)-tramadol.HCl-celecoxib (1:1).
12. A process for the preparation of an amorphous solid dispersion of (rac)-tramadol.HCl and celecoxib (1:1) comprising the steps of:
  - a) dissolving (rac)-tramadol.HCl, celecoxib in a suitable solvent or mixtures thereof,
  - b) adding a pharmaceutically acceptable excipient, and
  - c) removing the solvent to isolate the amorphous solid dispersion of (rac)-tramadol.HCl-celecoxib (1:1).
13. The process as claimed in claim 11 and 12, wherein the pharmaceutically acceptable excipient is selected from diluents, lubricants, binders, glidants, stabilizers, surface

active agents, anti-adherents, opacifiers, solvents, colorants, pigments, anti-foam agents, polishing agents, starches, lactose, mannitol, cellulose derivatives, confectioner's sugar, binders, powdered acacia, gelatin, guar gum, sodium starch glycolate, colloidal silicon dioxide, carbomers, methylcelluloses, polymethacrylates, carmellose calcium, carboxymethyl starch sodium, croscarmellose sodium, crospovidones, stearates, phospholipids, sorbitan esters, aliphatic alcohols, and polyethylene glycol ethers.

14. The process as claimed in claim 11 and 12, wherein the pharmaceutically acceptable excipient is selected from a 60:40 linear random copolymer of N-vinyl-2-pyrrolidone, polyvinylpyrrolidone, and silicon dioxide.
15. The process as claimed in claim 11 and 12, wherein the suitable solvent or mixture thereof is selected from a solvent capable of dissolving (rac)-tramadol.HCl; celecoxib.
16. The process as claimed in claim 15, wherein the suitable solvent is selected from chlorinated solvents selected from dichloromethane, chloroform, methanol, ethanol, propanol, butanol, 2-butanol, isopropanol, 3-methyl-1-butanol, 2-methyl-1-propanol, 1-pentanol, tetrahydrofuran, dioxane, dimethyl sulfoxide, acetonitrile, dimethyl formamide, N-methyl pyrrolidone, and mixtures thereof.
17. The process as claimed in claim 11 and 12, wherein the solvent is removed by evaporation, distillation, spray drying, lyophilization, or agitated thin film drying.

