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(54) Title: LONG-ACTING INJECTABLE FORMULATIONS AND CRYSTALLINE FORMS OF BUPRENORPHINE DERIVATIVES

(57) Abstract: This disclosure relates to crystalline forms of 3-acyl-buprenorphine derivatives and sustained release injectable pharmaceutical compositions for treatment of opioid dependence, pain or depression, including an aqueous suspension of crystalline 3-acyl-buprenoprhine, or a pharmaceutically acceptable salt thereof, wherein the composition does not include an organic solvent, a polylactide polymer, a polyglycolide polymer, or a copolymer of polylactide and polyglycolide. This disclosure also includes 3-acyl-buprenoprhine or a pharmaceutically acceptable salt thereof prepared in a controlled release matrix, including poly (lactide-co-glycolide), sucrose acetoisobutyrate, lecithin, diolein and a combination of two or more thereof.

LONG-ACTING INJECTABLE FORMULATIONS AND CRYSTALLINE FORMS OF BUPRENORPHINE DERIVATIVES

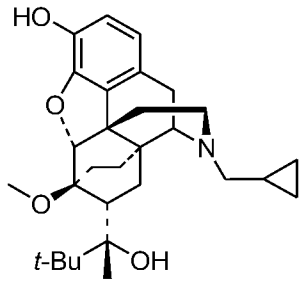
BACKGROUND

Technical Field

[0001] The present disclosure relates generally to crystalline forms and formulations of buprenorphine derivatives. In particular, the present disclosure relates to an injectable composition comprising buprenorphine derivatives, or the metabolite or prodrug thereof, its uses, as well as methods of treatment using the same for opioid dependence, pain, and depression.

Background

[0002] Buprenorphine, (5α,7α(s))-17-cyclopropylmethyl)-α-(1,1-dimethylethyl)-4,5-epoxy-18,19-dihydro-3-hydroxy-6-methoxy-α-methyl-6,14-ethenomorphinan-7-methanol, is a derivative of thebaine, which belongs to the family of opioid alkaloids. The structure of buprenorphine is shown by the following formula (Formula I) with a molecular weight of 467.64:



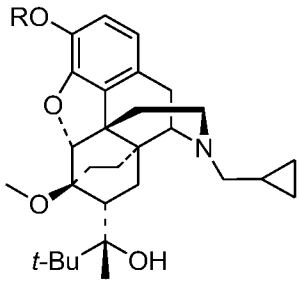
Formula I (buprenorphine).

[0003] As a partial and potent μ-receptor agonist, buprenorphine has a higher affinity to compete with other full agonists, such as morphine, methadone, etc. With 25 to 40 times higher potency than that of morphine, buprenorphine is indicated for the treatment of moderate to severe chronic pain, and pre-operative analgesia in several dosage forms, e.g., Buprenex® (intramuscular or intravenous injection), Norspan®, Butrans® (a transdermal patch), Temgesic® (a sublingual tablet), and Belbuca® (a buccal film). The therapeutic concentrations (C_{max}) of Butrans in healthy subjects range from 0.1 to 0.5 ng/mL, corresponding to a dose of 5 to 20 μg/hour. In addition, various products of buprenorphine hydrochloride are approved for treating opioid addiction in higher dosages, e.g., Subutex® (a sublingual tablet), Sublocade™ (a subcutaneous injection), and some are combination products of buprenorphine hydrochloride and naloxone hydrochloride, e.g., Suboxone® (a sublingual film, in a 4:1 ratio of buprenorphine hydrochloride and naloxone hydrochloride),

Zubsolv® (a sublingual tablet), and Bunavail® (a buccal film). The therapeutic concentrations (C_{max}) of Suboxone range from 1 to 6 ng/mL, corresponding to a dose of 2 to 16 mg sublingual films.

[0004] Furthermore, buprenorphine is also a potent antagonist of the κ-opioid receptor, and this could result in the reduction of tolerance and has an antidepressant effect. Recently, buprenorphine is utilized in a combination product, ALK-5461, which consists of buprenorphine (a κ-receptor antagonist) and samidorphan (a μ-receptor agonist) and has been announced for an anti-depressant effect.

[0005] In previous studies, various buprenorphine derivatives were disclosed. Among them, modifications of the phenol group by forming ester bond linkages are more common. These ester derivatives are synthesized and compared with buprenorphine and the hydrochloride salt thereof. In 1995, Stinchcomb *et al.* published an article related to 3-alkyl ester derivatives of buprenorphine in *Pharm. Res. (1995), 12, 1526-1529* (Formula II below, R = acetyl, propanoyl, butanoyl, pentanoyl, hexanoyl, heptanoyl). These derivatives were viewed as prodrugs and purported to improve the physiochemical characteristics of the parent compound to increase its relative permeability through skin in the following articles: *Biol. Pharm. Bull. (1996), 19, 263-267* and *Pharm. Res. (1996), 13, 1519-1523.*



Formula II

[0006] Thereafter, several C3-esterfied buprenorphine derivatives and applications thereof have been disclosed in various patents. For example, U.S. Patent No. 7,084,150, issued to Euro-Celtique S.A., describes a huge family of buprenorphine prodrugs and analogs, which include ester bonds or ether bond modified derivatives. EP Patent No. 1422230, issued to Jhi-Joung Wang, discloses dimerized derivatives of buprenorphine and similar alkylcarbonyl derivatives. Prodrug strategy and oil carrier of these derivatives were introduced by an intramuscular or subcutaneous injection, which displays prolonged analgesia actions for 5 hours to 96 hours.

[0007] A series of buprenorphine ester derivatives is also described in U.S. Patent No. 7,964,610, issued to Reckitt Benckiser Healthcare (UK) Limited. Buprenorphine was modified with dicarboxylic acids or esters. Then, these derivatives were used for the treatment of opiate abuse/dependence and for the treatment of moderate to severe pain.

[0008] There are a variety of sustained release designs for buprenorphine indicated for the treatment of opioid dependence and chronic pain. For example, Titan Pharmaceuticals, Inc. developed a subcutaneous implant product of buprenorphine hydrochloride, Probuphine®, using their novel drug delivery system, ProNeura™, which is made from a mixture of ethylene vinyl acetate (EVA) and drug substance. Probuphine® is administrated once every six months through surgical implantation and removed from patients after treatment by surgical procedures.

[0009] Camurus established a novel drug delivery system, FluidCrystal®, which is based on lipid liquid crystals that are composed of phosphatidyl choline and glycerol dioleate. The formulation disclosed in US Patent Application Publication No. 2013/0190341 is designed as a long-acting buprenorphine product to treat opioid dependence and chronic pain, and is administrated by subcutaneous injection weekly or monthly.

[0010] U.S. Patent Application Publication No. 2003/0152638, by Brookwood Pharmaceuticals, Inc., discloses an injectable slow-release microsphere formulation that comprises buprenorphine and poly(D,L-lactide). This formulation is able to treat heroin and alcohol abuse for a period of at least 28 days in a mammal.

[0011] U.S. Patent Application Publication No. 2014/0271869 (Oakwood Laboratories LLC) discloses a biodegradable formulation, which utilized their proprietary technology, Chroniject™. The platform is a polymer-based injectable microspheres system for drug delivery. The buprenorphine microspheres could be generated in higher drug load and claimed to achieve sustained release for at least one month to several months.

[0012] Indivior PLC (WO 2011/154724) developed a monthly depot, which employed Atrigel System to produce an injectable, flowable formulation for the treatment of opioid dependency. The composition includes a buprenorphine free base, biodegradable polymer, and a biocompatible solvent. The dissolved liquid could be injected and transformed *in situ* into a solid implant, providing 1-month and 3-month release profiles. In addition, suspension and solution designs are disclosed in WO 2011/154725 and WO 2015/136253, respectively. The suspension is composed of buprenorphine and polyethylene glycol polymer in aqueous conditions, providing a therapeutic period of between 7 and 30 days in dogs after a single intramuscular or subcutaneous injection. As for the disclosed solution, the composition consists of buprenorphine or a salt form thereof and a biocompatible organic solvent without a biodegradable polymer. After a single subcutaneous injection in beagle dogs, the formulation is able to provide at least a one-month therapeutic period.

[0013] Despite the fact that the prior pharmaceutical preparations described above are able to provide buprenorphine with extended release, there is still a need for formulation with better characteristics, such as a formulation without an organic solvent to diminish the risks of local site irritation, or a formulation having higher bioavailability, or a pharmacokinetic

profile with smaller fluctuation and without a significant burst effect after one single injection.

SUMMARY

[0014] The present disclosure relates to various sustained-release pharmaceutical compositions of buprenorphine, or a prodrug, a pharmaceutically acceptable salt, and a metabolite thereof, including aqueous suspension of buprenorphine derivatives, and controlled release matrix, such as aqueous suspension of microspheres, poly(lactic-co-glycolic acid (PLGA)-based solutions, lipid-based formulations, and sucrose acetate isobutyrate-based formulations. The formulations of the present disclosure perform a therapeutically effective duration of at least one week to several months.

[0015] One aspect of the present disclosure relates to injectable suspension or the combination thereof, without utilizing an organic solvent. It is known that utilizing organic solvents in parenteral pharmaceutical preparations would enhance solubility, whereas the risks of local site irritation would inevitably increase. An injectable pharmaceutical composition in accordance with one embodiment of the present disclosure includes a suspension of crystalline 3-acyl-buprenorphine, or a pharmaceutically acceptable salt thereof, in a diluent comprising polyethylene glycol (PEG) polymer, polysorbate, and phosphate buffer saline, wherein the injectable pharmaceutical composition exhibits a steady release profile over a period of at least one week and a minimal risk of local site irritation following a single injection.

[0016] In accordance with embodiments of the present disclosure, long-acting suspension formulations are prepared from crystalline 3-acyl-buprenorphine derivatives. The acyl group is an alkylcarbonyl group. An alkyl portion of the alkylcarbonyl group is a straight-chain, or a branched-chain, having 1 to 17 carbon atoms.

[0017] In one embodiment, the present disclosure provides crystalline 3-acyl-buprenoprhine derivatives having x-ray powder diffraction patterns as follows:

3-Acyl-buprenoprhine derivatives	X-ray diffraction pattern (degrees 2θ)
Buprenorphine acetate	4.70, 8.44, 9.38, 10.74, 12.42, 14.12, 17.72, 18.40, 18.78, 20.08, 20.56, 25.04, 26.88, 28.42, 28.46
Buprenorphine pivalate	5.93, 6.03, 9.08, 9.18, 9.33, 9.58, 9.68, 10.83, 10.93, 11.03, 12.18, 12.28, 12.78, 12.88, 12.98, 15.58, 15.73, 15.83, 15.98, 17.38, 17.53, 18.18, 18.28, 18.38, 19.43, 27.73, 27.83, 29.18
Buprenorphine pentanoate	2.33, 5.73, 5.83, 5.98, 6.13, 9.33, 9.43, 9.53, 9.63, 9.98, 10.08, 10.18,

	11.83, 11.93, 12.03, 12.53, 12.68, 12.83, 12.98, 13.08, 15.73, 15.88, 16.03, 16.38, 18.28, 18.38, 18.58, 19.28, 19.43, 22.23
Buprenorphine hexanoate	2.33, 7.53, 8.13, 9.05, 10.93, 11.08, 12.93, 13.13, 13.38, 13.48, 15.88, 16.03, 17.18, 17.28, 17.73, 17.93, 21.13, 21.23, 21.33
Buprenorphine decanoate	5.80, 8.00, 10.50, 11.50, 11.60, 13.82, 14.44, 14.96, 16.06, 17.34, 18.32, 18.58, 18.98, 19.44, 20.92, 23.06, 23.40, 24.22, 24.38, 24.92
Buprenorphine dodecanoate	5.68, 8.03, 9.88, 9.98, 10.93, 11.38, 11.48, 17.13, 17.23, 17.33, 18.18, 18.28, 18.38, 18.93, 19.13, 19.23, 19.53, 21.03

[0018] In accordance with embodiments of the present disclosure, it relates to aqueous suspension, wherein the 3-acyl-buprenorphine, or a pharmaceutically acceptable salt thereof, is present at a concentration of 1-99% w/v, 5-90% w/v, 5-60% w/v, or 10-30% w/v.

[0019] In accordance with embodiments of the present disclosure, it relates to controlled release matrix formulations. The biocompatible organic solvent utilized in PLGA-based formulations, lipid-based formulations, and sucrose acetate isobutyrate-based formulations is *N*-methyl-2-pyrrolidone, ethyl acetate, ethanol, butanol, 2-butanol, isobutanol, isopropanol, glycerin, benzyl benzoate, dimethyl sulfoxide, *N,N*-dimethylacetamide, propylene glycol, dimethyl glycol, benzyl alcohol, an ester, an ether, an amide, a carbonate, a lactam, a sulfonyl, or any combination thereof.

[0020] In accordance with embodiments of the present disclosure, an injectable pharmaceutical composition may further comprise a preservative. In accordance with embodiments of the present disclosure, the preservative is selected from the group consisting of methylparaben, propylparaben and benzylalcohol.

[0021] In accordance with embodiments of the present disclosure, an injectable pharmaceutical composition is formulated for subcutaneous, intramuscular or intradermal injection.

[0022] Another aspect of the present disclosure relates to methods for treating opioid addiction, pain, or depression. A method in accordance with one embodiment of the present disclosure comprises administering to a subject in need thereof a therapeutically effective amount of the injectable pharmaceutical composition according to any embodiments described above.

[0023] In accordance with embodiments of the present disclosure, the administering is performed at a frequency of once per week, once per month, or once every three months.

[0024] Other aspects of the present disclosure will become apparent with the attached drawings and the following detailed descriptions.

BRIEF DESCRIPTION OF THE DRAWINGS

[0025] FIG. 1 illustrates the X-ray powder diffraction pattern of buprenorphine acetate crystal form.

[0026] FIG. 2 illustrates the differential scanning calorimetry (DSC) pattern of buprenorphine acetate crystal form.

[0027] FIG. 3 illustrates the ^{1}H nuclear magnetic resonance (NMR) spectrum of buprenorphine acetate crystal form.

[0028] FIG. 4 illustrates the Fourier-transform infrared spectroscopy (FTIR) spectrum of buprenorphine acetate crystal form.

[0029] FIG. 5 illustrates the X-ray powder diffraction pattern of buprenorphine pivalate crystal form.

[0030] FIG. 6 illustrates the DSC pattern of buprenorphine pivalate crystal form.

[0031] FIG. 7 illustrates the ^{1}H NMR spectrum of buprenorphine pivalate crystal form.

[0032] FIG. 8 illustrates the FTIR spectrum of buprenorphine pivalate crystal form.

[0033] FIG. 9 illustrates the X-ray powder diffraction pattern of buprenorphine pentanoate crystal form.

[0034] FIG. 10 illustrates the DSC pattern of buprenorphine pentanoate crystal form.

[0035] FIG. 11 illustrates the ^{1}H NMR spectrum of buprenorphine pentanoate crystal form.

[0036] FIG. 12 illustrates the FTIR spectrum of buprenorphine pentanoate crystal form.

[0037] FIG. 13 illustrates the X-ray powder diffraction pattern of buprenorphine hexanoate crystal form.

[0038] FIG. 14 illustrates the DSC pattern of buprenorphine hexanoate crystal form.

[0039] FIG. 15 illustrates the ^{1}H NMR spectrum of buprenorphine hexanoate crystal form.

[0040] FIG. 16 illustrates the FTIR spectrum of buprenorphine hexanoate crystal form.

[0041] FIG. 17. illustrates the X-ray powder diffraction pattern of buprenorphine decanoate crystal form.

[0042] FIG. 18. illustrates the DSC pattern of buprenorphine decanoate crystal form.

[0043] FIG. 19. illustrates the ^{1}H NMR spectrum of buprenorphine decanoate crystal form.

[0044] FIG. 20. illustrates the FTIR spectrum of buprenorphine decanoate crystal form.

[0045] FIG. 21 illustrates the X-ray powder diffraction pattern of buprenorphine dodecanoate crystal form.

[0046] FIG. 22 illustrates the DSC pattern of buprenorphine dodecanoate crystal form.

[0047] FIG. 23 illustrates the ^{1}H NMR spectrum of buprenorphine dodecanoate crystal form.

[0048] FIG. 24 illustrates the FTIR spectrum of buprenorphine dodecanoate crystal form.

[0049] FIG. 25 illustrates the *in vitro* dissolution % release of AS01-07.

[0050] FIG. 26 illustrates the *in vitro* dissolution % release of AS08-09.

[0051] FIG. 27 illustrates the *in vitro* dissolution % release of MSA02 and MSA05.

[0052] FIG. 28 illustrates the *in vitro* dissolution % release of MSB01-05.

[0053] FIG. 29 illustrates the *in vitro* dissolution % release of PS01, PS02, PS09, and PS10.

[0054] FIG. 30 illustrates the *in vitro* dissolution % release of PS03-08.

[0055] FIG. 31 illustrates the *in vitro* dissolution % release of BDSB1 and LS01-04.

[0056] FIG. 32 illustrates the pharmacokinetic (PK) profile of AS01-04 in rats.

[0057] FIG. 33 illustrates the PK profile of AS05-07 in rats.

[0058] FIG. 34 illustrates the PK profile of AS08 in minipigs.

[0059] FIG. 35 illustrates the PK profile of MSA02-05 and MSB01-02 in rats.

[0060] FIG. 36 illustrates the PK profile of MSA01, MSA02, and MSA05 in dogs.

[0061] FIG. 37 illustrates the PK profile of PS03 and PS10 in rats.

DETAILED DESCRIPTION

[0062] Embodiments of the present disclosure relate to formulations of buprenorphine derivatives in the forms of aqueous suspension of crystalline buprenorphine derivatives, aqueous suspension of microspheres, PLGA-based solutions, lipid-based formulations, and sucrose acetate isobutyrate-based formulations, having long-lasting release profiles after

single dose administration and displaying minimal initial bursts for the treatment of opioid addiction, pain or depression. In accordance with embodiments of the present disclosure, the buprenorphine derivatives are 3-alkyl ester derivatives, i.e., esters formed between the 3-hydroxy (phenol) group of buprenorphine and alkylcarbonylation (acylation) reagents.

[0063] In accordance with embodiments of the present disclosure, an alkylcarbonyl reagent (R-CO-X), wherein R is an alkyl residue, may be an acyl chloride, an acyl anhydride, or an acyl active ester. The alkyl portion of an alkylcarbonyl group may be a straight-chain or branched alkyl group. The alkyl portion may contain any suitable number of carbons, such as 1-18 (C_1-C_{18}), 1-16 (C_1-C_{16}), 1-12 (C_1-C_{12}), 1-10 (C_1-C_{10}), 1-5 (C_1-C_5), or 1-3 (C_1-C_3). Examples of alkylcarbonyl (acyl) groups may include acetyl, propionyl, butyryl, pentanyl, hexanyl, decanyl, stearyl, and palmityl.

[0064] In accordance with embodiments of the present disclosure, the buprenorphine derivatives may be synthesized using conventional methods. Buprenorphine or its salt can be purchased from several commercial sources, such as Sigma-Aldrich. To prepare a buprenorphine derivative, buprenorphine (or its salt) may be reacted with an acyl chloride in the presence of a base (e.g., triethylamine) to form an ester bond. The product (3-acyl-buprenorphine or 3-alkylcarbonyl-buprenorphine) may be purified with conventional methods (e.g., column chromatography).

[0065] As used in this description, a buprenorphine derivative refers to 3-acyl-buprenorphine (3-alkylcarbonyl-buprenorphine) or a salt thereof. A buprenorphine derivative of the present disclosure may function as a prodrug, which may be converted into the parent compound, buprenorphine.

[0066] The crystalline buprenorphine derivatives were further characterized by X-ray diffraction (XRD), differential scanning calorimeters (DSC), nuclear magnetic resonance spectroscopy (NMR), and infrared spectroscopy (IR).

[0067] A formulation of the present disclosure may comprise a 3-acyl-buprenorphine derivative suspended in an aqueous diluent containing PEG polymer, polysorbate, and phosphate buffer saline. The aqueous suspended formulation may contain the buprenorphine derivative or a salt thereof in any suitable concentration, such as 1-99% w/v, 1-90% w/v, 5-90% w/v, 5-80% w/v, 10-70% w/v, or 10-60% w/v. It is noted that when a numerical range is disclosed in this description, it is intended to include all numbers within the ranges, as if each of these numbers have been individually disclosed.

[0068] A formulation of the present disclosure may further comprise another pharmaceutically acceptable excipient, carrier, diluent, or preservative. In accordance with embodiments of the present disclosure, a preservative may be selected from the group consisting of methylparaben, propylparaben and benzylalcohol.

[0069] A formulation of the present disclosure may comprise of microspheres of 3-acyl-buprenorphine derivative or a salt form thereof and an aqueous diluent containing phosphate-buffered saline, sodium carboxymethylcellulose, and polysorbate. The thermoplastic polymer utilized for microspheres may be a polylactide, a polyglycolide, a 50/50, 55/45, 60/40, 65/35, 70/30, 75/25, 80/20, 85/15, 90/10 or 95/5 poly(DL-lactic-co-glycolide) with a carboxyl terminal group or an ester terminated group or a combination thereof.