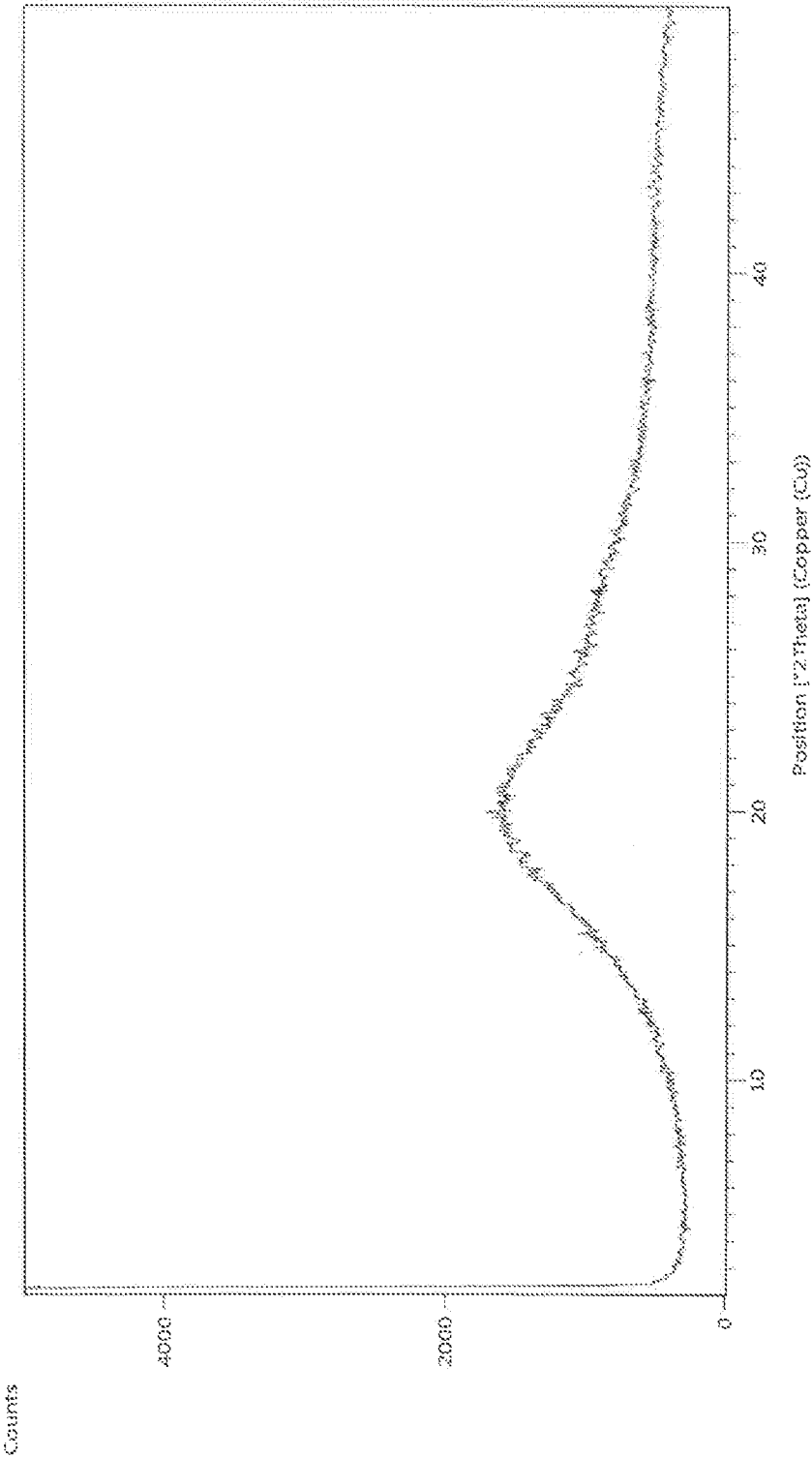


Figure: 1

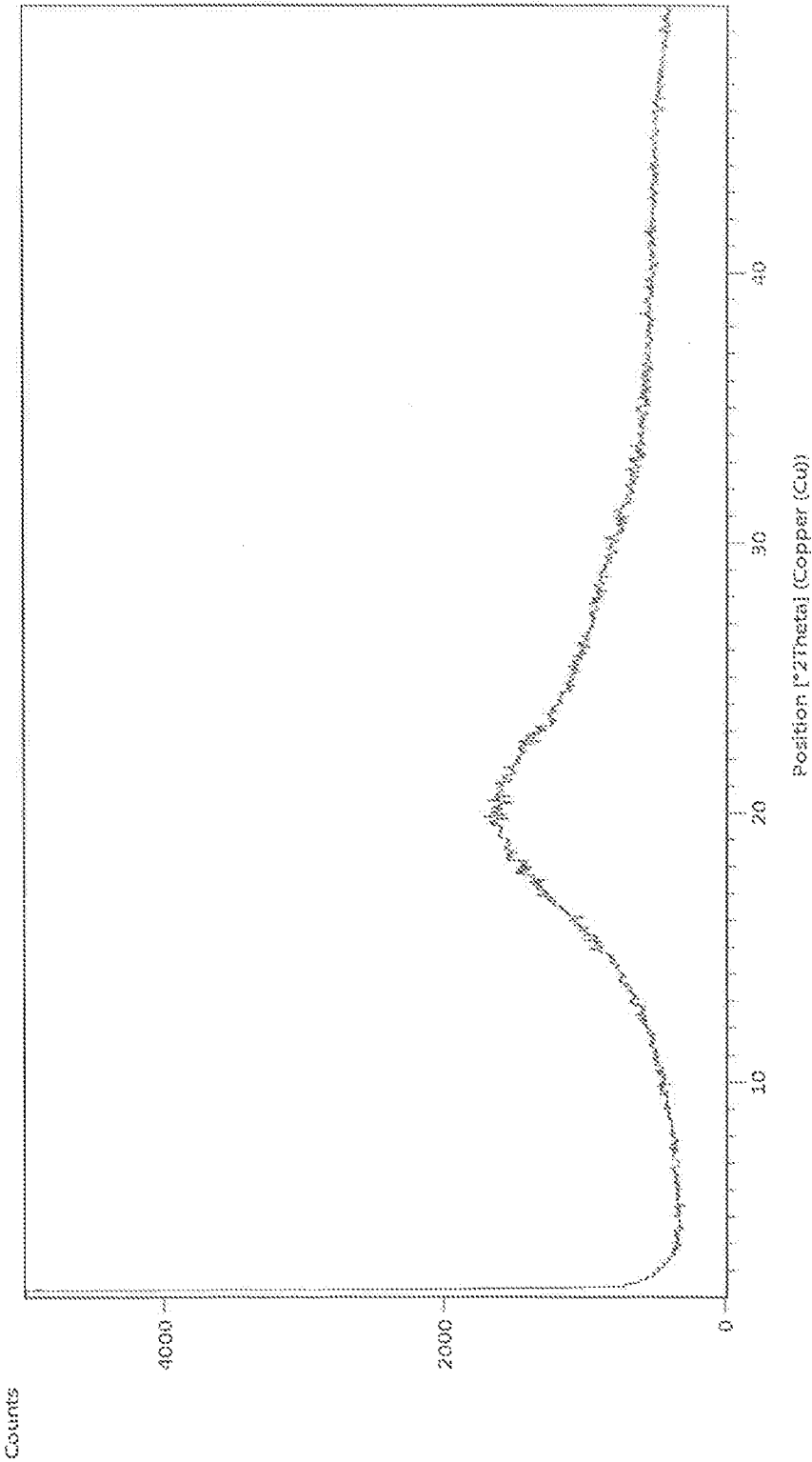


Figure: 2

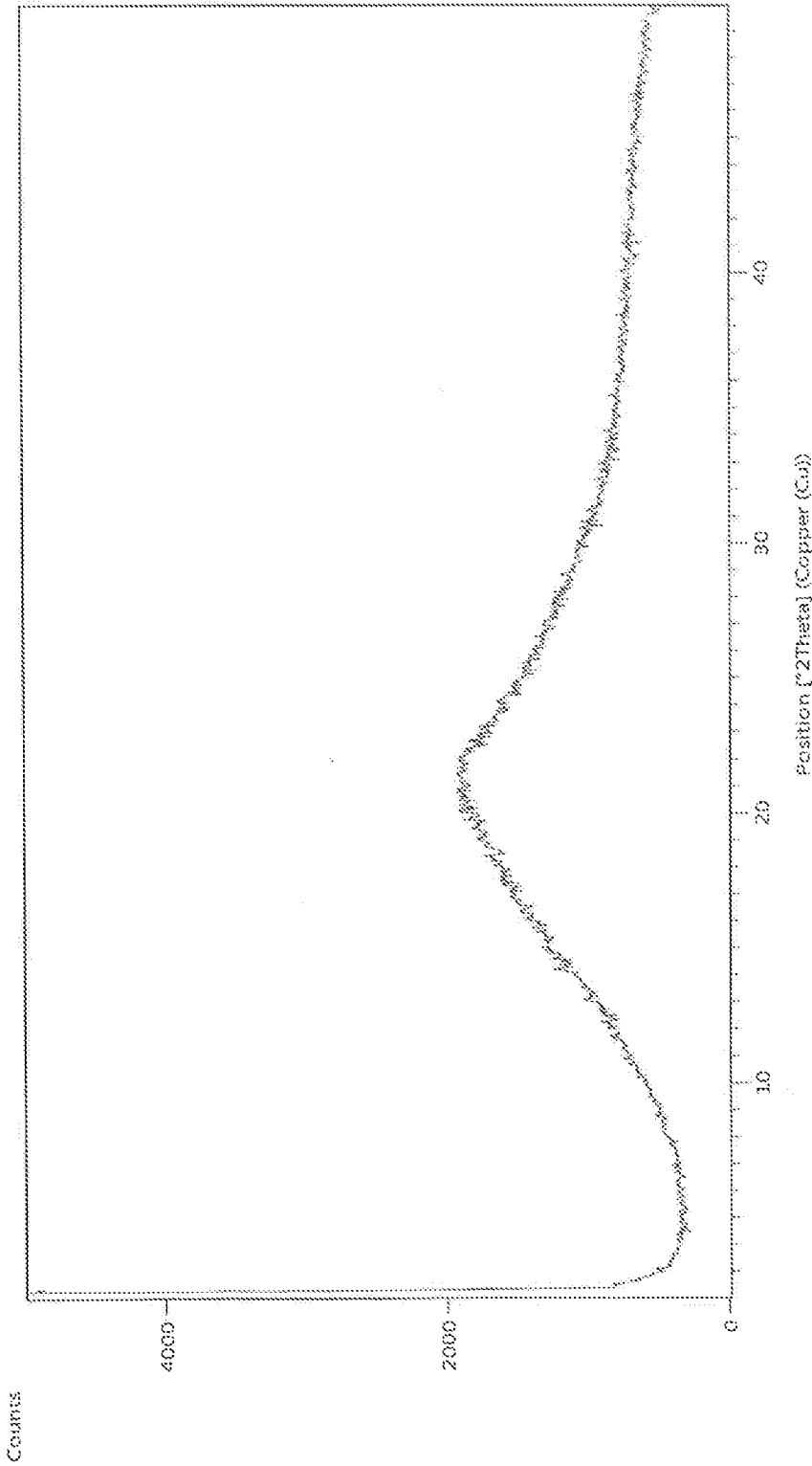


Figure: 3

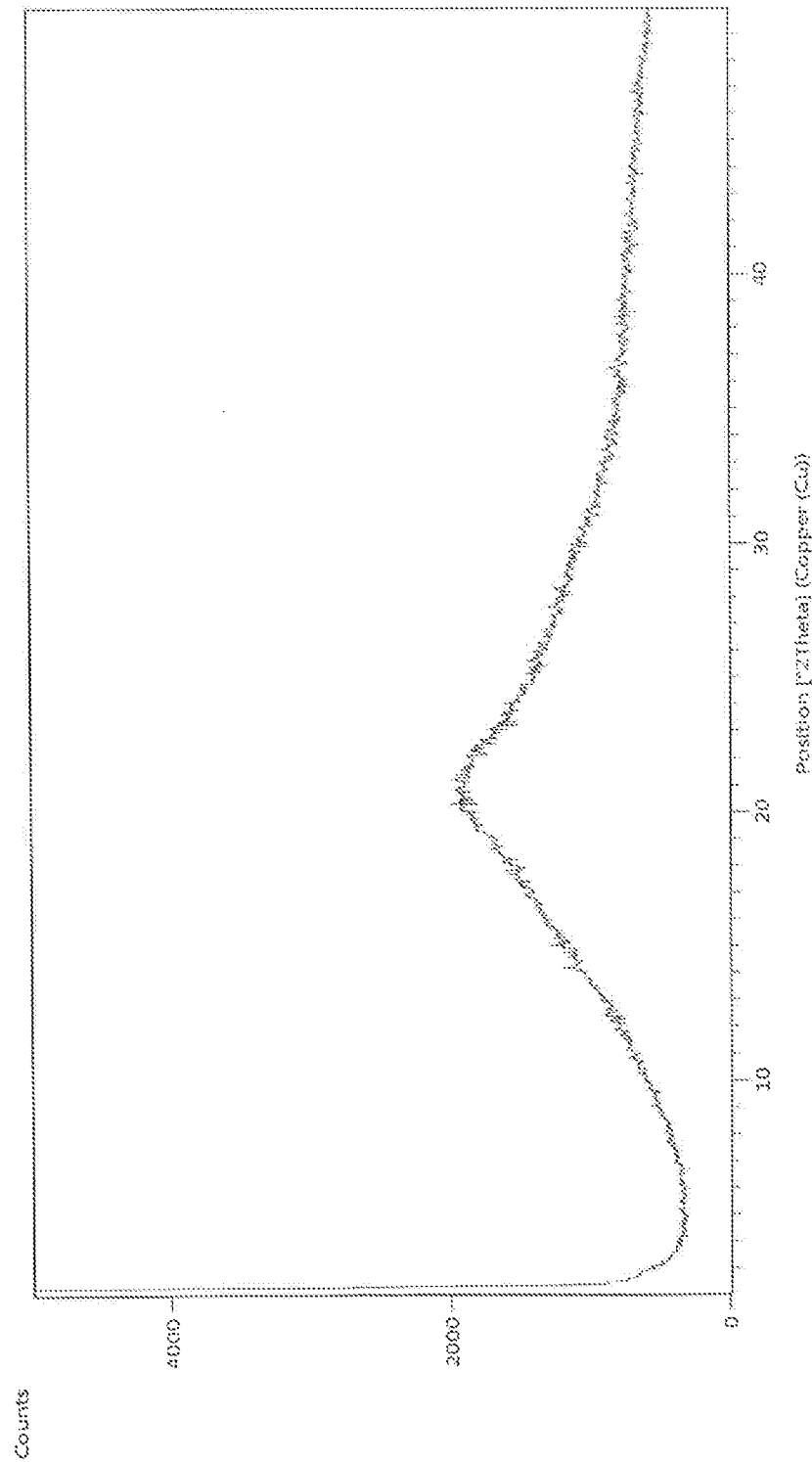


Figure: 4

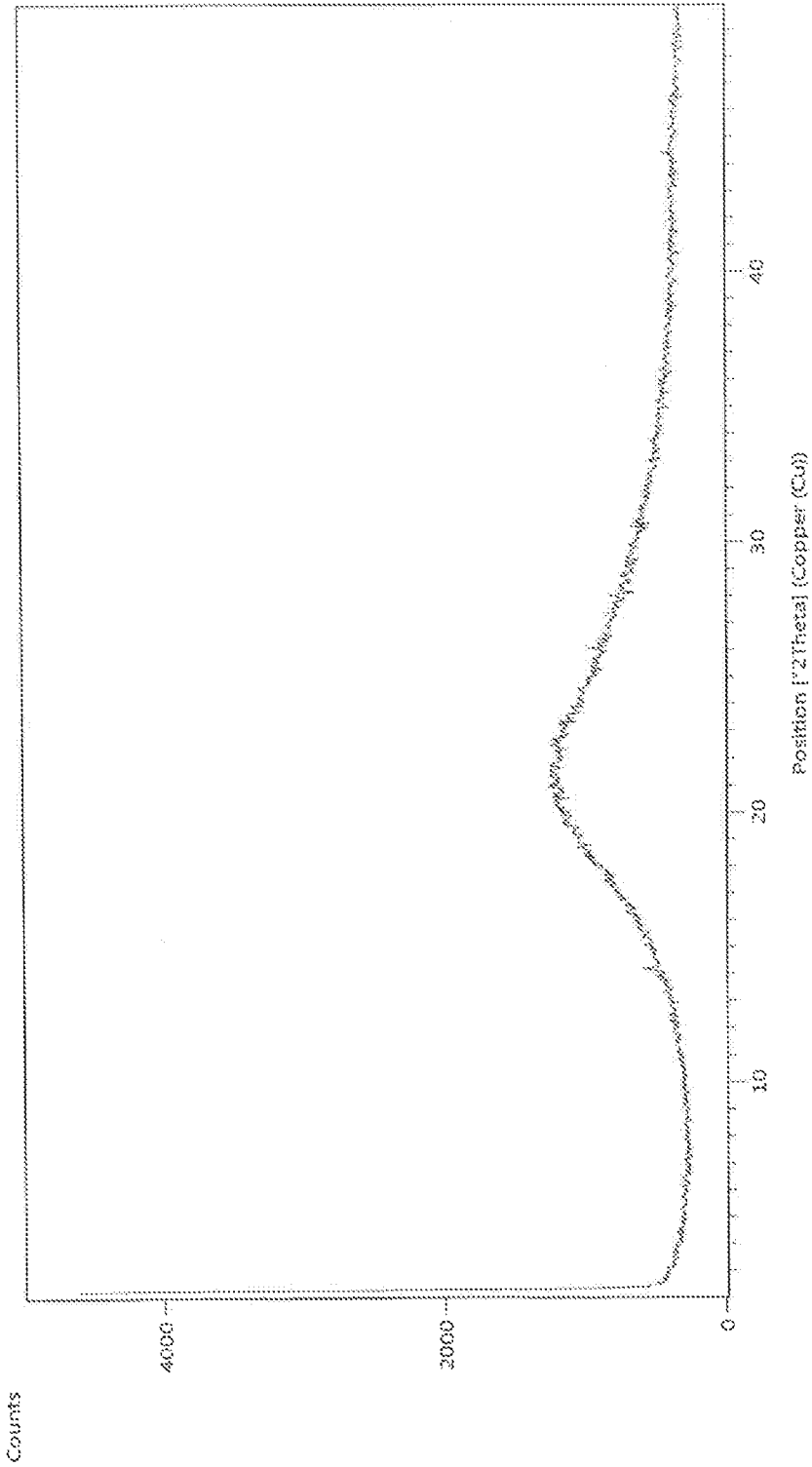


Figure: 5

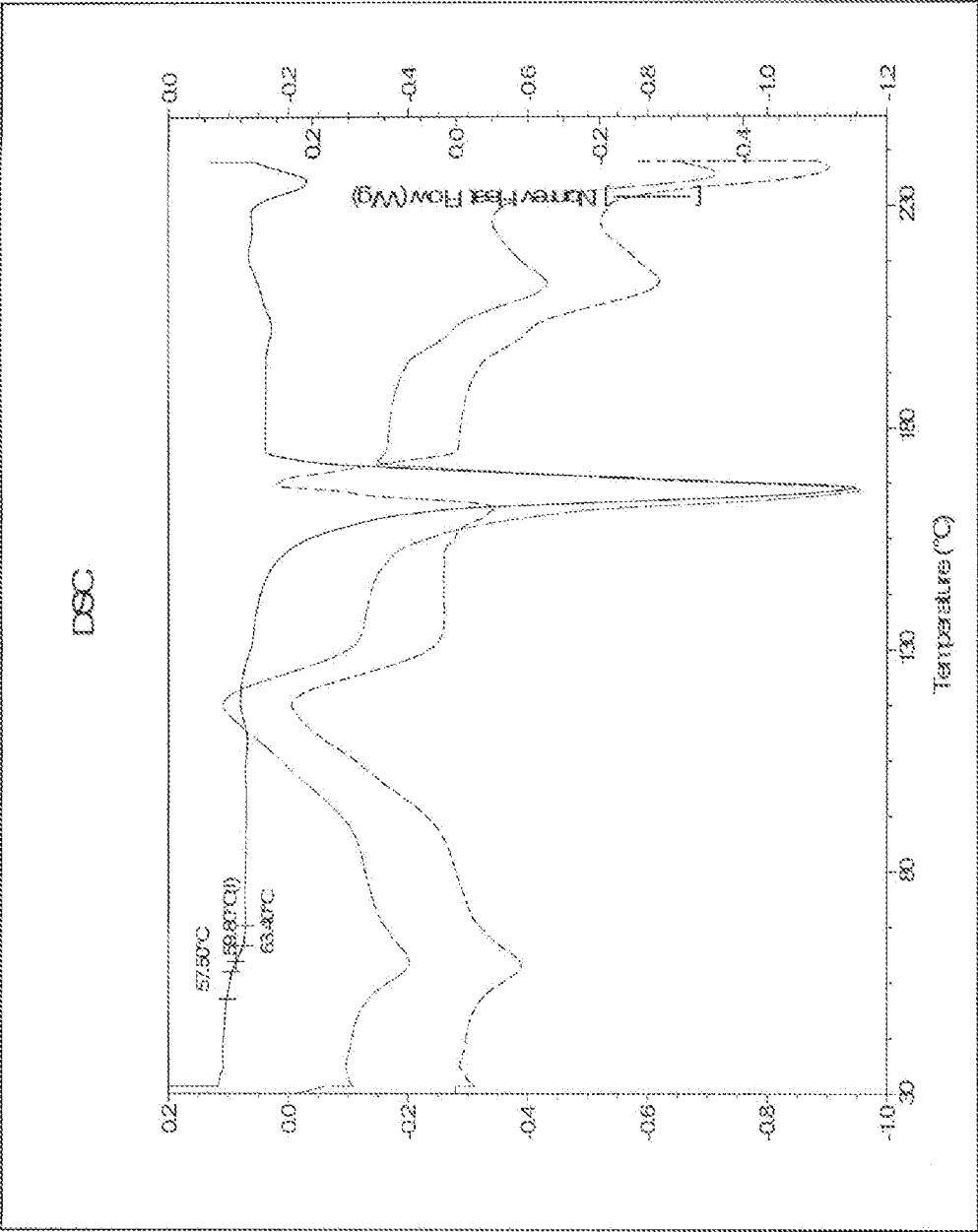


Figure: 6

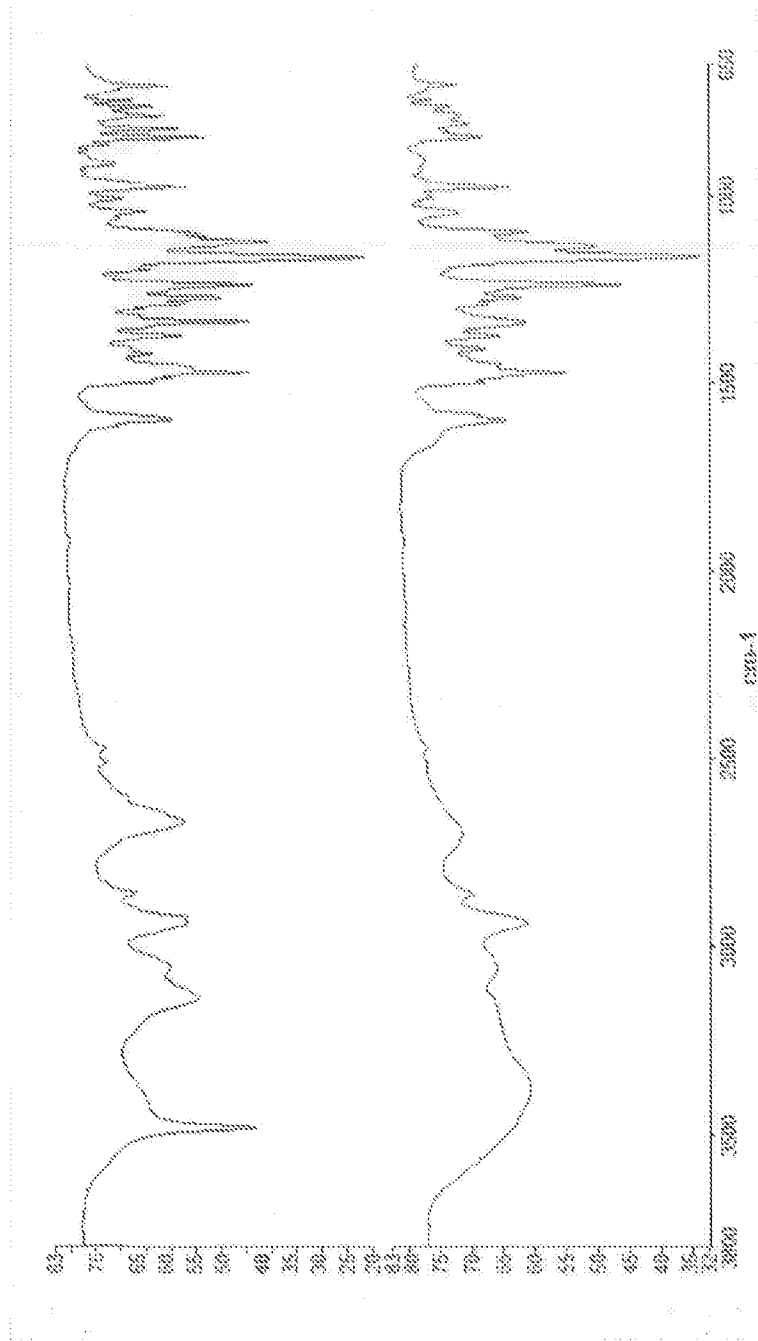


Figure: 7

8/10

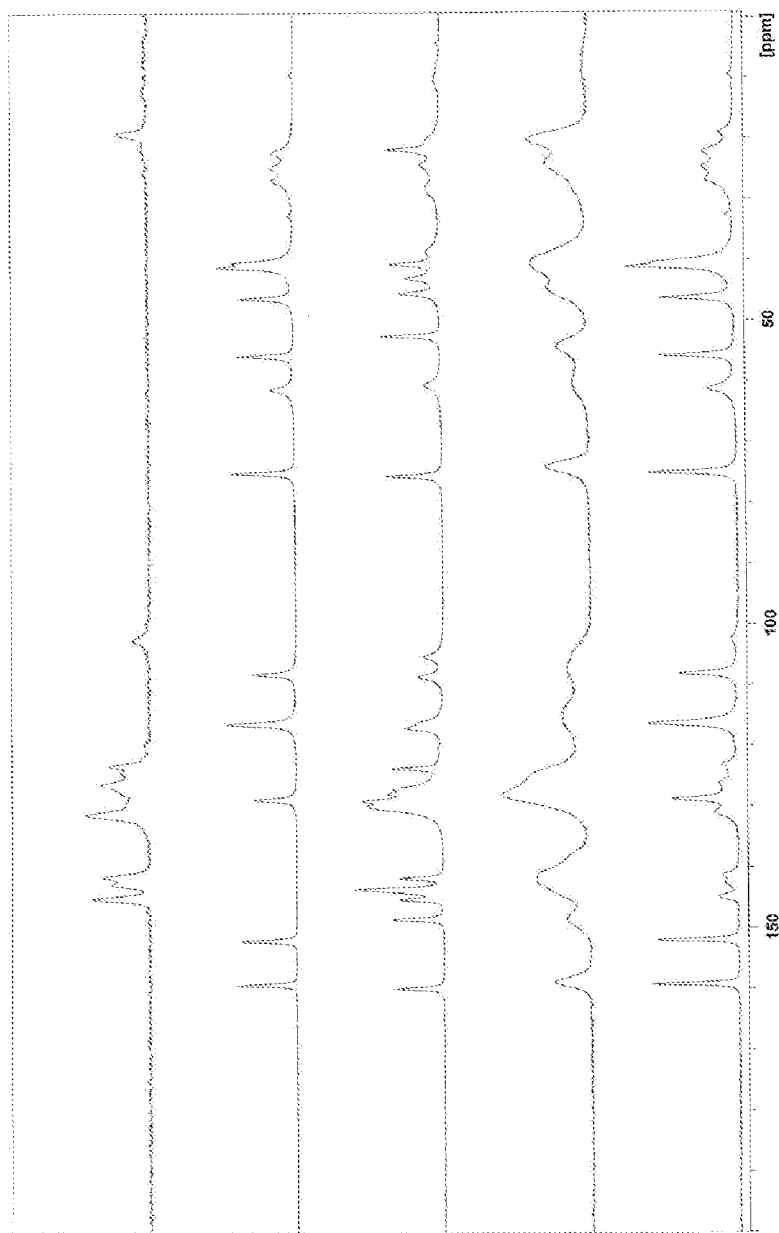


Figure: 8

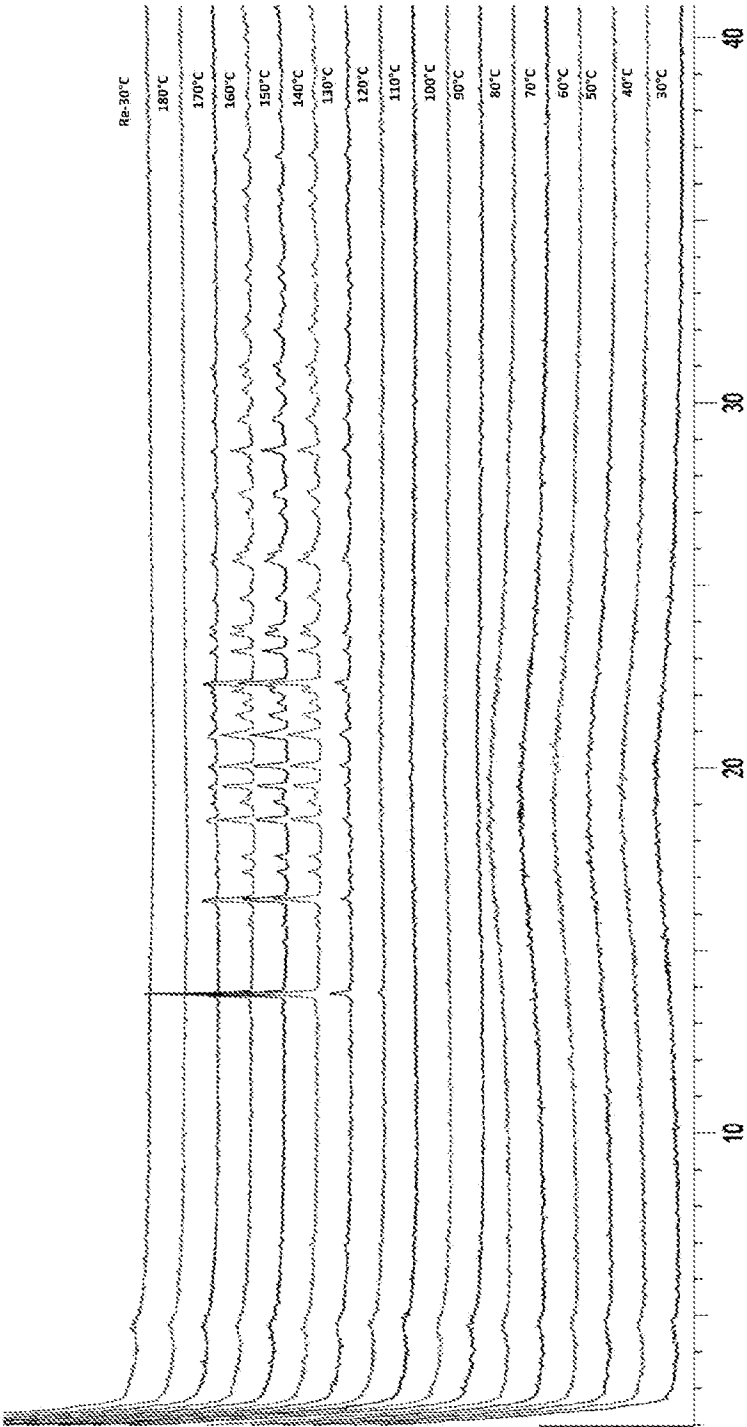


Figure: 9

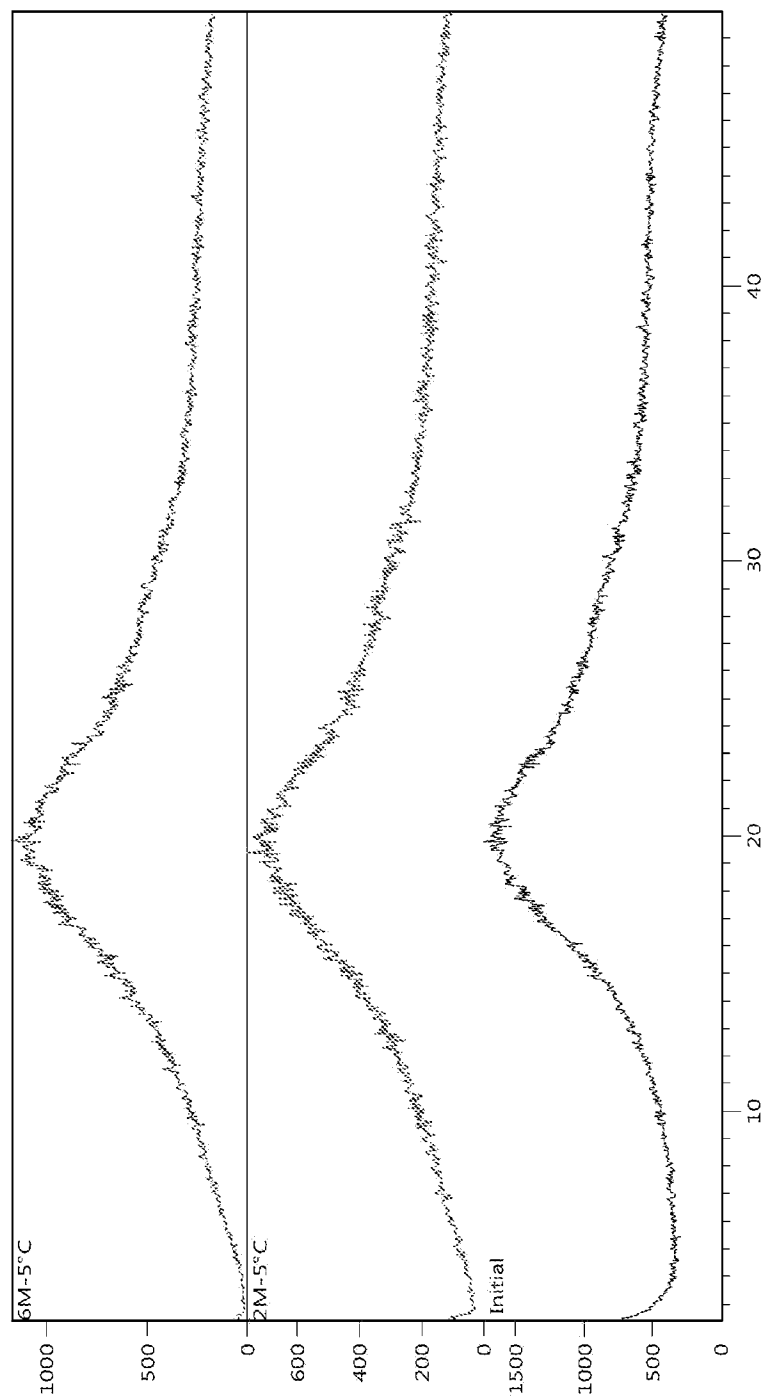


Figure: 10

## INTERNATIONAL SEARCH REPORT

International application No  
PCT/IN2019/050904

## A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D231/12 C07C217/74 A61K9/00  
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)

C07D C07C 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, 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         | US 8 598 152 B2 (PLATA SALAMAN CARLOS RAMON [ES]; TESSON NICOLAS [ES] ET AL.)<br>3 December 2013 (2013-12-03)<br>cited in the application<br>claim 1                                                                                                                                   | 1-17                  |