[0070] A formulation of the present disclosure may comprise of 3-acyl-buprenorphine derivative or a salt form thereof, thermoplastic polymer, and one or more suitable biocompatible solvents. The buprenorphine derivative may be in the form of a free base or a pharmaceutically acceptable salt thereof, such as a salt of HCL, formate, acetate, citric acid or the like. The thermoplastic polymer may be a polylactide, a polyglycolide, a 50/50, 55/45, 60/40, 65/35, 70/30, 75/25, 80/20, 85/15, 90/10 or 95/5 poly(DL-lactic-co-glycolide) with a carboxyl terminal group or an ester terminated group or a combination thereof. The biocompatible solvents may be organic solvents, such as *N*-methyl-2-pyrrolidone (NMP), ethyl acetate (EtOAc), ethanol (EtOH), butanol, 2-butanol, isobutanol, glycerin, benzyl benzoate (BnBzO), dimethyl sulfoxide, propylene glycol, dimethyl glycol, and benzyl alcohol.

[0071] A formulation of the present disclosure may comprise 3-acyl-buprenorphine derivative or a salt form thereof dissolved in a lipid-based solution comprising lecithin, diolein and biocompatible solvents. The biocompatible solvents may be organic solvents, such as *N*-methyl-2-pyrrolidone (NMP), ethyl acetate (EtOAc), ethanol (EtOH), butanol, 2-butanol, isobutanol, glycerin, benzyl benzoate (BnBzO), dimethyl sulfoxide, propylene glycol, dimethyl glycol, and benzyl alcohol.

[0072] A formulation of the present disclosure may comprise an ionic complex of 3-acyl-buprenorphine derivative or a salt form thereof, sucrose acetate isobutyrate (SAIB) dissolved or suspended in a biocompatible solvent. The biocompatible solvents may be organic solvents, such as *N*-methyl-2-pyrrolidone (NMP), ethyl acetate (EtOAc), ethanol (EtOH), butanol, 2-butanol, isobutanol, glycerin, benzyl benzoate (BnBzO), dimethyl sulfoxide, propylene glycol, dimethyl glycol, and benzyl alcohol.

[0073] The various formulations of the present disclosure do not have undesirable initial burst and may display a sustained releasing profile over 1 week, 2 weeks, 3 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months or longer. The formulations without the significant burst release of buprenorphine may not only reduce the risks of several systemic adverse effects, e.g., pinpoint pupils, sedation, hypotension, and respiratory depression, but also lessen the burden of physicians to monitor patients frequently. Furthermore, the aqueous suspension formulation of the buprenorphine derivative without an

organic solvent exhibits high bioavailability, pharmaceutically effective plasma concentration for at least one week, and minimal risk of local site reactions.

[0074] Embodiments of the present disclosure will be further illustrated with the following examples. However, one skilled in the art would appreciate that these examples are for illustration only and that other modifications and variations are possible without departing from the scope of the disclosure.

Example 1: Synthesis of 3-acyl-buprenorphine derivatives

[0075] The following description is the procedure for synthesis of 3-acyl-buprenorphine derivatives. To a suitable 3-necked round bottom flask, buprenorphine HCl and dichloromethane (DCM) were added for a suspension, which was placed in an ice bath for cooling. Afterwards, trimethylamine (TEA) was added slowly with stirring. Acyl chloride was then added dropwise into the flask. The ice bath was revoked after all the materials were added. The reaction mixture was carried out at ambient temperature for 1 to 4 hours. The reaction mixture was neutralized with saturated sodium bicarbonate aqueous solution. The organic layer was washed with brine and then dried with sodium sulfate. After condensation under reduced pressure, the crude buprenorphine derivative was obtained. (Table 1)

Table 1. Synthesis condition of various 3-acyl-buprenorphine derivatives

Entry	Buprenorphine HCl	Acyl chloride	Base	Solvent
1-1	20.00 g, 39.7 mmol	Acetyl chloride (3.74 g, 47.6 mmol)	TEA (8.03 g, 79.3 mmol)	DCM (200 mL)
1-2	1.00 g, 1.98 mmol	Trimethylacetyl chloride (0.29 mL, 2.38 mmol)	TEA (0.4 g, 3.96 mmol)	DCM (10 mL)
1-3	1.00 g, 1.98 mmol	Valeroyl chloride (0.28 mL, 2.38 mmol)	TEA (0.4 g, 3.96 mmol)	DCM (10 mL)
1-4	2.0 g, 3.97 mmol	Hexanoyl chloride (0.64 g, 4.76 mmol)	TEA (0.8 g, 7.93 mmol)	DCM (20 mL)
1-5	10.00 g, 19.84 mmol	Decanoyl chloride (4.54 g, 23.8 mmol)	TEA (5.53 mL, 39.68 mmol)	DCM (100 mL)

1-6	1.00 g, 1.98 mmol	Dodecanoyl chloride (0.52 g, 2.38 mmol)	TEA (0.4 g, 3.95 mmol)	DCM (10 mL)

Example 2: Crystallization of 3-acyl-buprenorphine derivatives

[0076] Following is the crystallization procedure of 3-acyl-buprenorphine derivatives. The crude 3-acyl-buprenorphine derivatives were dissolved in the solvents described in Table 2 at ambient temperature or heated oil or eater bath. Then, the dissolved mixtures were cooled with ice bath to form crystalline 3-acyl-buprenorphine derivatives.

Table 2. Crystallization condition of 3-acyl-buprenorphine derivatives

Entry	Crude Compound	Solvent composition	Temperature
2-1	Buprenorphine acetate, 9.6 g	Ethanol (95%, 90 mL)	60℃ water bath to dissolve, gradually cooled to ambient temperature
2-2	Buprenorphine decanoate, 17.51 g	Anhydrous ethanol (99.5%, 260 mL)	51℃ oil bath to dissolve, gradually cooled to ambient temperature
2-3	Buprenorphine decanoate, 12.35 g	Ethanol (95%, 100 mL)	56℃ oil bath to dissolve, gradually cooled to ambient temperature
2-4	Buprenorphine decanoate, 1.0 g	Isopropanol (10 mL)	59℃ water bath to dissolve, gradually cooled to ambient temperature
2-5	Buprenorphine decanoate, 1.0 g	*N*-methyl-2-pyrrolidone (NMP, 3 mL)	53℃ water bath to dissolve, cooled with ice bath
2-6	Buprenorphine decanoate, 0.5 g	Acetonitrile (ACN, 7.5 mL)	58℃ water bath to dissolve, gradually cooled to ambient temperature
2-7	Buprenorphine pivalate, 1.15 g	Ethanol (95%, 11 mL)	60℃ water bath to dissolve, cooled with ice bath
2-8	Buprenorphine pentanoate, 1.2 g	Ethanol (95%, 12 mL)	60℃ water bath to dissolve, cooled with ice bath
2-9	Buprenorphine hexanoate, 1.7 g	Ethanol (95%, 17 mL)	Dissolved at ambient temperature, cooled with ice bath

2-10	Buprenorphine dodecanoate, 1.38 g	Ethanol (95%, 13.8 mL)	60℃ water bath to dissolve, cooled with ice bath

[0077] The crystalline 3-acyl-buprenorphine derivatives obtained were characterized by XRD, DSC, NMR and IR.

[0078] The crystal form of buprenorphine acetate was characterized by X-ray diffraction pattern (Bruker, D8 DISCOVER SSS Multipurpose Thin-film X-ray Diffractometer) having peaks at 4.70, 8.44, 9.38, 10.74, 12.42, 14.12, 17.72, 18.40, 18.78, 20.08, 20.56, 25.04, 26.88, 28.42, 28.46 degrees 2θ (FIG. 1), and its melting point was determined to be 167.69℃ by differential scanning calorimetry, DSC (Mettler-Toledo, TGA/DSC 3+ STARe System) (FIG. 2). The structure of the buprenorphine acetate crystal form was confirmed with Nuclear Magnetic Resonance, NMR (Bruker, Ascend TM 400 MHz) and Fourier Transform Infrared Spectroscopy, FTIR (Thermo, Nicolet-IS10 Mattson Satellite-5000 spectrometer) (FIGs. 3 and 4). Representative ^{1}H NMR (400 MHz, $CDCl_3$): 6.81 (d, 1H, *J*=8.4 Hz), 6.62 (d, 1H, *J*=8.0 Hz), 5.93 (s, 1H), 4.45 (s, 1H), 3.49 (s, 3H), 3.03 (m, 2H), 2.94-2.81 (m, 1H), 2.64 (dd, 1H, *J*=4.8, 12.0 Hz), 2.40-2.24 (m, 7H), 2.14 (t, 1H, *J*=10.0 Hz), 2.04-1.78 (m, 3H), 1.77-1.68 (dd, 1H, *J*=2.8, 13.2 Hz), 1.42-1.38 (m, 4H), 1.15-1.01 (m, 10H), 0.89-0.77 (m, 1H), 0.77-0.65 (m, 1H), 0.51 (m, 2H), 0.14 (m, 2H). FTIR absorption band (cm^{-1}): 3439, 2928, 1760, 1610, 1450, 1399, 1192, 1136, 1094, 963, 827, 668 (±1 cm^{-1}).

[0079] The crystal form of buprenorphine pivalate was characterized by X-ray diffraction pattern (PHILIPS X'PERT Pro, PHILIPS X'PERT Pro MPD) having peaks at 5.93, 6.03, 9.08, 9.18, 9.33, 9.58, 9.68, 10.83, 10.93, 11.03, 12.18, 12.28, 12.78, 12.88, 12.98, 15.58, 15.73, 15.83, 15.98, 17.38, 17.53, 18.18, 18.28, 18.38, 19.43, 27.73, 27.83, 29.18 degrees 2θ (FIG. 5), and its melting point was determined to be 145.43℃ by means of differential scanning calorimetry, DSC (Mettler-Toledo, TGA/DSC 3+ STARe System) (FIG. 6). The structure of the buprenorphine pivalate crystal form was identified with Nuclear Magnetic Resonance, NMR (Bruker, Ascend TM 400 MHz) and Fourier Transform Infrared Spectroscopy, FTIR (Thermo, Nicolet-IS10 Mattson Satellite-5000 spectrometer). (FIGs. 7 and 8). Representative ^{1}H NMR (400 MHz, $CDCl_3$): 6.78 (d, 1H, J=8.0 Hz), 6.61 (d, 1H, J=8.0 Hz), 5.94 (s, 1H), 4.44 (d, 1H, *J*=1.6 Hz), 3.48 (s, 3H), 3.04 (m, 2H), 2.91 (m, 1H), 2.64 (dd, 1H, *J*=4.8, 12.0 Hz), 2.42-2.20 (m, 4H), 2.13 (t, 1H, *J*=10.0 Hz), 2.05-1.89 (m, 2H), 1.89-1.68 (m, 2H), 1.37 (s, 3H), 1.34 (m, 10H), 1.06 (m, 10H), 0.82 (m, 1H), 0.69 (m, 1H), 0.51 (m, 2H), 0.14 (m, 2H). FTIR absorption band (cm^{-1}): 3428, 2954, 2827, 1753, 1614, 1478, 1448, 1407 (±1 cm^{-1}).

[0080] The crystal form of buprenorphine pentanoate was characterized by X-ray diffraction pattern (PHILIPS X'PERT Pro, PHILIPS X'PERT Pro MPD) having peaks at 2.33, 5.73, 5.83, 5.98, 6.13, 9.33, 9.43, 9.53, 9.63, 9.98, 10.08, 10.18, 11.83, 11.93, 12.03, 12.53, 12.68, 12.83, 12.98, 13.08, 15.73, 15.88, 16.03, 16.38, 18.28, 18.38, 18.58, 19.28, 19.43, 22.23 degrees 2θ (FIG. 9), and its melting point was determined to be 104.98 to 108.32℃ by means of differential scanning calorimetry, DSC (Mettler-Toledo, TGA/DSC 3+ STARe System) (FIG. 10). The structure of the buprenorphine pentanoate crystal form was identified with Nuclear Magnetic Resonance, NMR (Bruker, Ascend TM 400 MHz) and Fourier Transform Infrared Spectroscopy, FTIR (Thermo, Nicolet-IS10 Mattson Satellite-5000 spectrometer) (FIGs. 11 and 12). Representative ^{1}H NMR (400 MHz, $CDCl_3$): 6.79 (d, 1H, *J*=8.0 Hz), 6.61 (d, 1H, *J*=8.0 Hz), 5.93 (s, 1H), 4.44 (d, 1H, *J*=1.6 Hz), 3.48 (s, 3H), 3.04 (m, 2H), 2.91 (m, 1H), 2.64 (dd, 1H, *J*=4.8, 12.0 Hz), 2.55 (t, 2H, *J*=7.6 Hz), 2.40-2.20 (m, 4H), 2.14 (t, 1H), 2.07-1.78 (m, 3H), 1.78-1.68 (m, 3H), 1.48-1.28 (m, 6H), 1.15-1.01 (m, 10H), 0.94 (t, 3H, *J*=7.2 Hz), 0.83 (m, 1H), 0.71 (m, 1H), 0.51 (m, 2H), 0.14 (m, 2H). FTIR absorption band (cm^{-1}): 3438, 2950, 2926, 2816, 1760, 1607, 1492, 1447, 1401 (±1 cm^{-1}).

[0081] The crystal form of buprenorphine hexanoate was characterized by X-ray diffraction pattern (PHILIPS X'PERT Pro, PHILIPS X'PERT Pro MPD) having peaks at 2.33, 7.53, 8.13, 9.05, 10.93, 11.08, 12.93, 13.13, 13.38, 13.48, 15.88, 16.03, 17.18, 17.28, 17.73, 17.93, 21.13, 21.23, 21.33 degrees 2θ (FIG. 13), and its melting point was determined to be 80.30 to 84.31℃ by means of differential scanning calorimetry, DSC (Mettler-Toledo, TGA/DSC 3+ STARe System) (FIG. 14). The structure of the buprenorphine hexanoate crystal form was identified with Nuclear Magnetic Resonance, NMR (Bruker, Ascend TM 400 MHz) and Fourier Transform Infrared Spectroscopy, FTIR (Thermo, Nicolet-IS10 Mattson Satellite-5000 spectrometer) (FIGs. 15 and 16). Representative ^{1}H NMR (400 MHz, $CDCl_3$): 6.79 (d, 1H, *J*=8.0 Hz), 6.61 (d, 1H, *J*=8.0 Hz), 5.93 (s, 1H), 4.44 (d, 1H, *J*=1.6 Hz), 3.48 (s, 3H), 3.04 (m, 2H), 2.91 (m, 1H), 2.64 (dd, 1H, *J*=4.8, 12.0 Hz), 2.54 (t, 2H, *J*=7.6 Hz), 2.45-2.20 (m, 4H), 2.14 (t, 1H), 2.08-1.65 (m, 6H), 1.42-1.30 (m, 8H), 1.16-1.02 (m, 10H), 0.93 (t, 3H, *J*=6.8 Hz), 0.83 (m, 1H), 0.71 (m, 1H), 0.51 (m, 2H), 0.14 (m, 2H). FTIR absorption band (cm^{-1}): 3453, 2944, 2923, 2865, 1760, 1610, 1449, 1398 (±1 cm^{-1}).

[0082] The crystal form of buprenorphine decanoate was characterized with X-ray diffraction pattern (Bruker, D8 DISCOVER SSS Multipurpose Thin-film X-ray Diffractometer), which shows peaks at 5.80, 8.00, 10.50, 11.50, 11.60, 13.82, 14.44, 14.96, 16.06, 17.34, 18.32, 18.58, 18.98, 19.44, 20.92, 23.06, 23.40, 24.22, 24.38, 24.92 degrees 2θ (FIG. 17), and its melting point of the crystal product was determined to be 86.37℃ by means of differential scanning calorimetry, DSC (Mettler-Toledo, TGA/DSC 3+ STARe System) (FIG. 18). The structure of buprenorphine decanoate was identified with Nuclear Magnetic Resonance, NMR (Bruker, Ascend TM 400 MHz) and Fourier Transform Infrared

Spectroscopy, FTIR (Thermo, Nicolet-IS10 Mattson Satellite-5000 spectrometer). (FIGs. 19 and 20). Representative ^{1}H NMR (400 MHz, $CDCl_3$): 6.79 (d, 1H, *J*=8.0 Hz), 6.61 (d, 1H, *J*=8.0 Hz), 5.94 (s, 1H), 4.44 (d, 1H, *J*=1.6 Hz), 3.48 (s, 3H), 3.04 (m, 2H), 2.91 (m, 1H), 2.64 (dd, 1H, J=5.2, 12.0 Hz), 2.54 (t, 2H, *J*=7.2 Hz), 2.40-2.25 (m, 4H), 2.14 (t, 1H, *J*=9.6 Hz), 2.03-1.90 (m, 2H), 1.87-1.80 (m, 1H), 1.75-1.68 (m, 3H), 1.42-1.29 (m, 17H), 1.12-1.06 (m, 9H), 0.94 (t, 3H, *J*=6.8 Hz), 0.83 (m, 1H), 0.71 (m, 1H), 0.51 (m, 2H), 0.14 (m, 2H). FTIR absorption band (cm^{-1}): 3439, 2928, 1760, 1610, 1450, 1399, 1192, 1136, 1094, 963, 827, and 668 (±1 cm^{-1}).

[0083] The crystal form of buprenorphine dodecanoate was characterized by X-ray diffraction pattern (PHILIPS X'PERT Pro, PHILIPS X'PERT Pro MPD) having peaks at 5.68, 8.03, 9.88, 9.98, 10.93, 11.38, 11.48, 17.13, 17.23, 17.33, 18.18, 18.28, 18.38, 18.93, 19.13, 19.23, 19.53, 21.03 degrees 2θ (FIG. 21) and its melting point was determined to be 74.99 to 77.30℃ by means of differential scanning calorimetry, DSC (Mettler-Toledo, TGA/DSC 3+ STARe System) (FIG. 22). The structure of the buprenorphine dodecanoate crystal form was identified with Nuclear Magnetic Resonance, NMR (Bruker, Ascend TM 400 MHz) and Fourier Transform Infrared Spectroscopy, FTIR (Thermo, Nicolet-IS10 Mattson Satellite-5000 spectrometer) (FIGs. 23 and 24). Representative ^{1}H NMR (400 MHz, $CDCl_3$): 6.79 (d, 1H, *J*=8.0 Hz), 6.61 (d, 1H, *J*=8.0 Hz), 5.94 (s, 1H), 4.44 (d, 1H, *J*=2.0 Hz), 3.48 (s, 3H), 3.10-3.00 (m, 2H), 2.97-2.87 (m, 1H), 2.64 (dd, 1H, *J*=4.8, 12.0 Hz), 2.54 (t, 2H, *J*=7.6 Hz), 2.42-2.22 (m, 4H), 2.14 (t, 1H, *J*=9.6 Hz), 2.07-1.78 (m, 3H), 1.77-1.66 (m, 3H), 1.46-1.22 (m, 20H), 1.14-1.01 (m, 10H), 0.90 (t, 3H, *J*=6.8 Hz), 0.87-0.78 (m, 1H), 0.77-0.65 (m, 1H), 0.58-0.45 (m, 2H), 0.19-0.08 (m, 2H). FTIR absorption band (cm^{-1}): 3453, 2944, 2923, 2865, 1760, 1610, 1449, 1398 (±1 cm^{-1}).

[0084] The above examples show limited numbers of ester derivatives of the disclosure. One skilled in the art would appreciate that other similar ester derivatives may be prepared in similar manners.

Example 3: Solubility of buprenorphine derivatives and salt form thereof in dissolution medium

[0085] Excess amount of compounds, including buprenorphine free base, buprenorphine derivatives, or salt form thereof were weighed into a glass tube containing 5 mL dissolution medium. The medium was the same as in previous examples. The tube was then sealed and placed into a reciprocal shaker at the rate of 60 rpm in a 55℃ water bath. The solution was filtered with 0.45 μm Nylon filter. Afterwards, the filtrate was further diluted with acetonitrile. The content of each compound was measured with the HPLC method.

Table 3. Solubility of buprenorphine derivatives

Compound	Solubility (mg/mL)
Buprenorphine free base	1.176
Buprenorphine acetate (crystal form)	0.697
Buprenorphine pentanoate (crystal form)	0.498
Buprenorphine hexanoate (crystal form)	0.670
Buprenorphine pivalate (crystal form)	0.160
Buprenorphine decanoate (crystal form)	0.112
Buprenorphine dodecaonate (crystal form)	0.269
Buprenorphine palmitate	0.027
Buprenorphine stearate	0.020

Table 4. Solubility of salt forms of buprenorphine derivatives

Compound	Solubility (mg/mL)
Buprenorphine-pamoic acid salt	2.095
Buprenorphine acetate-citric acid salt	1.377
Buprenorphine acetate-maleic acid salt	1.481
Buprenorphine acetate-hydrochloride salt	1.716
Buprenorphine acetate-pamoic acid salt	1.546
Buprenorphine decanoate-citric acid salt	2.696
Burpenorphine decaonate-L-tartaric acid salt	1.507
Buprenorphine stearate-citric acid salt	2.452
Buprenorphine stearate-L-tartaric acid salt	3.504

[0086] Table 3 shows that the solubilities of the buprenorphine derivatives (in crystal form) were less than their parent compound (buprenorphine free base). The solubility of buprenorphine decanoate crystal form was nearly 10 times poorer than that of the parent compound. After preparation of the salt forms, the solubilities of salt forms of buprenorphine derivatives were found to be superior to their free base and parent compound (Table 4).

Example 4: Preparation of aqueous suspension of buprenorphine derivatives

[0087] Weighed known amount of 3-acyl-buprenorphine derivative and suspended it with diluent, which was composed of PEG4000 (30 mg/mL) and Tween 20 (3 to 6 mg/mL) in PBS buffer. Mixed the formulation by sonicating and shaking. The formulations were further milled. The composition and process were listed in Table 5. The particle size distribution results were shown in Table 6.

Table 5. Composition, milling process and administration route of buprenorphine derivatives aqueous suspension

Code	Buprenorphine derivatives	Milling Process	Administration route
AS01	Buprenorphine decanoate, 10% w/v	Agate mortar	IM
AS02	Buprenorphine decanoate, 10% w/v	-	IM
AS03	Buprenorphine decanoate, 10% w/v	-	SC
AS04	Buprenorphine decanoate, 10% w/v	-	IM
AS05	Buprenorphine decanoate, 20% w/v	Bead milling, 6 mm Iron beads	SC
AS06	Buprenorphine decanoate, 20% w/v	Bead milling, 0.50 mm Zirconia Grinding Media	SC
AS07	Buprenorphine hexanoate, 10% w/v	Bead milling, 2 mm glass beads	SC
AS08	Buprenorphine hexanoate, 20% w/v	Bead milling, 0.50 mm Zirconia Grinding Media	SC
AS09	Buprenorphine hexanoate, 15% w/v	High pressure homogenizers (6000 rpm, 20000 psi)	-
AS10	Buprenorphine hexanoate, 30% w/v	Bead milling, 0.50 mm Zirconia Grinding Media	-

Table 6. Particle size distributions of aqueous suspension of buprenorphine derivatives

Formulation	Volume Statistics			
	d10 (μm)	d50 (μm)	d90 (μm)	Specific Surface Area (cm^2/g)
AS01	2.15	17.07	62.33	10319
AS02/AS03	3.22	15.68	44.43	8816
AS08	8.90	11.33	36.83	4521
AS09	1.58	4.99	14.60	18183

Example 5: Preparation of microspheres

Method A

[0088] The process of microsphere preparation in Method A was carried out by double emulsion. A known amount of poly(lactide-co-glycolide) and active pharmaceutical ingredient were weighed into a glass vial. Dichloromethane (3 mL) was used to dissolve the mixture. Polyvinyl alcohol aqueous solution (1%, 6 mL) was added thereto. The mixture was suspended using a homogenizer at the rate of 5000 rpm for 5 minutes in an ice bath. The homogenous suspension was then dropped into a beaker containing polyvinyl alcohol aqueous solution (1%, 1000 mL) with stirring (800 rpm) at 40℃ under a heating condition. After 3 hours, the microparticles were collected with centrifuge and washed with dd-water several times sequentially. The residual water in microparticles was removed by freeze drying. The formulation compositions are listed in Table 7 below.

Table 7. Composition of microspheres (Method A)

Formulation	API		PLGA type	E.E. (%)	Particle size
	Compound	wt%	LA/GA ratio		(mean, μm)
MSA01	Buprenorphine decanoate	40%	75/25 (iv 0.21, ester capped)	100.2±1.5	24.6±7.7
MSA02	Buprenorphine decanoate citric acid salt	40%	50/50 (iv 0.30, acid terminated)	108.9±5.1	24.6±7.9
MSA03	Buprenorphine decanoate citric acid salt	50%	50/50 (iv 0.21, acid terminated)	115.9±2.9	8.4±6.3
MSA04	Buprenorphine decanoate citric acid salt	40%	50/50 (iv 0.21, acid terminated)	115.6±1.7	5.6±6.2
MSA05	Buprenorphine decanoate citric acid salt	40%	75/25 (iv 0.21, ester capped)	111.0±3.6	20.8±7.2

Method B

[0089] Method B was conducted using a T-shaped loop (Western Analytical, Tee Asy Tefzel 1/16" 0.020" thru). The terminal inlet was inserted with one set of syringe and needle (Hamilton 81520 5mL, Model 1005 TLL and Hamilton Metal Hub N726S NDL 6/PK (26S/2"/3)) as a dispersing phase part. One of the lateral inlets was connected with a pump with a tubing as a continuous phase part.

[0090] The microspheres were prepared using a continuous emulsification/solvent extraction procedure. The dispersing phase was filled into a syringe with an API-containing

polymer solution, which was composed of PLGA and dichloromethane. The flow rate of the dispersing phase was controlled by an infusion syringe pump (KDS 100, KD Scientific) at a rate of 0.3 mL/min. At the same time, the continuous phase containing 1% polyvinyl alcohol aqueous solution was pumped at a rate of 2 mL/min. The outlet was connected to a beaker containing 1% polyvinyl alcohol aqueous solution through a tubing. The quenching process was carried out at ambient or heating condition. The microspheres were filtered with 0.45 μm membrane and washed with dd-water several times. Thereafter, the microspheres were dried in vacuum at ambient temperature. The formulation compositions are listed in Table 8.

Table 8. Composition of microsphere (Method B)

Formulation	API		PLGA type		E.E.	Particle size (mean, μm)
	Compound	wt%	LA/GA	I.V. (dL/g)		
MSB0	Buprenorphine decanoate	40%	75/25	0.7	101.6%	NA
MSB02	Buprenorphine hexanoate	40%	75/25	0.2	108.7%	NA
MSB03	Buprenorphine decanoate citric acid salt	40%	75/25	0.2	101.6	57.4
MSB04	Buprenorphine acetate	40%	75/25	0.2	101.2	30
MSB05	Buprenorphine dodecanoate	40%	75/25	0.2	106.8	25

Example 6: Preparation of PLGA-based formulation

[0091] The buprenorphine derivatives, poly(lactide-co-glycolide), and a biocompatible solvent were added into a glass vial. The mixture was placed into a 50℃ water bath with constant stirring until all the ingredients were dissolved. The mixture was removed from water bath, and the solution was generated at ambient temperature with stirring simultaneously. The compositions of the PLGA-based formulations are listed in Table 9 below.

Table 9. Compositions of PLGA-based formulations

Formulation	Buprenorphine derivatives, wt%	PLGA type, wt%	Solvent, wt%
PS01	Buprenorphine decanoate, 20%	50/50 (17 kD, ester capped), 20%	EtOAc, 60%
PS02	Buprenorphine decanoate, 20%	75/25 (95 kD, ester capped), 20%	EtOAc, 60%
PS03	Buprenorphine decanoate, 30%	75/25 (17 kD, ester capped), 10%	NMP, 60%
PS04	Buprenorphine decanoate, 30%	75/25 (95 kD, ester capped), 10%	NMP, 60%
PS05	Buprenorphine decanoate, 30%	Polylactide, (17 kD, ester capped), 10%	NMP, 60%
PS06	Buprenorphine decanoate, 30%	Polylactide, (17 kD, acid terminated), 10%	NMP, 60%

PS07	Buprenorphine decanoate, 30%	50/50 (17 kD, ester capped), 10%	NMP, 60%
PS08	Buprenorphine decanoate, 30%	50/50 (44kD, ester capped), 10%	NMP, 60%
PS09	Buprenorphine decanoate citric acid salt, 20%	75/25 (17 kD, ester capped), 20%	EtOAc, 60%
PS10	Buprenorphine hexanoate, 40%	75/25 (17 kD, ester capped), 10%	EtOAc, 50%

Example 7: Preparation of lipid-based formulations

[0092] The lipid-based formulations were prepared by mixing buprenorphine derivatives, lecithin, diolein, and a biocompatible solvent. The compositions of the lipid-based formulations are listed in Table 10 below.

Table 10. Compositions of lipid-based formulations

Formulation	Composition w/w%			
	Buprenorphine derivatives	Lecithin	Diolein	Solvent
LS01	Buprenorphine hexanoate, 35%	17.5%	17.5%	*N*-Methyl-2-Pyrrolidone, 30%
LS02	Buprenorphine hexanoate, 35%	17.5%	17.5%	Benzyl benzoate, 30%
LS03	Buprenorphine decanoate, 25%	20%	20%	*N*-Methyl-2-Pyrrolidone, 35%
LS04	Buprenorphine decanoate, 25%	20%	20%	Benzyl benzoate, 35%

Example 8: Preparation of SAIB-based liquid formulations

[0093] Buprenorphine decanoate (203.1 mg, 1.0 eq.) was dissolved in ethanol (2 mL). Sodium dodecyl sulfate (SDS) was dissolved in distilled deionized water (20 mL). The buprenorphine decanoate solution was added into the SDS solution dropwise and generated tiny precipitates in the mixture solution. The mixture was concentrated under reduced pressure to form buprenorphine decanoate-SDS ionic complex. The ionic complex (6% w/w) was further mixed with sucrose acetate isobutyrate (SAIB, 38% w/w) and NMP (56% w/w) to form formulation BDSB1.

Example 9. *In vitro* dissolution test of formulations

[0094] The formulations in examples 4-8 were further investigated for their *in vitro* dissolution profile. The dissolution medium composed of 1% sodium dodecyl sulfate and 0.02% sodium azide in phosphate buffered saline. The tubes were incubated in a reciprocal shaker at the rate of 60 rpm with 37℃ or 55℃ water bath simultaneously. The tubes were pulled, sampled as 1 mL solution, and then refilled with 1 mL fresh medium subsequently at specific timepoints. These samples were analyzed through HPLC for buprenorphine derivatives and their parent compound, i.e., buprenorphine free base. The *in vitro* releasing profiles are revealed in FIGs. 25 to 31 and Tables 11 to 18.

Table 11. *In vitro* dissolution % release of AS01-04

Time (days)	% Release at 55℃			
	AS01	AS02	AS03	AS04
0	0.0	0.0	0.0	0.0
0.042	1.5	0.9	0.9	0.0
0.083	3.7	2.1	2.1	0.6
0.167	7.0	4.2	4.1	1.2
1	24.3	16.0	15.7	5.8
2	34.8	25.6	24.6	10.4
3	42.3	32.7	31.1	13.0
4	49.5	40.8	38.4	17.2
5	54.9	47.1	44.4	21.1
6	56.7	53.3	49.7	24.4
7	60.6	57.7	53.7	26.6
8	63.2	59.3	55.4	28.3
9	66.8	63.9	59.7	31.2
10	68.7	67.5	61.7	33.2
11	67.4	70.7	66.3	35.8
12	72.3	72.3	67.2	37.2
14	75.5	77.0	71.7	41.7
16	77.8	80.2	75.3	43.5
17	78.1	81.6	76.2	42.3
21	79.8	85.4	79.6	48.4
24	84.2	88.5	83.6	51.5
28	83.8	89.4	84.7	55.7
31	84.5	89.9	86.8	58.1
35	89.0	92.9	86.6	61.8

Table 12. *In vitro* dissolution % release of AS05-07

% Release at 55℃				
Time (days)	AS05	AS06	Time (days)	AS07
0	0	0	0	0
0.042	7.6	9.3	0.042	58.00
0.083	11.8	15.0	0.167	90.67
0.167	18.1	24.9	1	102.33
1	42.0	61.1	2	103.92
2	49.4	75.3	5	101.94
5	60.8	82.0	—	—
6	66.9	88.0	—	—

Table 13. *In vitro* dissolution % release of AS08-09

% Release at 37℃			
Time (hours)	AS08	Time (hours)	AS09
0	0.24	0	0.00
1	56.5	0.5	80.39
2	60.0	1	97.96
4	65.6	2	99.98
6	69.1	4	101.69
8	71.7	6	99.96
24	80.9	8	102.72
48	99.7	24	105.61

Table 14. *In vitro* dissolution % release of MSA02 and MSA05

% Release at 37℃		
Time (days)	MSA02	MSA05
0	0.00	0.00
1	7.35	10.02
7	12.90	12.40
14	20.54	13.58
21	36.11	14.75
28	53.02	15.23
35	78.19	15.87
42	89.62	16.35

49	95.97	16.92
56	97.28	18.38
63	—	25.50
70	—	48.79
77	—	64.91
84	—	71.65

Table 15. *In vitro* dissolution % release of MSB01-05

% Release at 55℃									
Time (days)	MSB01	Time (days)	MSB02	Time (days)	MSB03	Time (days)	MSB04	Time (days)	MSB05
0	0	0	0	0	0	0	0	0	0
0.042	12	0.042	6	0.042	1.3	0.042	19.1	0.042	3.4
0.083	12	0.083	8	0.083	2.3	0.083	23.1	0.083	3.5
0.167	14	0.146	11	0.167	3.9	0.167	26.4	0.146	3.7
1	20	1	30	1	13.1	1	45.8	1	4.9
2	25	2	46	2	19.9	2	56.6	3	10.0
3	29	3	55	3	26.7	3	59.5	7	18.5
4	33	6	67	4	36	5	70.6	8	18.0
7	46	9	68	5	40.5	6	70.5	9	19.7
8	50	13	68	6	44.5	7	71.9	10	22.7
9	55	21	68	8	48.5	8	74.2	11	26.4
10	58	27	70	10	58.1	9	75.3	15	33.5
11	63	—	—	14	72.2	10	76.5	21	42.5
14	69	—	—	21	95.4	13	73.4	28	55.3
17	70	—	—	24	97.1	16	78.8	36	72.4
21	75	—	—	—	—	—	—	—	—
24	77	—	—	—	—	—	—	—	—
29	80	—	—	—	—	—	—	—	—
35	83	—	—	—	—	—	—	—	—

Table 16. *In vitro* dissolution % release of PS01, PS02, PS09, and PS10

% Release at 55℃						
Time (days)	PS01	PS02	Time (days)	PS09	Time (days)	PS10
0	0	0	0	0	0	0
0.042	15	6	0.042	20.7	0.042	0.7
0.083	20	10	0.083	29.5	0.083	1.1

0.167	25	15	0.167	39.4	0.167	2.6
1	54	34	1	55.5	1	5.3
2	75	48	2	60	4	18.1
3	87	57	3	62.1	7	25.4
4	95	66	4	64.5	13	34.9
5	102	71	5	66.9	15	38.7
6	—	75	—	—	19	44.1
7	—	77	—	—	27	58
8	—	79	—	—	—	—
9	—	82	—	—	—	—
10	—	84	—	—	—	—
16	—	104	—	—	—	—

Table 17. *In vitro* dissolution % release of PS03-08

% Release at 55℃								
Time (days)	PS03	Time (days)	PS04	Time (days)	PS05	PS06	PS07	PS08
0	0	0	0	0	0	0	0	0
0.042	2	0.042	1	0.042	0.9	0.9	0.7	0.4
0.083	2	0.083	1	0.083	1.2	1.4	1.1	0.4
0.167	2	1	5	0.167	2.1	2.4	2	0.8
1	8	2	9	1	10.1	8.7	8.9	2.9
2	12	7	27	2	18.7	14	15.2	5.1
3	17	9	31	3	26.6	19	21	7.4
5	25	12	43	5	37.8	26.7	28.6	11.8
6	28	13	46	6	42	30.1	31.7	14.2
7	32	15	50	7	45.9	33.4	34.8	16.6
8	36	19	59	8	48.7	36	37	19.2
9	40	22	62	9	51.7	39	39.4	21.8
14	65	26	64	12	58.6	46.7	47.5	27.6
19	85	29	69	19	68.2	58.5	60.6	37.8
22	91	35	75	26	75	69.3	73.3	46.4
26	95	37	73	33	76.4	74.6	80.1	52.1
—	—	40	82	41	79	79.7	83.9	58.5
—	—	43	84	47	79.4	81.8	83.8	62.4
—	—	47	84	54	77.2	84.3	84.5	65
—	—	50	86	—	—	—	—	—
—	—	54	87	—	—	—	—	—

—	—	57	85	—	—	—	—	—
—	—	61	88	—	—	—	—	—
—	—	65	90	—	—	—	—	—

Table 18. *In vitro* dissolution % release of BDSB1, LS01-04

% Release at 55℃							
Time (days)	BDSB1	Time (days)	LS01	LS02	Time (days)	LS03	LS04
0	0	0	0	0	0	0	0
0.042	1	0.063	1.98	0.00	0.125	5.48	0.50
0.083	1	0.208	5.12	3.40	0.271	8.58	1.75
0.167	2	1	19.7	6.85	1	15.5	4.82
1	3	2	28.9	7.10	2	23.8	9.16
2	5	3	35.4	7.75	5	50.6	12.1
6	13	6	60.0	9.85	8	70.6	14.5
7	16	10	75.3	21.9	12	88.2	17.4
8	17	13	84.1	24.6	15	94.8	19.7
10	20	16	87.1	26.0	20	100.7	21.8
14	26	20	89.7	29.2	—	—	—
22	32	24	99.2	32.2	—	—	—
27	35	28	—	33.8	—	—	—
35	42	—	—	—	—	—	—
42	47	—	—	—	—	—	—
48	50	—	—	—	—	—	—

Example 10: Pharmacokinetic profile of aqueous suspension of buprenorphine derivatives in rats and minipigs

[0095] The aqueous suspension formulations of buprenorphine derivatives in Example 4 were administered subcutaneously or intramuscularly in SD male rats at a dose of 60 mg/kg buprenorphine equivalent. The resulted mean plasma concentrations of buprenorphine versus time profiles were shown in FIGs. 32-33 and Tables 19-20. Formulation AS08 was injected in Lanyu male minipigs subcutaneously. The mean plasma concentrations of buprenorphine versus time profiles are shown in FIG. 34 and Table 21.

Table 19. Mean plasma concentrations of buprenorphine after injection in rats

Time	AS01		AS02		AS03		AS04	
(days)	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.

	(ng/mL)	(n = 3)	(ng/mL)	(n = 3)	(ng/mL)	(n = 3)	(ng/mL)	(n = 3)
0	0.04	0.07	0.00	0.00	0.00	0.00	0.00	0.00
0.021	14.61	9.36	3.59	0.86	1.89	0.20	3.40	3.30
0.042	18.5	6.94	11.4	5.84	4.92	3.08	6.93	1.50
0.083	9.51	2.72	7.25	2.54	2.12	0.56	10.0	1.95
0.17	11.63	1.42	8.01	3.48	1.67	0.40	7.41	1.18
0.25	12.32	2.63	7.25	2.09	2.13	0.30	6.71	3.02
1	16.8	5.28	9.05	4.06	4.67	1.37	5.25	0.35
3	24.5	1.42	16.7	3.87	6.15	1.87	3.95	0.56
7	54.9	7.28	46.3	11.1	15.9	5.8	14.0	3.27
10	53.8	7.46	47.2	16.3	25.4	6.67	23.1	2.81
14	25.1	7.15	25.6	0.96	27.1	0.66	23.3	6.09
21	10.5	4.61	14.3	6.07	17.6	3.02	14.3	5.48
28	2.73	1.78	6.56	2.99	7.74	2.22	7.42	3.88
35	0.52	0.41	4.2	2.28	5.28	2.23	4.00	2.80
42	0.23	0.22	1.66	1.07	2.87	1.15	1.94	1.64
49	0.00	0.00	0.68	0.36	1.62	0.82	0.88	0.77
56	—	—	—	—	1.41	0.54	—	—
63	—	—	—	—	1.17	0.40	—	—
70	—	—	—	—	0.89	0.47	—	—

Table 20. Mean plasma concentrations of buprenorphine after injection in rats

Time (days)	AS05 Mean (ng/mL)	AS05 S.D. (n = 4)	AS06 Mean (ng/mL)	AS06 S.D. (n = 4)	Time (days)	AS07 Mean (ng/mL)	AS07 S.D. (n = 3)
0	3.26	0.07	2.02	2.39	0	0	0
0.042	3.04	1.82	3.09	2.77	0.083	1.72	0.63
0.083	2.73	1.55	3.27	1.93	0.167	2.82	0.65
0.25	3.59	2.64	3.84	2.85	0.25	3.54	0.68
1	5.11	3.13	5.30	3.36	1	6.69	2.68
2	4.83	3.10	6.54	2.70	2	6.18	1.48
3	5.01	2.76	6.40	2.65	3	6.78	2.13
4	6.79	4.10	6.15	1.42	7	2.92	0.92
7	10.5	4.69	13.1	1.88	10	1.21	0.75
10	8.73	3.32	11.0	3.05	14	0.27	0.23
14	7.25	4.72	7.78	2.97	—	—	—
17	4.90	3.41	4.07	3.35	—	—	—

Table 21. Mean plasma concentrations of buprenorphine after injection in minipig

Time (days)	AS08	
	Mean (ng/mL)	S.D. (n = 3)
0	0.177	0.21
0.08	0.228	0.30
0.17	0.227	0.28
0.25	0.217	0.26
1	1.01	0.20
2	1.70	0.69
3	1.54	0.70
4	1.66	0.57
5	2.19	0.80
6	2.98	1.14
7	3.20	0.93
8	3.37	0.73
9	3.15	0.61
10	2.89	0.50
12	2.51	0.51
14	2.15	0.35
21	1.46	0.73

Example 11: Pharmacokinetic profile of aqueous suspension of microspheres containing buprenorphine derivatives in rats and dogs

[0096] Four buprenorphine decanoate citric acid salt-containing microspheres formulations as shown in Example 5 were prepared as suspension at a concentration of 100 to 150 mg/mL. The diluent was composed of 10 mM phosphate-buffered saline, 1.25% sodium carboxymethylcellulose, and 0.05% Tween 80. The suspension formulations were intramuscularly or subcutaneously injected in SD male rats at dose of 60 mg/kg buprenorphine equivalent. The pharmacokinetic profile results are shown in FIG. 35 and Tables 22-23.