| X         | -----<br>CARMEN ALMANSA ET AL: "A Novel API-API Co-crystal for the Treatment of Pain", CRYSTAL GROWTH & DESIGN., vol. 17, no. 4, 20 March 2017 (2017-03-20), pages 1884-1892, XP055636403, US<br>ISSN: 1528-7483, DOI: 10.1021/acs.cgd.6b01848<br>wet grinding, p.1886<br>-----<br>-/- | 1,2                   |



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

17 February 2020

Date of mailing of the international search report

25/02/2020

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040,  
Fax: (+31-70) 340-3016

Authorized officer

Schuemacher, Anne

## INTERNATIONAL SEARCH REPORT

International application No  
PCT/IN2019/050904

| C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT |                                                                                                                                                                                                                                                                                                                                                                                   |                       |
|------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| Category*                                            | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                                                                                                                                                                                                                | Relevant to claim No. |
| Y                                                    | <p>YU L ED - KWON ICK CHAN ET AL:<br/>"AMORPHOUS PHARMACEUTICAL SOLIDS:<br/>PREPARATION, CHARACTERIZATION AND<br/>STABILIZATION",<br/>ADVANCED DRUG DELIVERY REVIEWS, ELSEVIER,<br/>AMSTERDAM, NL,<br/>vol. 48, no. 1, 16 May 2001 (2001-05-16),<br/>pages 27-42, XP009065056,<br/>ISSN: 0169-409X, DOI:<br/>10.1016/S0169-409X(01)00098-9<br/>Introduction on p.28<br/>-----</p> | 1-17                  |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IN2019/050904

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s) | Publication<br>date |