Table 22. Mean plasma buprenorphine levels after intramuscular injection of MSA02-05 in rats

Time (Day)	MSA02		MSA03		MSA04		MSA05	
	Mean (ng/mL)	S.D. (n = 3)	Mean (ng/mL)	S.D. (n = 3)	Mean (ng/mL)	S.D. (n = 3)	Mean (ng/mL)	S.D. (n = 3)
0	0.03	0.05	0.21	0.37	0.32	0.28	0.09	0.01

0.007	1.18	0.24	2.10	0.73	4.26	2.27	1.45	0.60
0.021	2.41	0.95	5.30	1.03	6.36	2.05	3.18	0.87
0.042	5.93	2.2	9.23	1.99	12.1	1.49	6.26	1.01
0.083	13.9	4.02	13.0	1.74	16.3	3.02	14.3	0.95
0.167	20.4	2.27	16.1	2.22	19.2	1.12	22.0	2.44
0.25	22.4	2.74	15.6	1.57	20.4	7.90	20.1	3.16
1	18.8	2.86	18.7	11.0	15.6	4.48	8.13	1.02
4	18.30	2.84	36.4	16.6	22.2	4.54	12.31	5.09
7	24.8	2.55	96.2	15.90	75.8	21.3	20.2	7.30
10	33.0	7.60	38.4	17.30	47.7	3.15	18.2	6.77
14	27.47	2.12	10.8	2.65	11.6	5.69	13.0	1.04
17	19.7	3.05	6.43	3.18	4.72	5.09	12.6	1.92
21	13.7	2.57	2.98	1.24	2.42	3.24	12.4	0.75
24	16.1	3.00	1.53	0.56	1.49	2.16	11.1	2.16
28	11.0	2.40	0.80	0.71	0.81	1.02	8.69	2.68
31	7.59	1.83	—	—	—	—	7.74	2.46
35	3.62	0.93	—	—	—	—	5.54	1.75
38	1.67	0.54	—	—	—	—	5.77	2.26
42	0.49	0.46	—	—	—	—	5.03	1.43
45	0.21	0.21	—	—	—	—	4.70	1.47
49	—	—	—	—	—	—	4.04	1.03
53	—	—	—	—	—	—	3.98	1.23
56	—	—	—	—	—	—	2.98	0.61
59	—	—	—	—	—	—	3.55	1.55
63	—	—	—	—	—	—	2.86	0.57
66	—	—	—	—	—	—	2.52	0.77
70	—	—	—	—	—	—	2.37	0.38
73	—	—	—	—	—	—	2.20	0.70
77	—	—	—	—	—	—	2.02	0.30
79	—	—	—	—	—	—	1.90	0.39
84	—	—	—	—	—	—	2.14	0.18
88	—	—	—	—	—	—	1.71	0.43

Table 23. Mean plasma buprenorphine levels after subcutaneous injection of MSB01-02 in rats

Time (days)	MSB01		MSB02	
	Mean (ng/mL)	S.D. (n = 4)	Mean (ng/mL)	S.D. (n = 4)

0	0.00	0.00	0.00	0.00
0.042	1.04	0.64	6.32	2.80
0.083	2.01	0.68	18.8	5.97
0.25	3.09	0.63	24.2	8.30
1	3.88	0.99	13.2	1.59
3	4.78	1.06	7.22	0.70
7	11.4	3.84	8.63	3.25
10	13.0	3.54	5.67	2.24
14	14.2	0.79	5.47	2.58
21	14.4	1.90	6.04	4.94
28	11.7	2.74	7.58	5.38
35	9.01	1.05	7.64	3.13
42	6.54	1.78	8.31	1.61
49	4.43	0.85	8.19	2.16
56	4.41	0.24	9.74	1.58
63	5.53	1.37	10.2	2.67
70	4.78	0.64	8.45	3.55
77	3.51	1.04	6.30	1.82
84	2.02	0.54	5.39	1.62

[0097] Three buprenorphine decanoate and citric acid salt thereof contained microspheres formulations as shown in Example 5 were prepared as suspension at the concentration of 300 mg/mL. The diluent was composed of 10 mM phosphate-buffered saline, 1.25% sodium carboxymethylcellulose, and 0.05% Tween 80. The suspension formulations were intramuscularly injected in beagle dogs at dose of 18.9 mg/kg buprenorphine equivalent. The pharmacokinetic profile results are shown in FIG. 36 and Table 24.

Table 24. Mean plasma buprenorphine levels after intramuscular injection in dogs

Time (day)	MSA01		MSA02		MSA05	
	Mean (ng/mL)	Standard deviation	Mean (ng/mL)	Standard deviation	Mean (ng/mL)	Standard deviation
0	0.0	0.0	0.0	0.0	0.0	0.0
0.04	0.0	0.0	0.6	0.2	0.5	0.1
0.08	0.1	0.1	0.8	0.1	1.4	0.8
0.17	0.6	0.1	2.0	0.6	2.8	1.3
0.25	1.5	0.2	3.7	0.9	3.5	3.7
1	7.0	5.0	15.6	1.4	14.2	10.3

3	10.1	5.4	16.8	5.7	12.7	8.0
7	16.1	12.4	11.6	4.3	11.9	7.8
10	14.2	6.0	14.1	4.1	11.9	6.0
14	14.4	1.9	14.7	3.1	10.1	4.8
21	10.6	1.5	15.2	4.9	6.6	3.8
28	9.3	4.4	11.8	1.5	6.7	3.4
35	5.3	1.6	8.4	4.5	6.0	3.0
42	4.9	2.4	4.4	0.8	4.1	2.3
49	5.8	5.2	1.7	0.6	4.2	3.0
56	1.6	1.3	0.7	0.9	2.5	1.3
63	1.4	1.1	0.4	0.7	3.1	1.2
70	0.5	0.7	0.0	0.0	2.5	1.1
77	0.6	0.6	0.3	0.5	2.4	1.2
84	0.5	0.7	0.0	0.0	1.9	1.1
91	0.4	0.4	0.1	0.2	0.9	1.0

Example 12: Pharmacokinetic profile of PLGA-based formulations in rats

[0098] The PLGA-based formulations, PS03 and PS10, as prepared in Example 6 were injected subcutaneously or in SD male rats at a dose of 60 mg /kg buprenorphine equivalent. The pharmacokinetic profile results are shown in FIG. 37 and Table 25.

Table 25. Mean plasma buprenorphine levels after intramuscular injection in rats

Time (days)	PS03 Mean (ng/mL)	S.D. (n = 3)	Time (days)	PS10 Mean (ng/mL)	S.D. (n = 4)
0	0.00	0.00	0	0.00	0.00
0.021	0.070	0.12	0.042	2.67	0.23
0.042	0.690	0.38	0.083	4.76	0.87
0.083	1.51	0.78	0.25	10.3	1.63
0.17	3.58	0.92	1	6.98	2.08
0.25	4.07	2.65	3	5.78	1.23
1	1.76	0.33	7	9.39	3.13
3	1.23	0.72	10	8.39	2.73
7	1.66	0.32	14	9.11	4.73
10	2.06	0.23	21	7.31	2.63
14	4.38	1.06	28	8.80	5.57
21	5.02	0.45	35	7.32	3.27

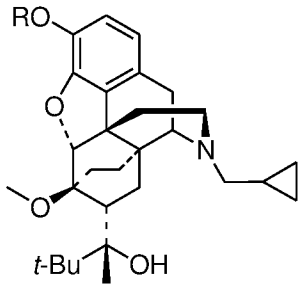
28	4.21	0.26	42	6.22	2.85
35	5.52	1.48	49	5.03	2.03
42	3.09	0.35	56	4.13	1.10
49	2.75	0.32	63	4.75	1.81
56	1.99	0.46	70	4.70	1.69
63	2.23	0.43	77	3.90	0.92
70	2.01	0.38	84	3.27	0.61
77	1.83	0.31	—	—	—
84	1.09	0.45	—	—	—
91	1.25	0.22	—	—	—
98	0.830	0.25	—	—	—
105	1.09	0.32	—	—	—
112	1.10	0.29	—	—	—
119	1.09	0.31	—	—	—
126	1.04	0.26	—	—	—
133	1.02	0.44	—	—	—
140	0.950	0.12	—	—	—
147	0.870	0.23	—	—	—

[0099] The embodiments described above are intended to be merely exemplary, and those skilled in the art will recognize, or will be able to ascertain using no more than routine experimentation, numerous equivalents of specific compounds, materials, and procedures. All such equivalents are considered to be within the scope of the disclosure and are encompassed by the appended claims.

CLAIMS

What is claimed is:

1. A crystalline form of 3-acyl-buprenorphine represented by Formula II:



(II)

wherein R is an acyl group having a straight chain or a branched chain alkyl portion of 1 to 17 carbon atoms, and the crystalline form is characterized by an X-ray powder diffraction pattern comprising peaks at 4.70, 8.44, 9.38, 20.56, or peaks at 6.03, 9.08, 9.58, 9.68, or peaks at 5.98, 9.43, 11.83, 11.93, or peaks at 7.53, 8.13, 13.48, 16.03, or peaks at 5.80, 8.00, 11.50, 17.34 or peaks at 5.68, 8.03, 11.38, 17.23 degrees 2θ ± 0.2 degrees 2θ.

2. The crystalline form of claim 1, wherein the 3-acyl-buprenorphine is buprenorphine acetate having an X-ray powder diffraction pattern substantially in accordance with that shown in FIG. 1, or wherein the 3-acyl-buprenorphine is buprenorphine pivalate having an X-ray powder diffraction pattern substantially in accordance with that shown in FIG. 5, or wherein the 3-acyl-buprenorphine is buprenorphine pentanoate having an X-ray powder diffraction pattern substantially in accordance with that shown in FIG. 9, or wherein the 3-acyl-buprenorphine is buprenorphine hexanoate having an X-ray powder diffraction pattern substantially in accordance with that shown in FIG. 13, or wherein the 3-acyl-buprenorphine is buprenorphine decanoate having an X-ray powder diffraction pattern substantially in accordance with that shown in FIG. 17, or wherein the 3-acyl-buprenorphine is buprenorphine dodecanoate having an X-ray powder diffraction pattern substantially in accordance with that shown in FIG. 21.

3. A sustained release pharmaceutical composition comprising the crystalline form of claim 1 or 2, and a pharmaceutically acceptable carrier thereof.

4. An aqueous injectable pharmaceutical suspension comprising the crystalline form of claim 1 or 2, or a pharmaceutically acceptable salt thereof, in a suspending aqueous diluent, exhibiting a steady release profile lasting over at least one week when injected into a patient or an animal and without including an organic solvent, a polylactide polymer, a polyglycolide polymer, or a copolymer of polylactide and polyglycolide.

5. The injectable pharmaceutical suspension according to claim 4, having an average particle size of less than 80 μm.

6. The injectable pharmaceutical suspension according to claim 4, wherein the suspending aqueous diluent comprising a polyethylene glycol polymer and polysorbate in phosphate buffered saline.

7. The injectable pharmaceutical suspension according to claim 4, wherein the 3-acyl-buprenorphine or a pharmaceutically acceptable salt thereof is present at a concentration of 5% to 30% w/w.

8. An injectable pharmaceutical composition, comprising 3-acyl-buprenorphine or a pharmaceutically acceptable salt thereof in a controlled release matrix and a biocompatible solvent, exhibiting a steady release profile lasting over at least one month when injected into a patient or an animal.

9. The injectable pharmaceutical composition according to claim 8, wherein the controlled released matrix is selected from poly(lactide-co-glycolide), sucrose acetoisobutyrate, lecithin, diolein or a combination of two or more thereof.

10. The injectable pharmaceutical composition according to claim 8, wherein the biocompatible solvent is selected from the group consisting of *N*-methyl-2-pyrrolidone, ethyl acetate, ethanol, butanol, 2-butanol, isobutanol, isopropanol, glycerin, benzyl benzoate, dimethyl sulfoxide, *N*,*N*-dimethylacetamide, propylene glycol, dimethyl glycol, benzyl alcohol, and a combination of two or more thereof.

11. The injectable pharmaceutical formulation according to claim 8, wherein the 3-acyl-buprenorphine has an acyl group having a straight chain or a branched chain alkyl portion of 1 to 17 carbon atoms.

12. An injectable sustained release microspheres formulation comprising a pharmaceutically effective amount of 3-acyl-buprenorphine or a salt form thereof encapsulated with poly(lactide-co-glycolide) suspended in an aqueous diluent, exhibiting a steady release profile lasting over at least one month when injected into a patient or an animal.

13. The injectable sustained release microspheres formulation according to claim 12, wherein the 3-acyl-buprenorphine has an acyl group having a straight chain or a branched chain alkyl portion of 1 to 17 carbon atoms.

14. A method for treating opioid addiction, pain or depression, the method comprising administrating the aqueous injectable pharmaceutical suspension according to claim 4, the injectable pharmaceutical composition according to claim 8, or the injectable sustained release microspheres formulation according to claim 12 to a subject in need thereof subcutaneously or intramuscularly with a therapeutically effective duration of at least one week.

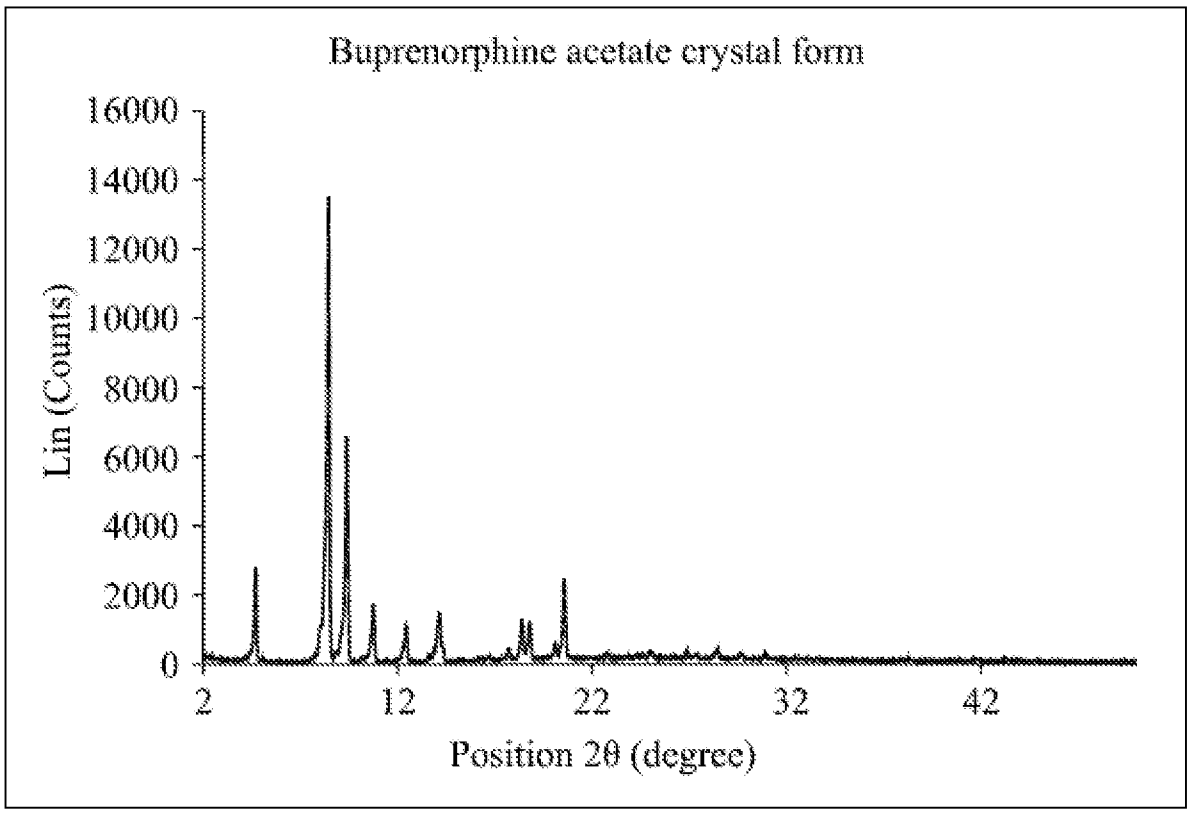

Buprenorphine acetate crystal form
16000
14000
12000
10000
8000
6000
4000
2000
0
Lin (Counts)
2
12
22
32
42
Position 2θ (degree)

FIG. 1

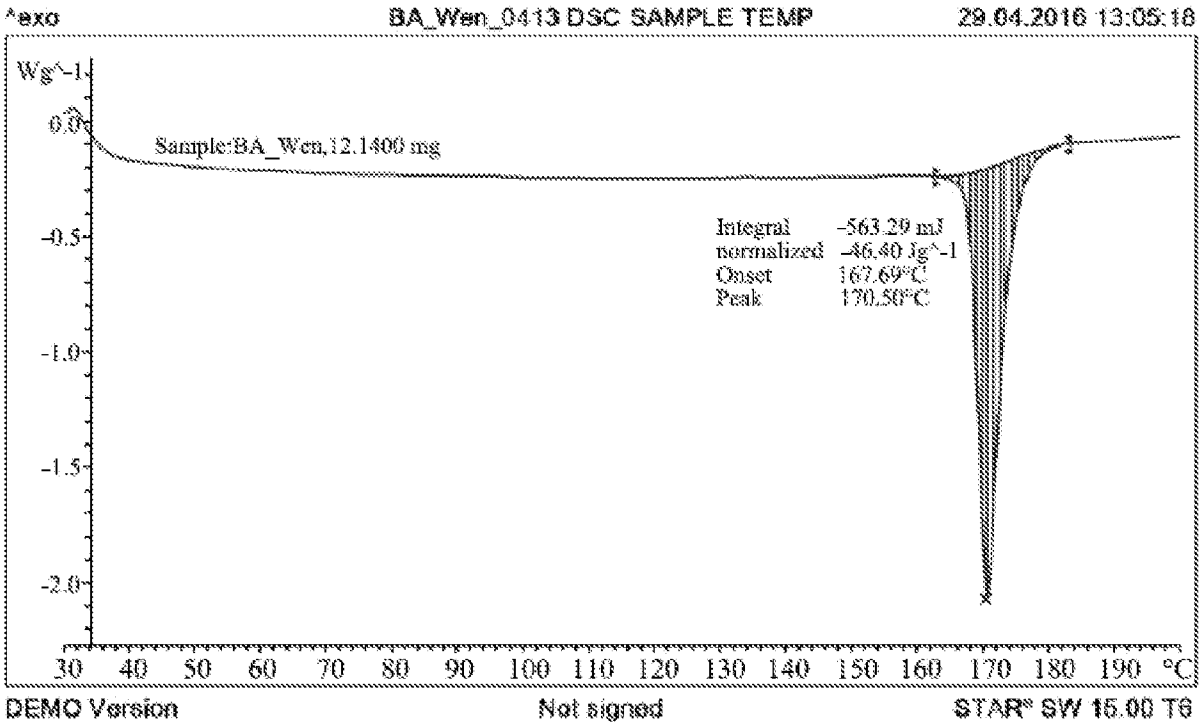

^exo
BA_Wen_0413 DSC SAMPLE TEMP
29.04.2016 13:05:18
Wg^-1
0.0
-0.5
-1.0
-1.5
-2.0
Sample:BA_Wen,12.1400 mg
Integral -563.29 mJ
normalized -46.40 Jg^-1
Onset 167.69°C
Peak 170.50°C
30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 °C
DEMO Version
Not signed
STAR° SW 15.00 T6

FIG. 2

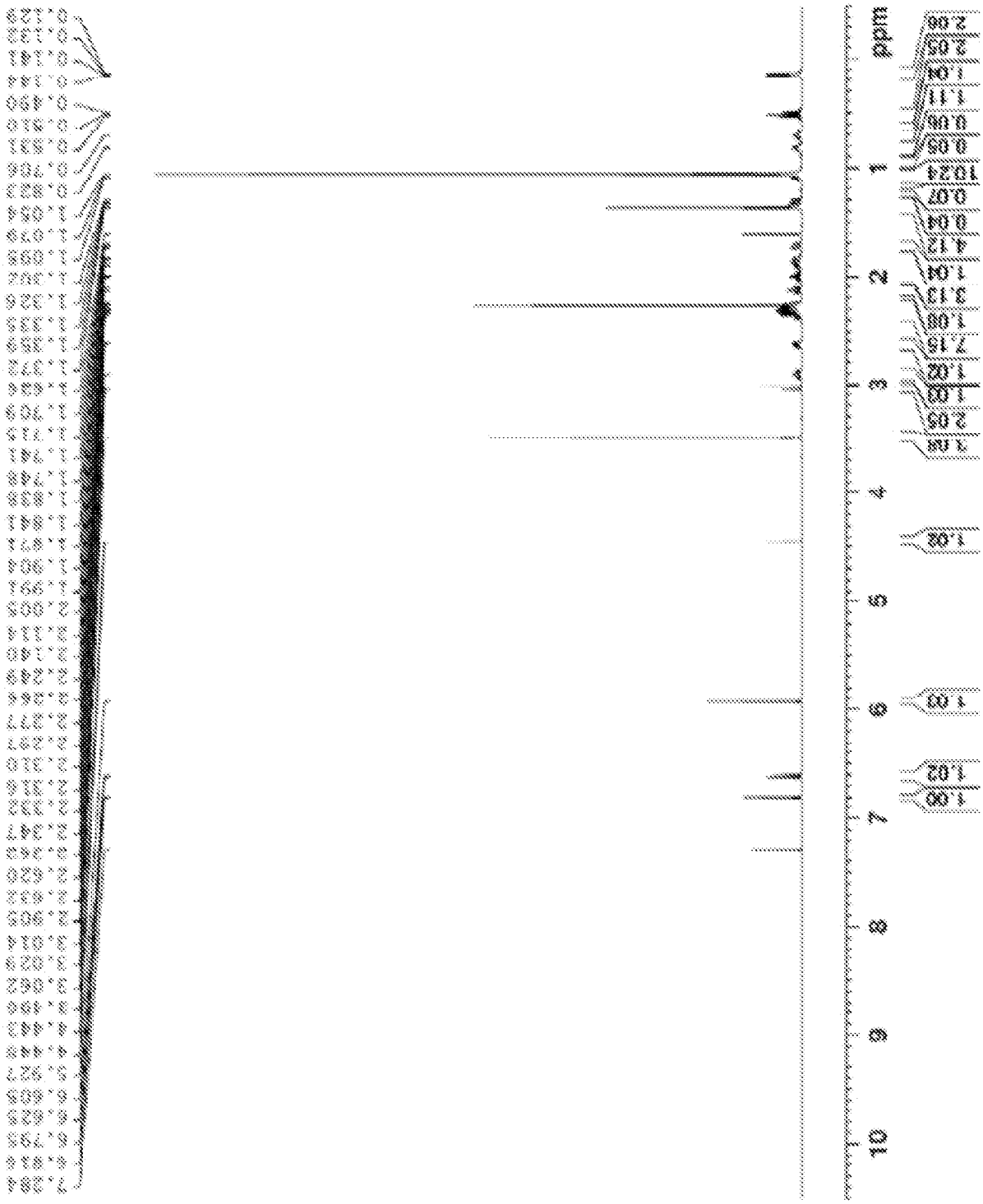

ppm
1 2 3 4 5 6 7 8 9 10
2.06
2.05
1.04
1.11
0.96
0.95
10.24
0.07
0.04
4.12
1.04
3.13
1.08
7.15
1.02
1.03
2.05
1.08
1.02
1.03
1.00

FIG. 3

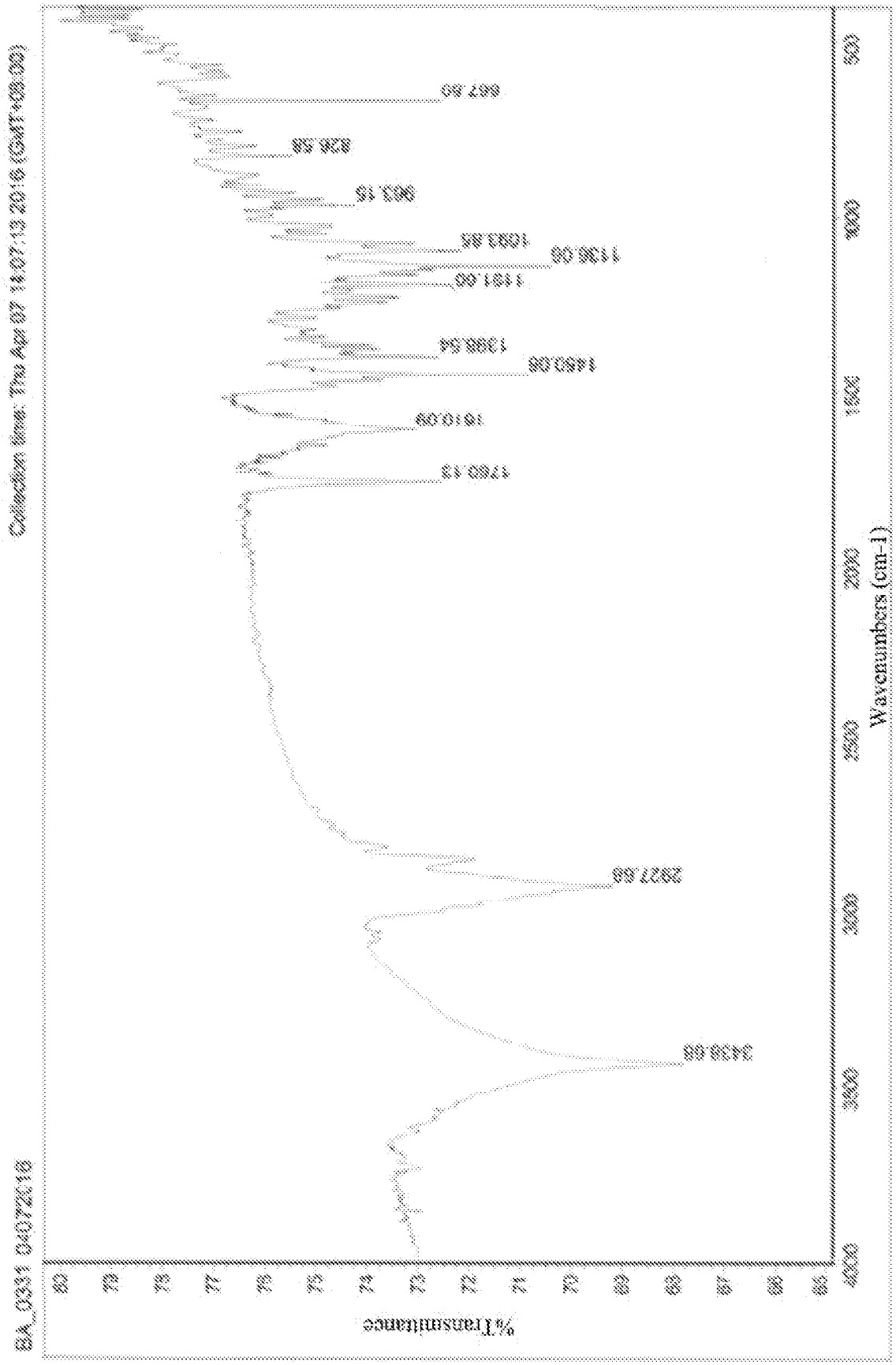

Collection time: Thu Apr 07 14:07:13 2016 (GMT+08:00)
BA_0331 040722C18
%Transmittance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
500
667.80
826.58
903.15
1093.85
1136.08
1191.60
1388.54
1450.08
1610.09
1760.13
2927.69
3439.08

FIG. 4

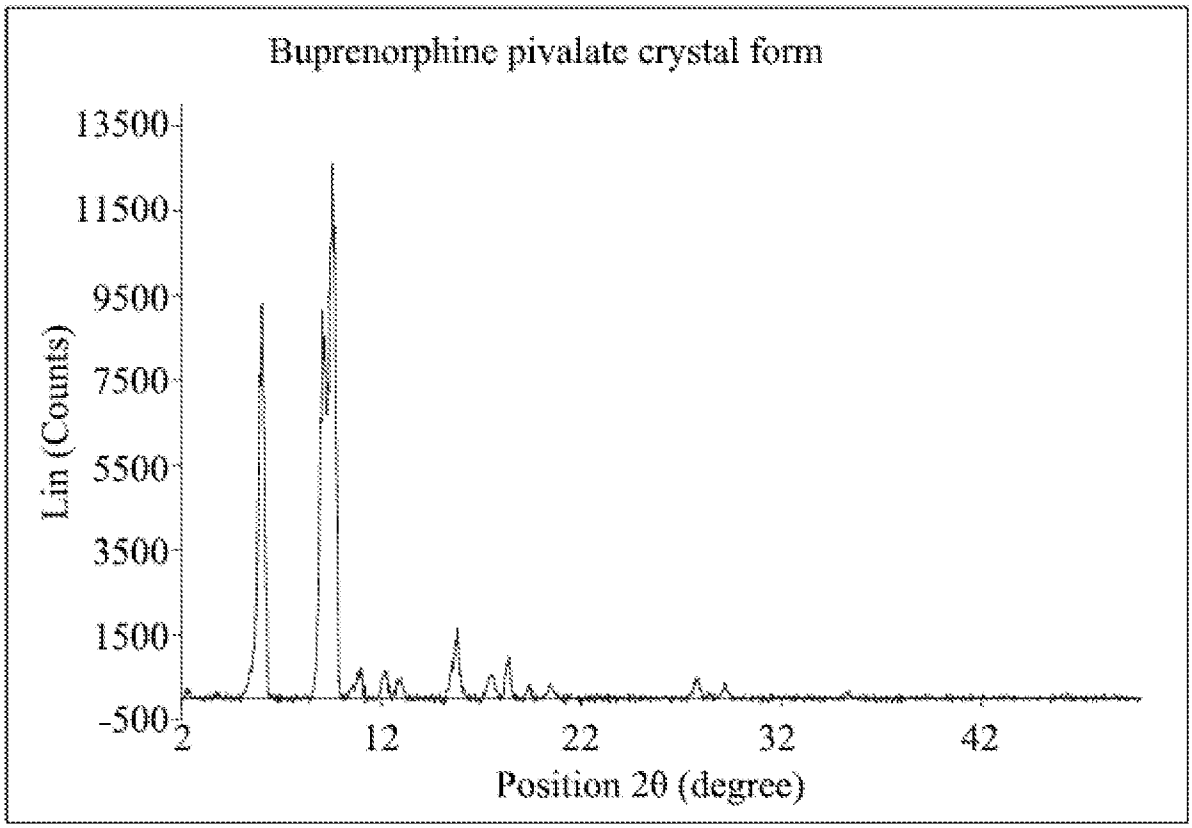

Buprenorphine pivalate crystal form
13500
11500
9500
7500
5500
3500
1500
-500
Lin (Counts)
2
12
22
32
42
Position 2θ (degree)

FIG. 5

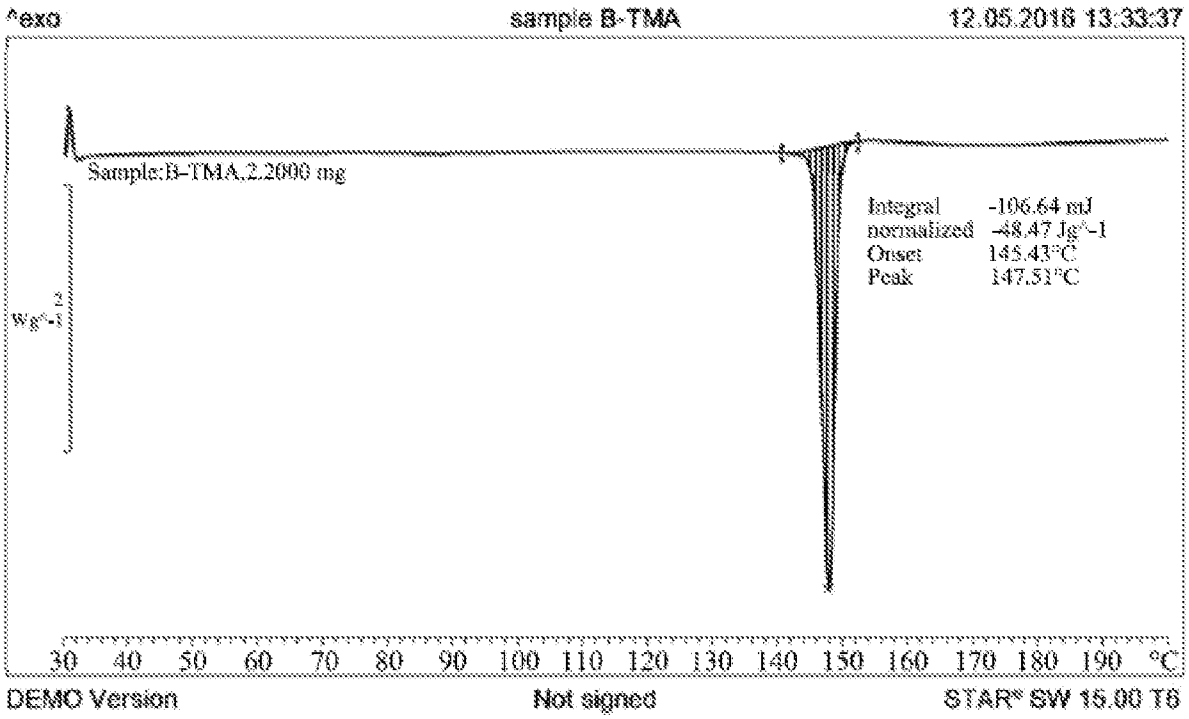

^exo
sample B-TMA
12.05.2016 13:33:37
Sample:B-TMA,2.2000 mg
Integral -106.64 mJ
normalized -48.47 Jg^-1
Onset 145.43°C
Peak 147.51°C
30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 °C
DEMO Version
Not signed
STAR^e SW 15.00 T6

FIG. 6

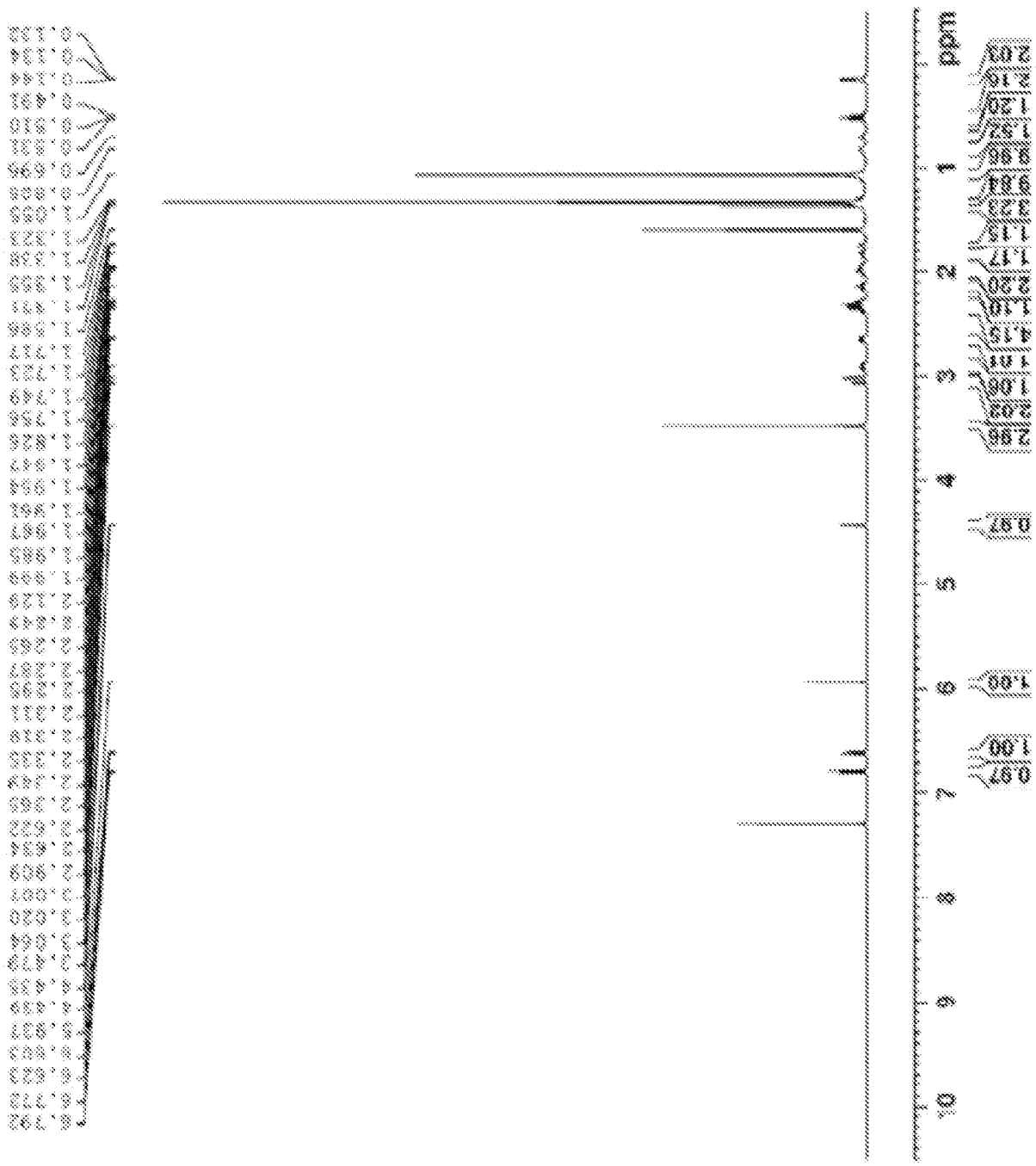

ppm
0 1 2 3 4 5 6 7 8 9 10
2.03
2.15
1.20
1.52
3.86
3.24
3.23
1.15
1.17
2.20
1.10
4.15
1.06
2.02
2.96
0.97
1.00
0.97
1.00

FIG. 7

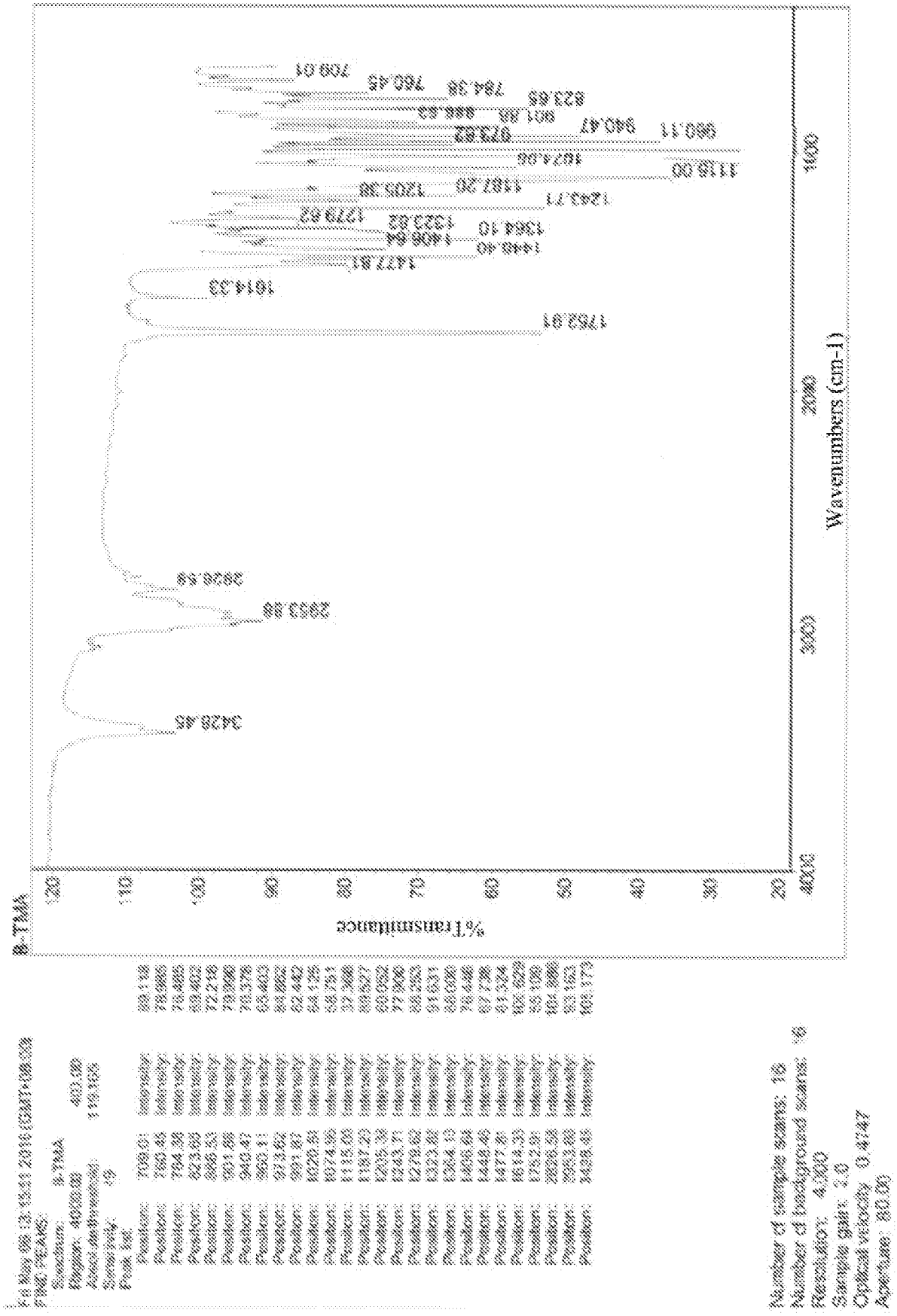

B-TMA
%Transmittance
Wavenumbers (cm-1)
4000
3000
2000
1000
3428.45
2953.88
3926.59
1753.91
1614.33
1477.81
1448.40
1406.64
1364.10
1323.02
1279.62
1243.71
1205.38
1167.20
1139.00
1074.06
973.62
940.47
860.11
823.65
784.38
760.45
709.01