|-------------------------------------------|---------------------|----------------------------|---------------------|
| US 8598152                                | B2                  | 03-12-2013                 |                     |
|                                           |                     | AU 2009304235 A1           | 22-04-2010          |
|                                           |                     | CA 2737754 A1              | 22-04-2010          |
|                                           |                     | CN 102186465 A             | 14-09-2011          |
|                                           |                     | CY 1118374 T1              | 28-06-2017          |
|                                           |                     | DK 2349238 T3              | 12-12-2016          |
|                                           |                     | EP 2177215 A1              | 21-04-2010          |
|                                           |                     | EP 2349238 A1              | 03-08-2011          |
|                                           |                     | ES 2603962 T3              | 02-03-2017          |
|                                           |                     | HR P20161526 T1            | 16-12-2016          |
|                                           |                     | HU E030976 T2              | 28-06-2017          |
|                                           |                     | IL 211785 A                | 31-07-2016          |
|                                           |                     | JP 5645830 B2              | 24-12-2014          |
|                                           |                     | JP 2012505847 A            | 08-03-2012          |
|                                           |                     | KR 20110069860 A           | 23-06-2011          |
|                                           |                     | LT 2349238 T               | 27-12-2016          |
|                                           |                     | MX 336318 B                | 14-01-2016          |