FIG. 8

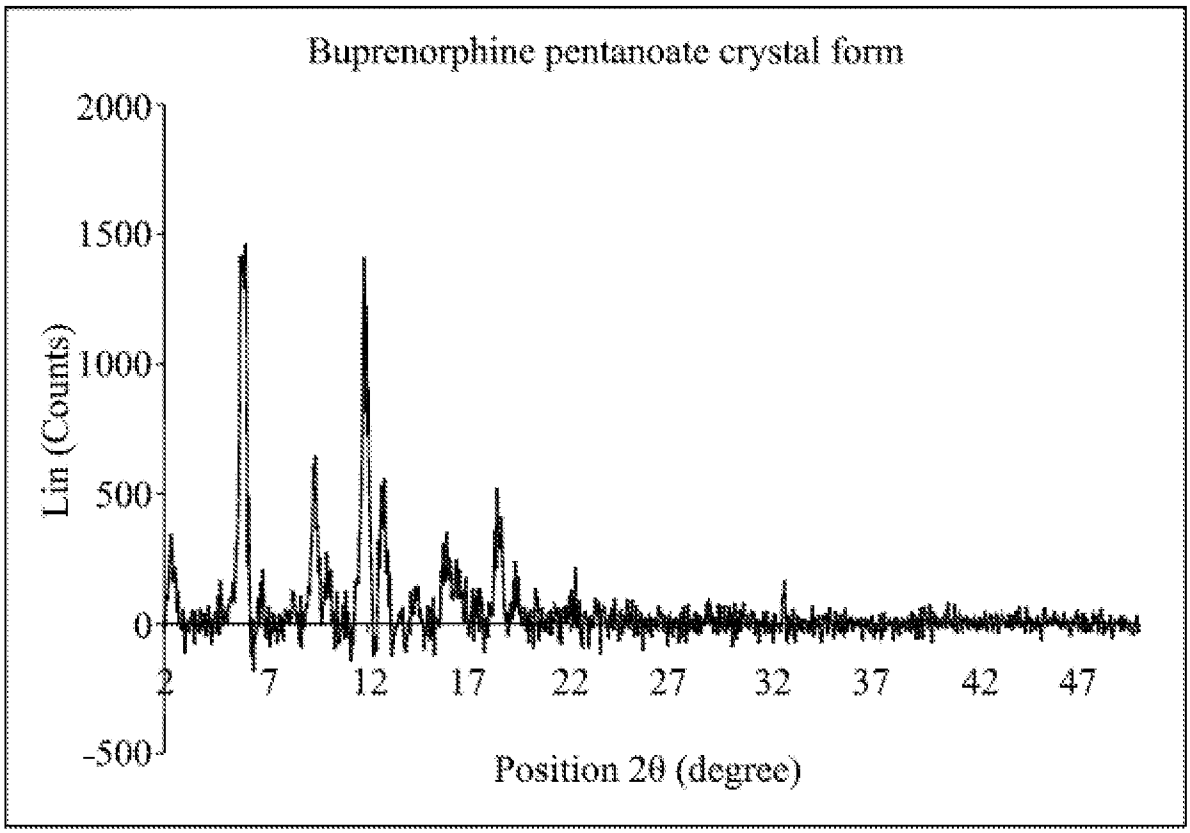

Buprenorphine pentanoate crystal form
2000
1500
1000
500
0
-500
Lin (Counts)
2
7
12
17
22
27
32
37
42
47
Position 2θ (degree)

FIG. 9

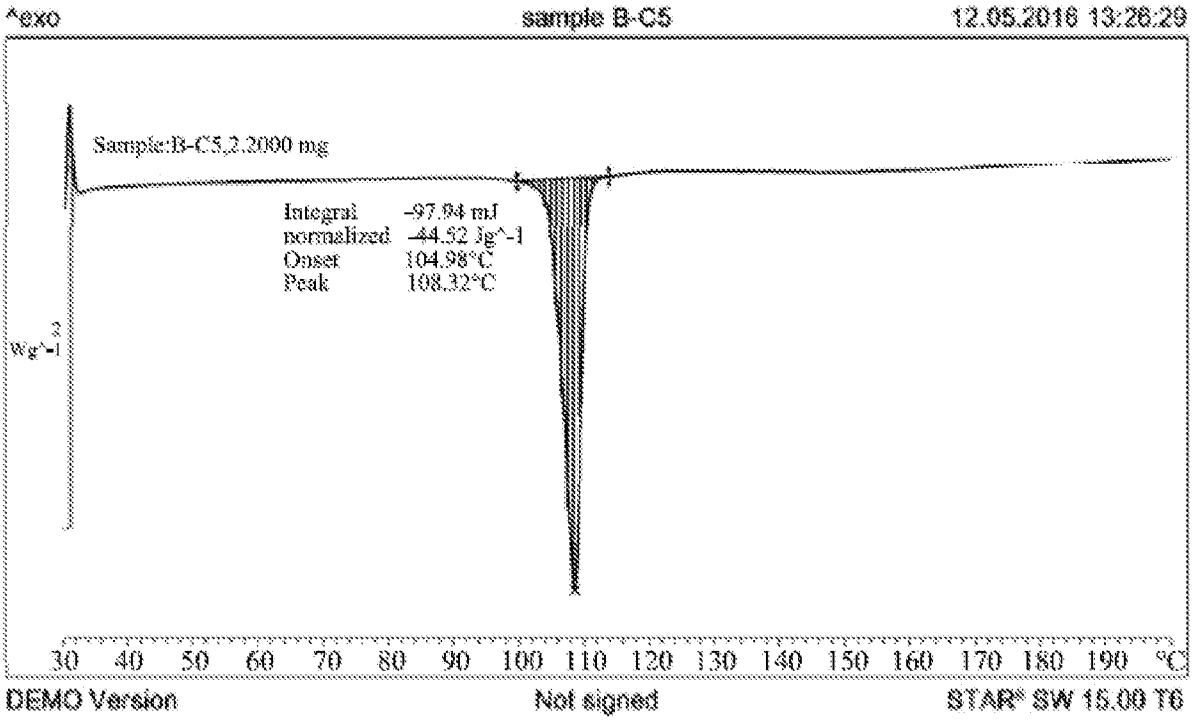

^exo
sample B-C5
12.05.2016 13:28:29
Sample:B-C5,2.2000 mg
Integral -97.94 mJ
normalized -44.52 Jg^-1
Onset 104.98°C
Peak 108.32°C
30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 °C
DEMO Version
Not signed
STAR® SW 15.00 T6

FIG. 10

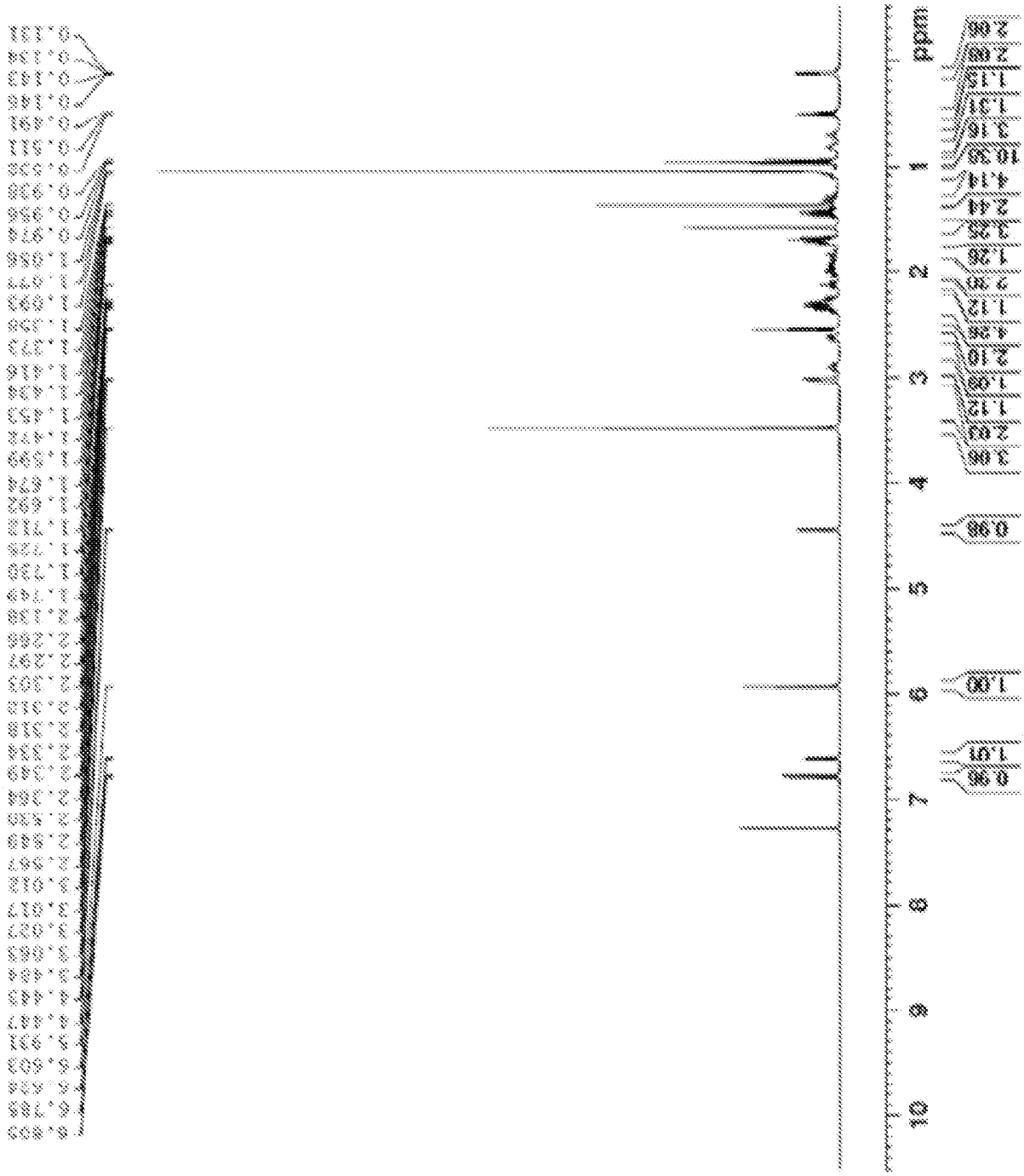

ppm
1 2 3 4 5 6 7 8 9 10
2.06
2.08
1.15
1.31
3.16
10.30
4.14
2.14
3.25
1.28
2.30
1.12
4.26
2.10
1.09
1.12
2.03
3.06
0.98
1.00
1.01
0.96

FIG. 11

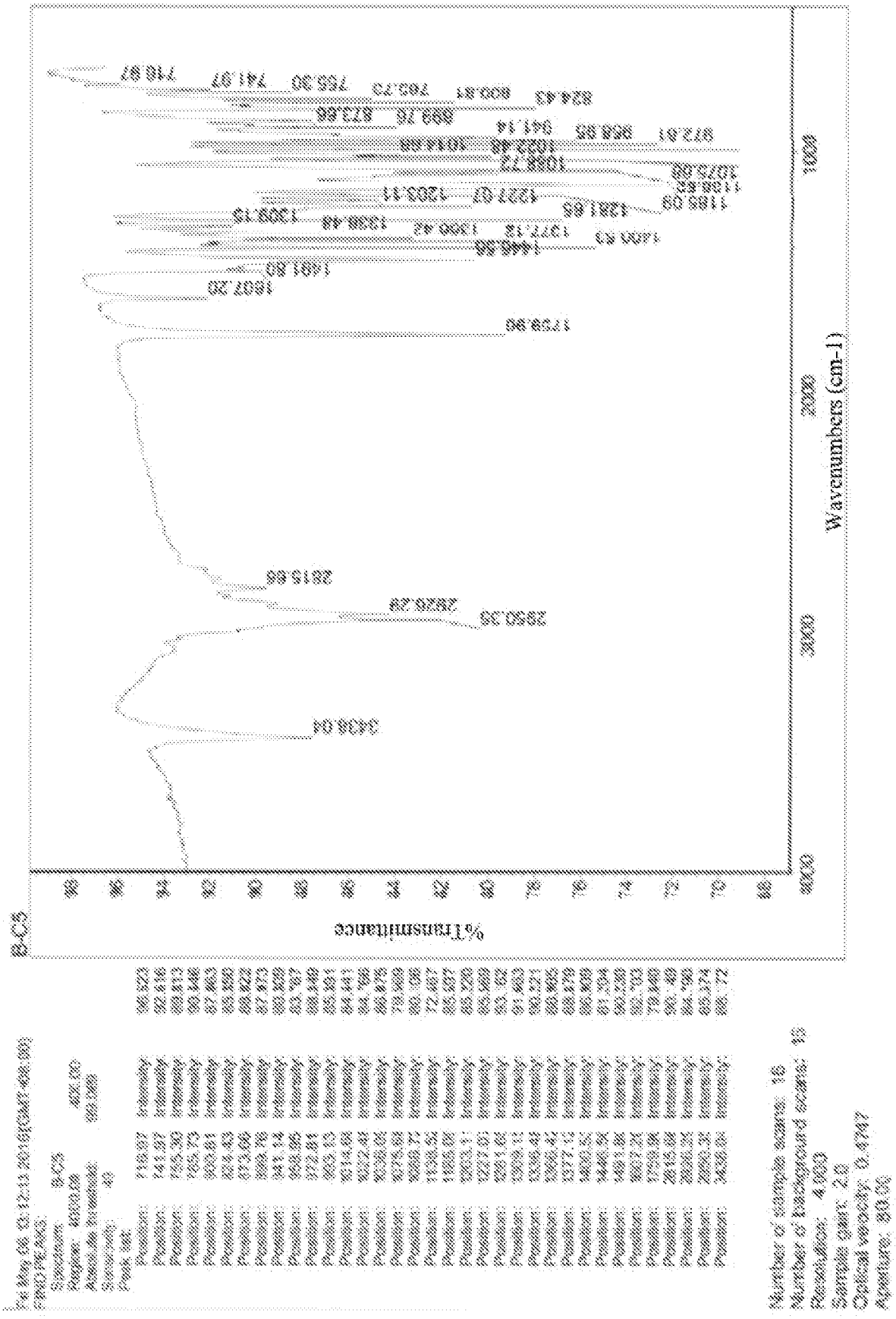

Wavenumbers (cm-1)
%Transmittance
3438.04
2950.35
2926.29
2815.66
1727.38
1602.20
1458.58
1377.13
1238.48
1227.07
1203.11
1128.62
1075.68
1023.46
1014.08
898.26
841.14
755.30
741.07
718.87

FIG. 12

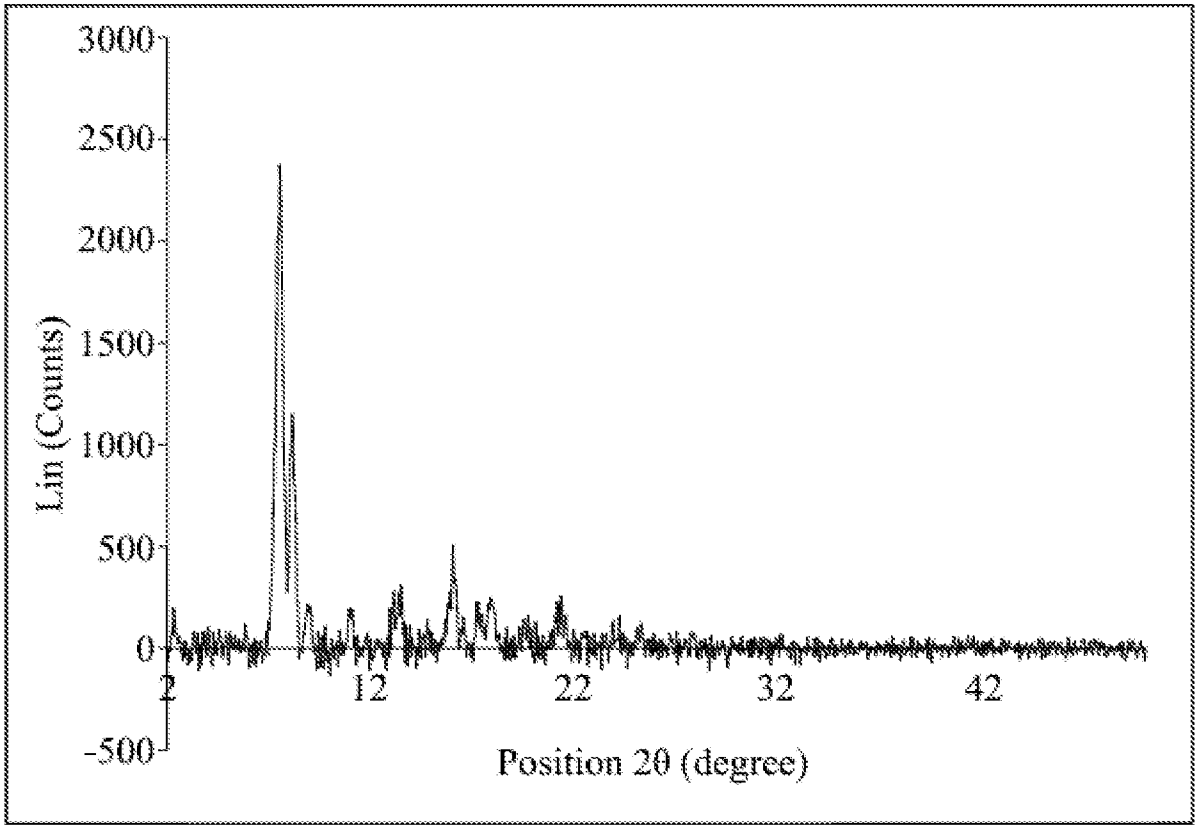

3000
2500
2000
1500
1000
500
0
-500
Lin (Counts)
2
12
22
32
42
Position 2θ (degree)

FIG. 13

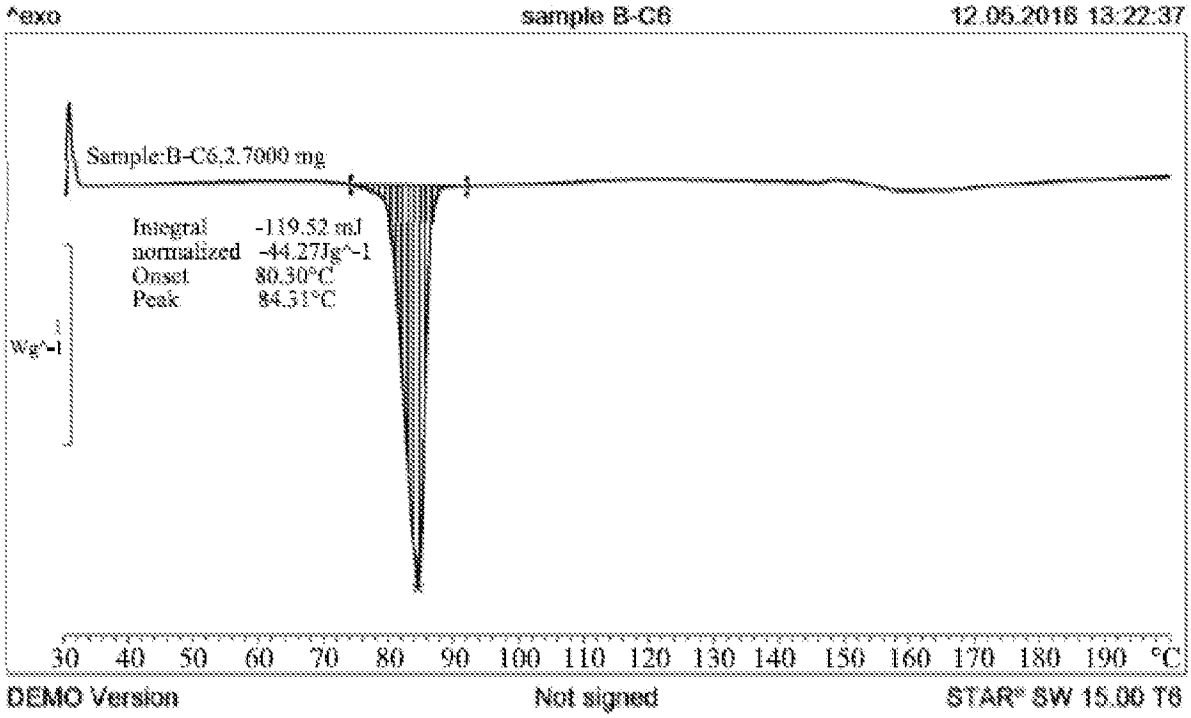

^exo
sample B-C6
12.05.2016 13:22:37
Sample:B-C6,2.7000 mg
Integral -119.52 mJ
normalized -44.27Jg^-1
Onset 80.30°C
Peak 84.31°C
W/g^-1
30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 °C
DEMO Version
Not signed
STAR° SW 15.00 T8

FIG. 14

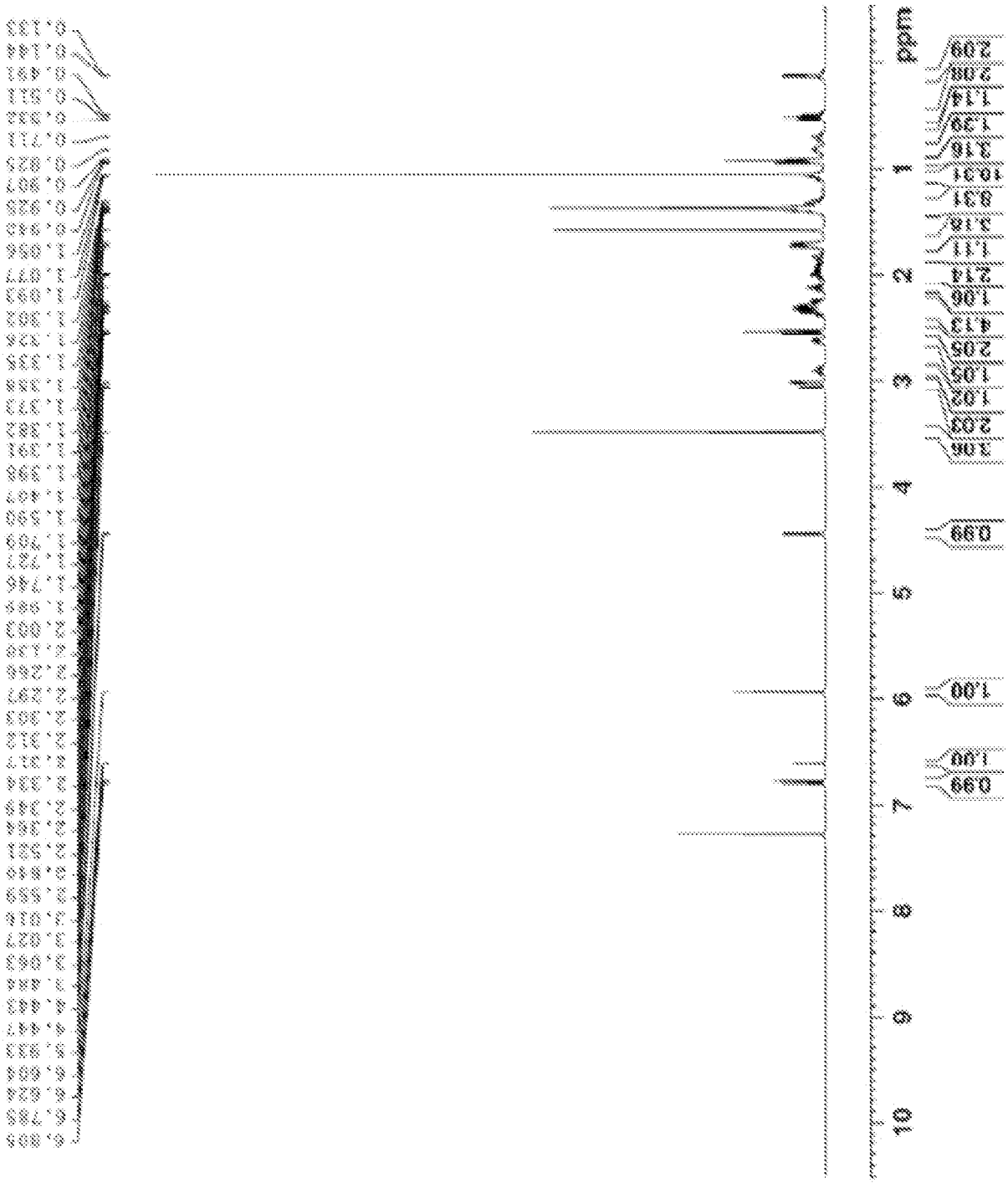

ppm
1
2
3
4
5
6
7
8
9
10
2.09
2.08
1.14
1.39
3.16
10.31
8.31
3.16
1.11
2.13
1.06
4.13
2.05
1.05
1.02
2.03
3.06
0.99
1.00
1.09
0.99

FIG. 15

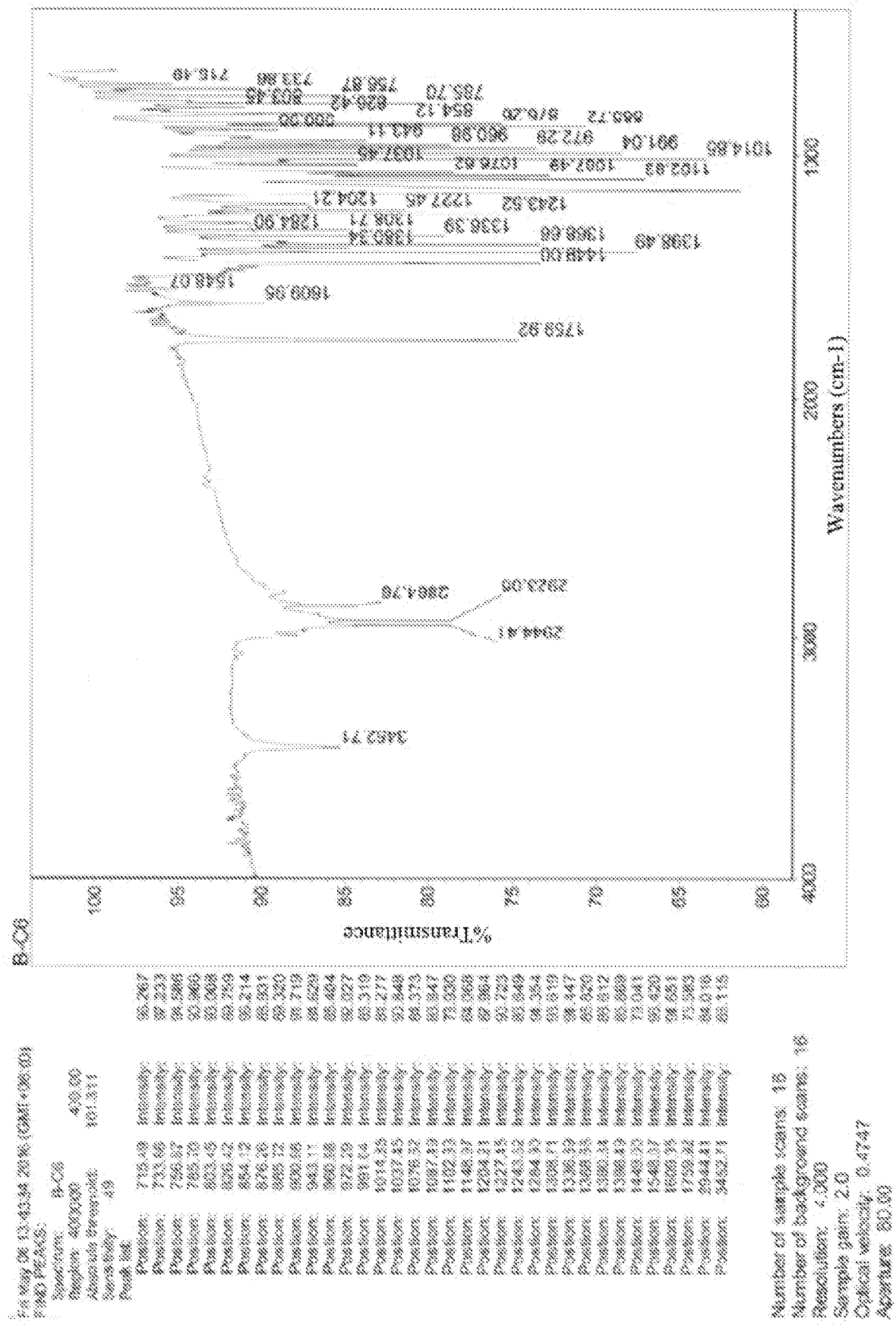

B-C6
%Transmittance
Wavenumbers (cm-1)
4000
3000
2000
1000
3452.71
2944.41
2923.06
2854.12
1736.62
1727.45
1454.00
1384.78
1336.39
1284.90
1243.02
1204.21
1102.83
1082.49
1037.45
1014.86
972.29
901.04
854.12
820.42
803.45
785.70
750.87
733.86
716.49
1750.92
1600.35
1548.07
1308.49
Number of sample scans: 16
Number of background scans: 16
Resolution: 4.000
Sample gain: 2.0
Optical velocity: 0.47747
Aperture: 80.00

FIG. 16

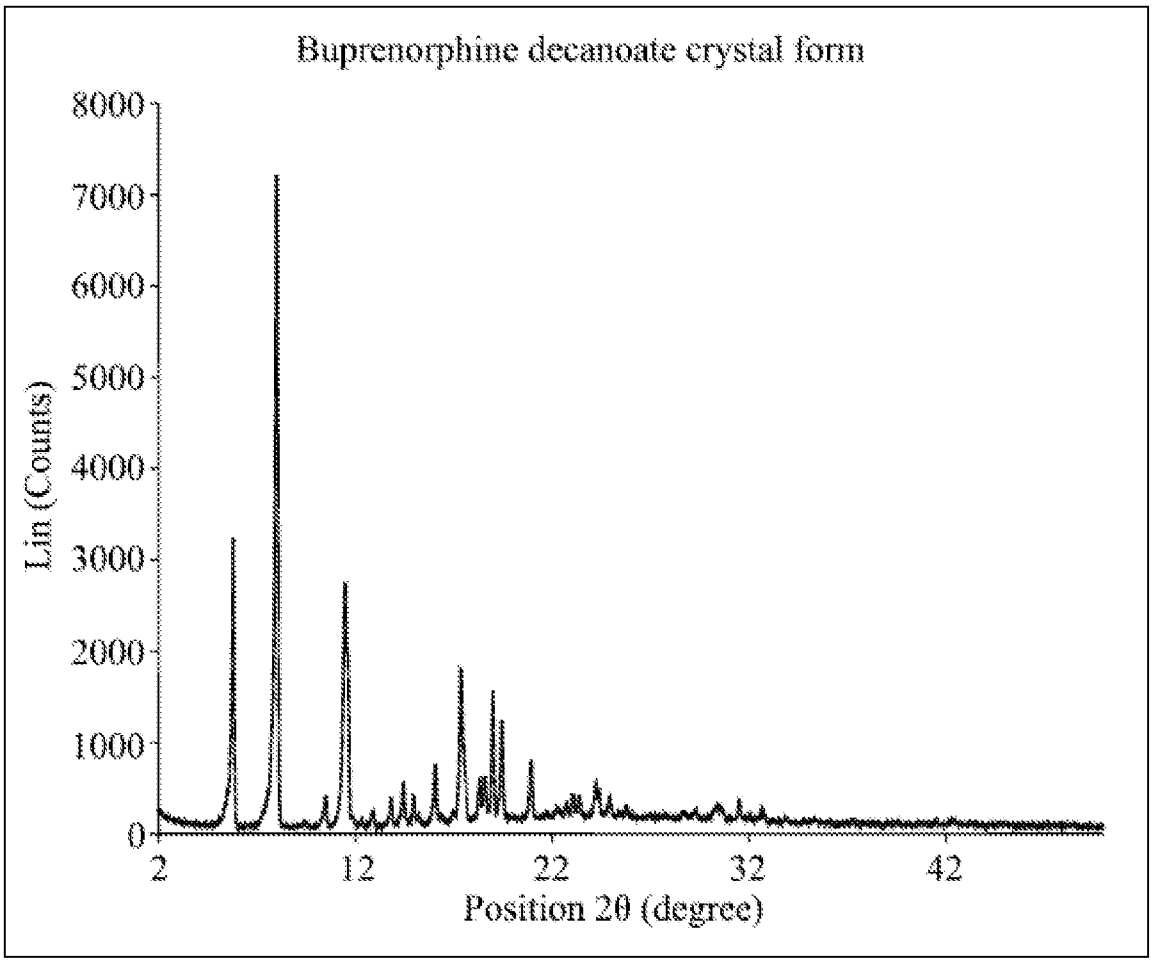

Buprenorphine decanoate crystal form
Lin (Counts)
8000
7000
6000
5000
4000
3000
2000
1000
0
2
12
22
32
42
Position 20 (degree)

FIG. 17

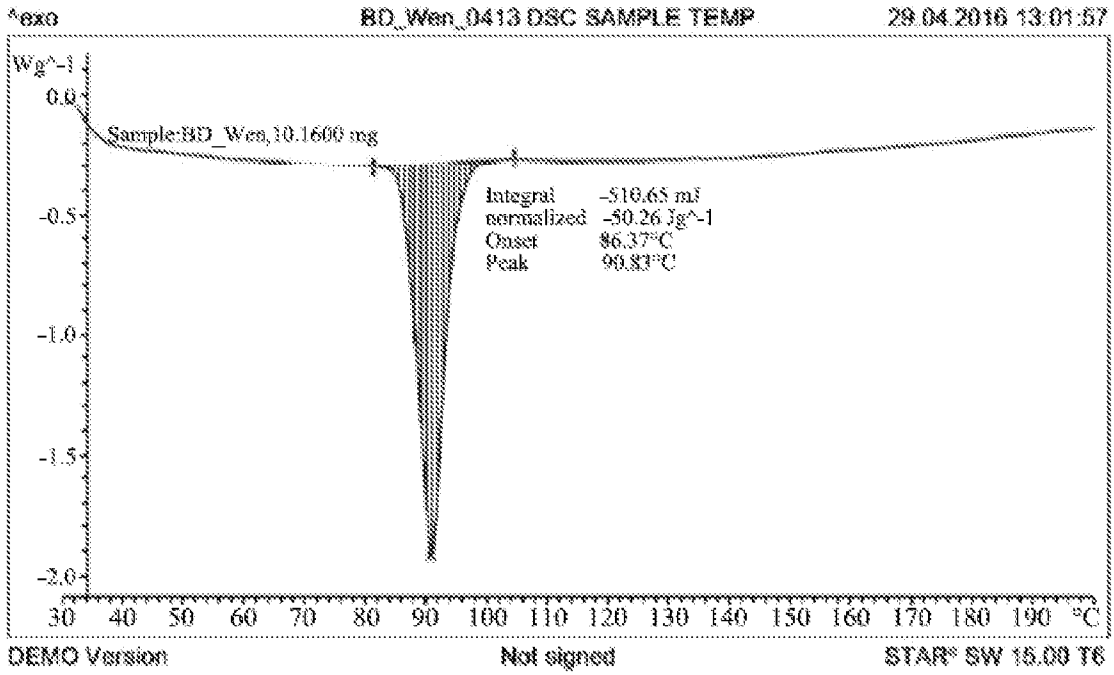

^exo
BD_Wen_0413 DSC SAMPLE TEMP
29.04.2016 13:01:57
Wg^-1
0.0
-0.5
-1.0
-1.5
-2.0
Sample:BD_Wen,10.1600 mg
Integral -516.65 mJ
normalized -50.26 Jg^-1
Onset 86.37°C
Peak 90.83°C
30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 °C
DEMO Version
Not signed
STAR° SW 15.00 T6

FIG. 18

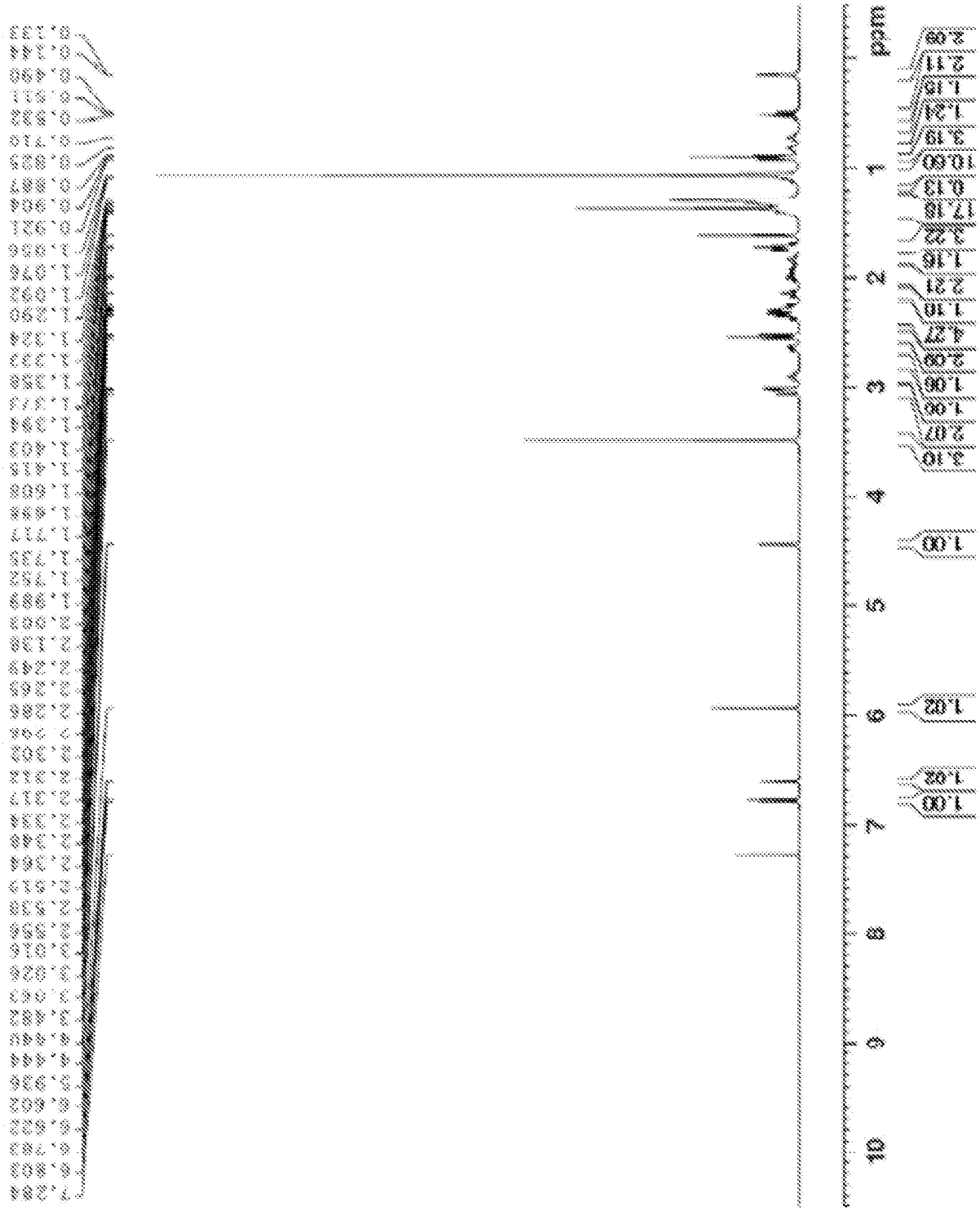


FIG. 19

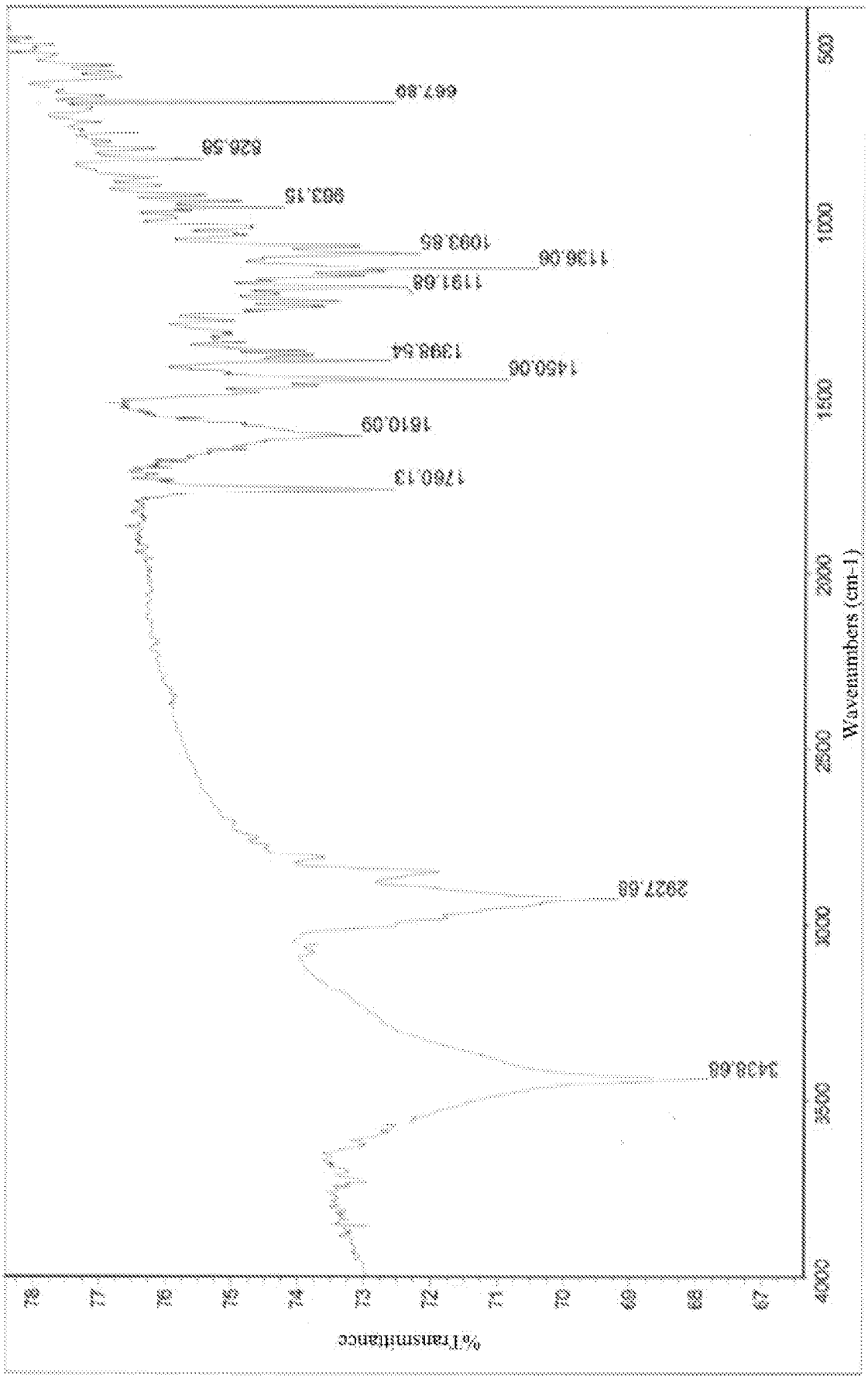

667.89
826.58
883.15
1093.65
1136.06
1191.68
1398.54
1450.06
1610.09
1760.13
2927.69
3428.63
%Transmittance
Wavenumbers (cm-1)