|                                           |                     | MY 156285 A                | 29-01-2016          |
|                                           |                     | NZ 591873 A                | 21-12-2012          |
|                                           |                     | PL 2349238 T3              | 30-06-2017          |
|                                           |                     | PT 2349238 T               | 24-11-2016          |
|                                           |                     | RU 2011119608 A            | 27-11-2012          |
|                                           |                     | SM T201600439 B            | 10-01-2017          |
|                                           |                     | UA 109534 C2               | 10-09-2015          |
|                                           |                     | US 2011257134 A1           | 20-10-2011          |
|                                           |                     | US 2012172398 A1           | 05-07-2012          |
|                                           |                     | US 2014057879 A1           | 27-02-2014          |
|                                           |                     | US 2014350110 A1           | 27-11-2014          |
|                                           |                     | US 2015196503 A1           | 16-07-2015          |
|                                           |                     | US 2015196504 A1           | 16-07-2015          |
|                                           |                     | US 2017000806 A1           | 05-01-2017          |
|                                           |                     | US 2017027965 A1           | 02-02-2017          |
|                                           |                     | US 2019231800 A1           | 01-08-2019          |
|                                           |                     | WO 2010043412 A1           | 22-04-2010          |
|                                           |                     | ZA 201102762 B             | 28-12-2011          |
| -----                                     |                     |                            |                     |