FIG. 20

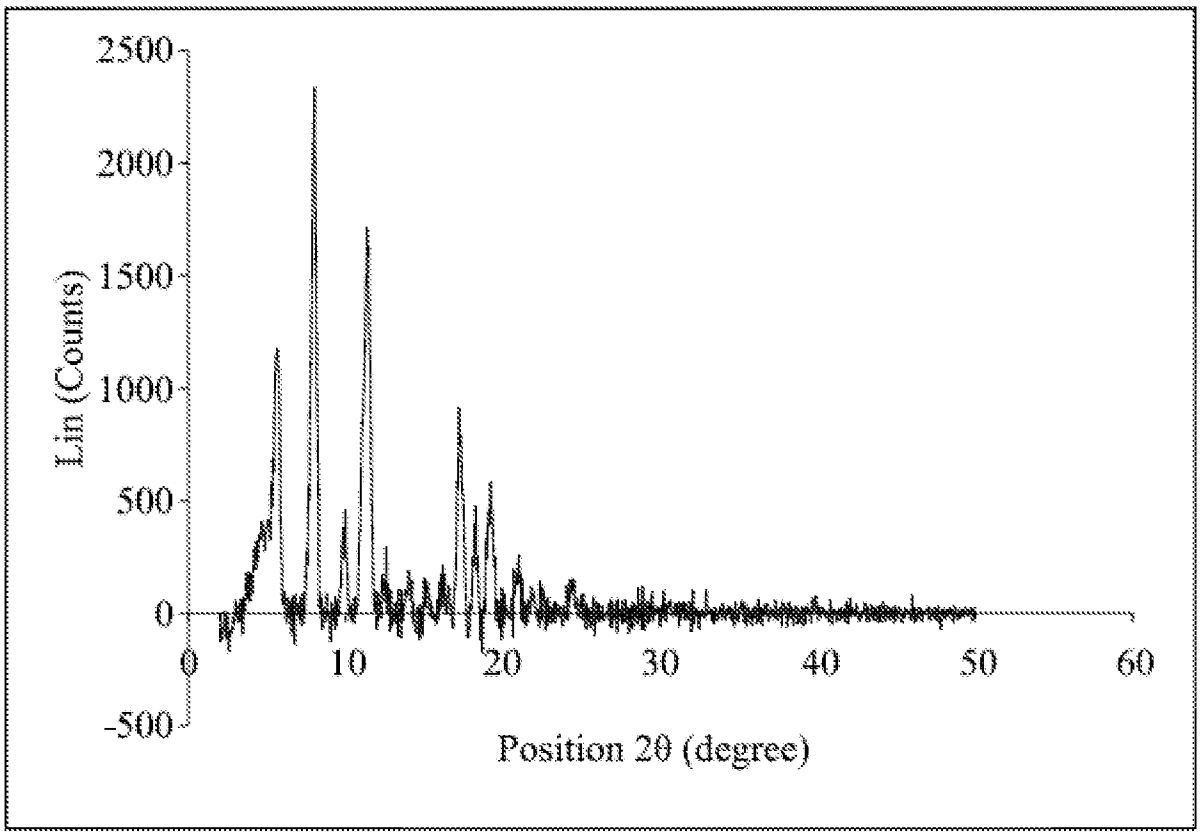

2500
2000
1500
1000
500
0
-500
Lin (Counts)
0
10
20
30
40
50
60
Position 2θ (degree)

FIG. 21

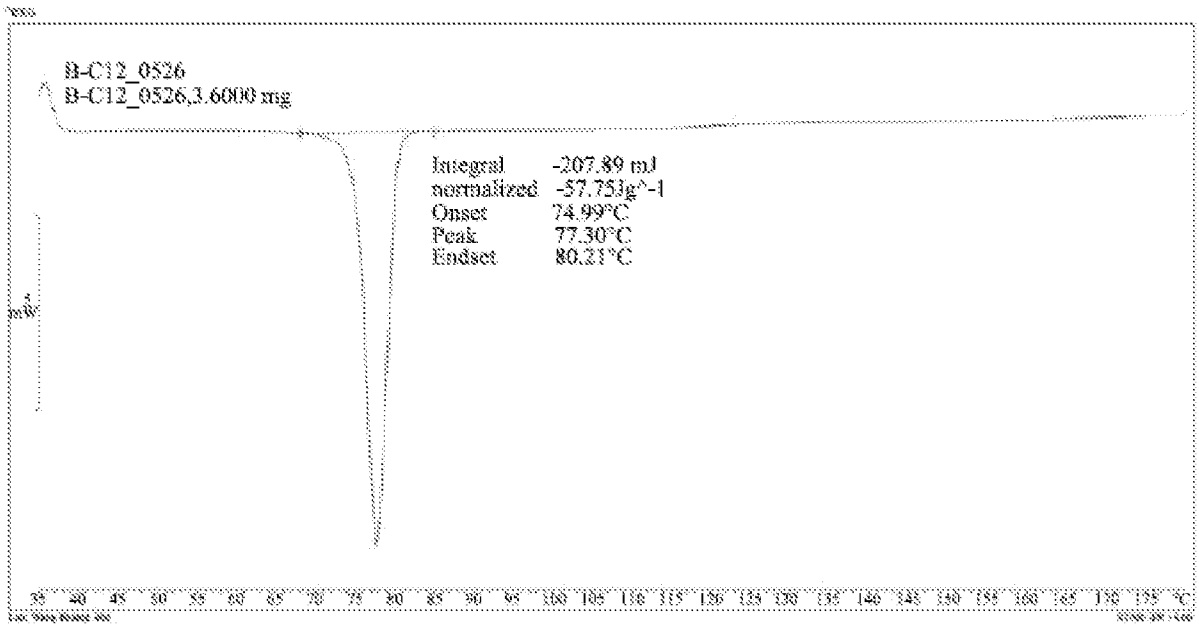

B-C12_0526
B-C12_0526,3.6000 mg
Integral -207.89 mJ
normalized -57.753g^-1
Onset 74.99°C
Peak 77.30°C
Endset 80.21°C

FIG. 22

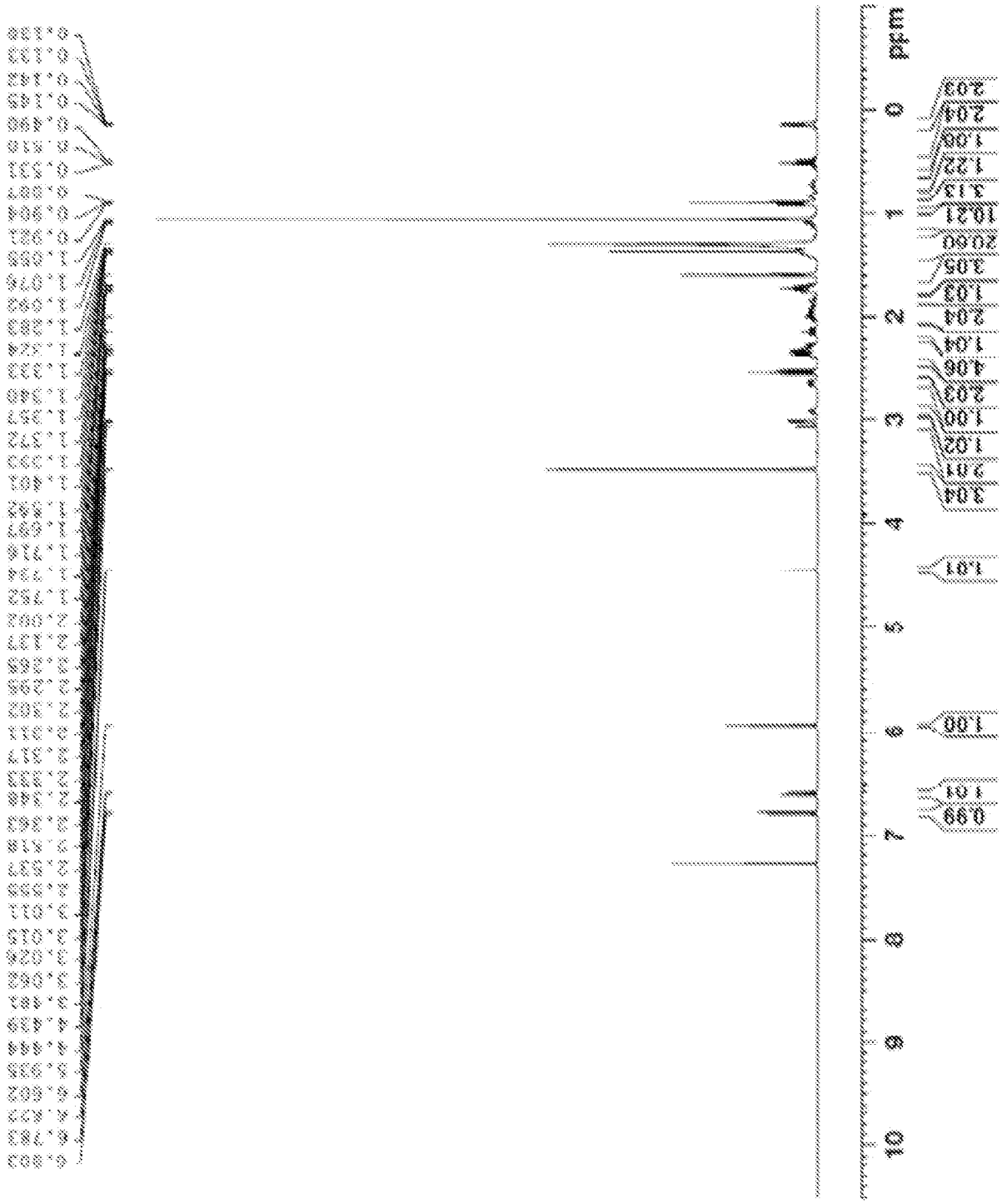

ppm
0
1
2
3
4
5
6
7
8
9
10
3.04
2.01
1.02
1.00
2.03
4.06
1.04
2.04
1.03
3.05
2.00
10.21
3.13
1.22
1.09
2.04
2.03
1.01
1.00
0.99
1.01

FIG. 23

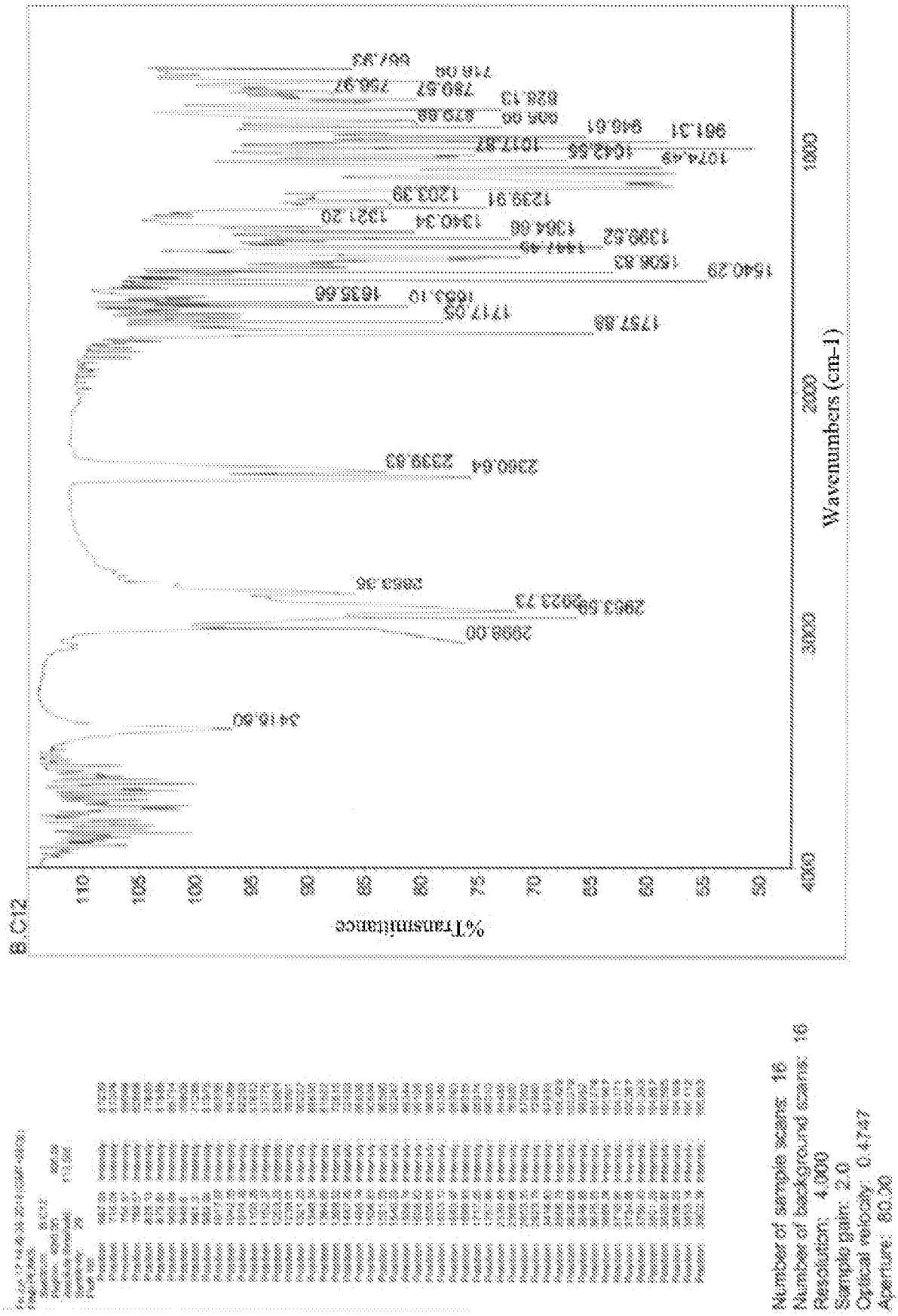

%Transmittance
Wavenumbers (cm-1)
4000
3000
2000
1000
2916.80
2850.36
2923.73
2359.83
1737.08
1540.29
1398.62
1074.49
901.31
840.61
730.97
667.36

FIG. 24

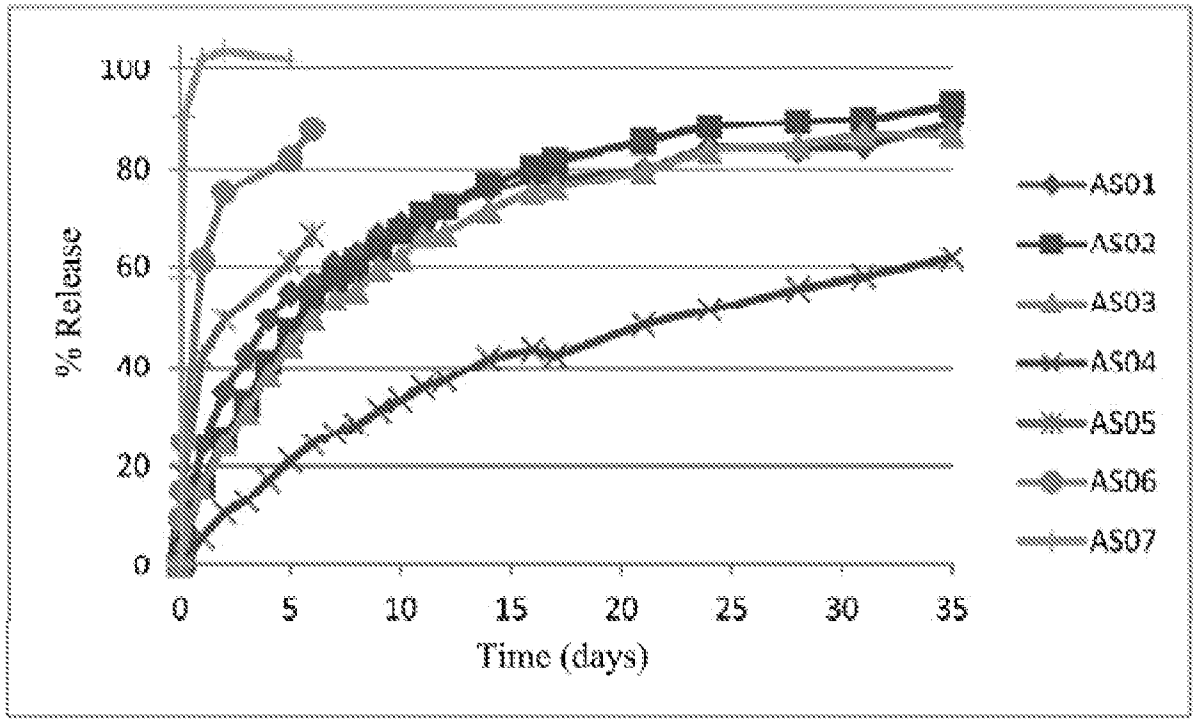

100
80
60
40
20
0
% Release
0
5
10
15
20
25
30
35
Time (days)
AS01
AS02
AS03
AS04
AS05
AS06
AS07

FIG. 25

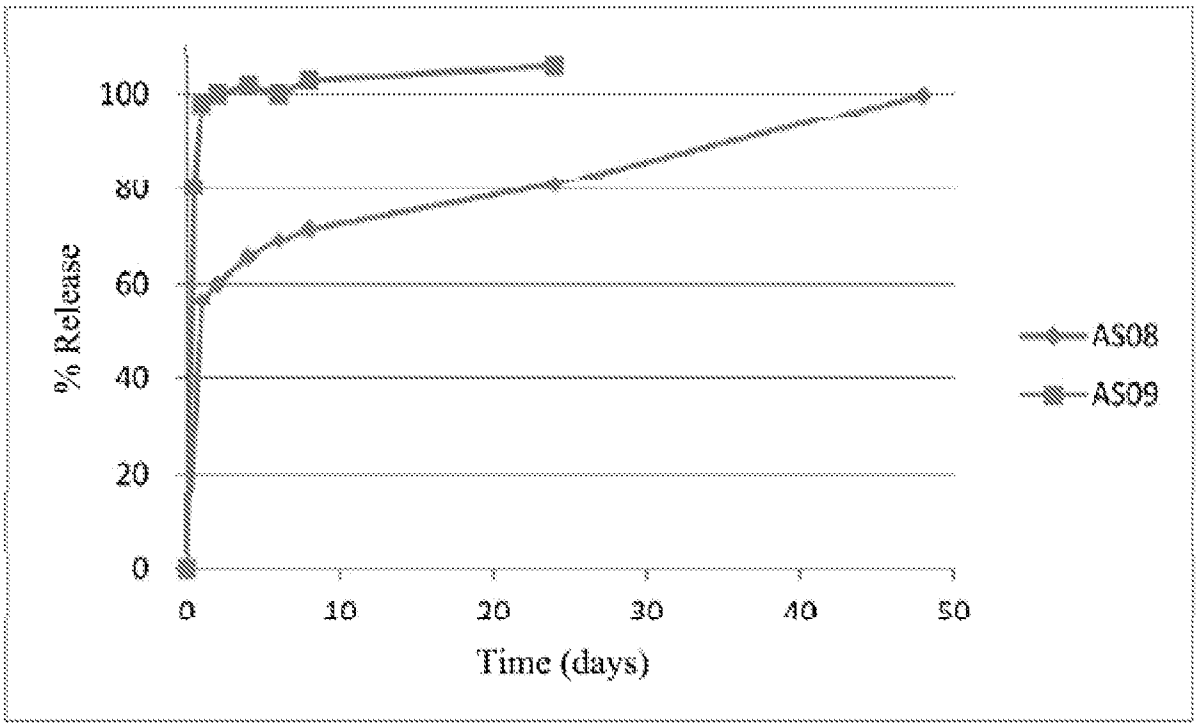

100
80
60
40
20
0
% Release
0
10
20
30
40
50
Time (days)
AS08
AS09

FIG. 26

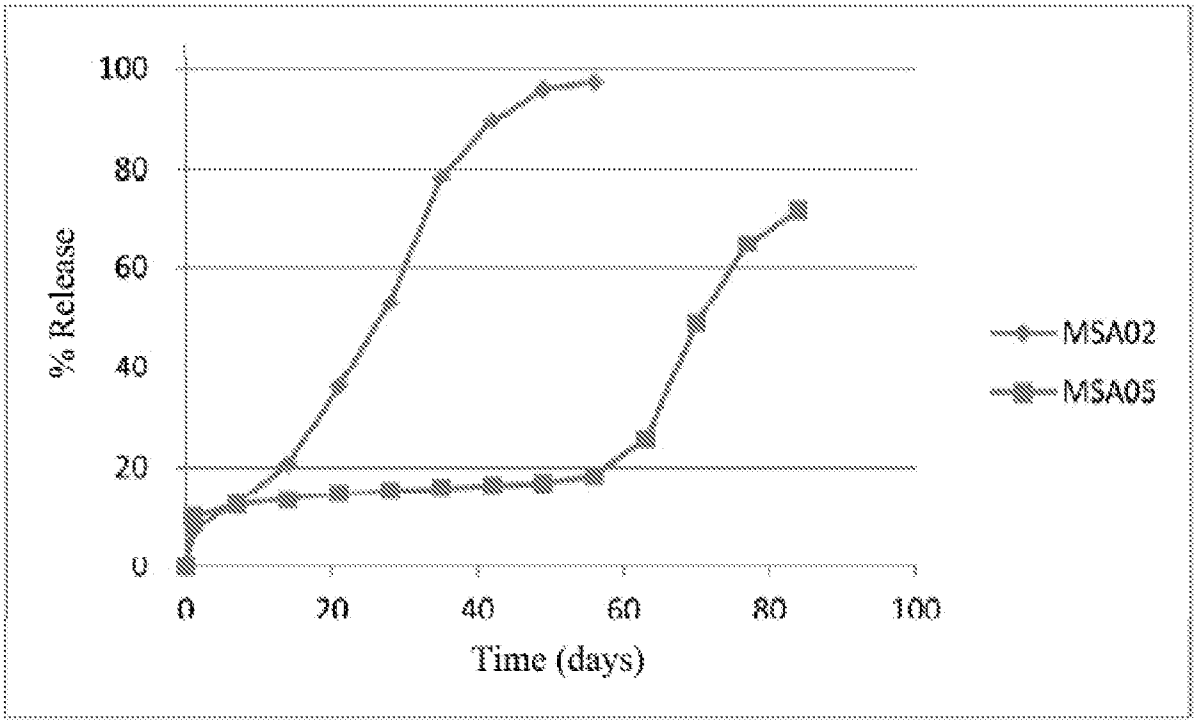

100
80
60
40
20
0
% Release
0
20
40
60
80
100
Time (days)
MSA02
MSA05

FIG. 27

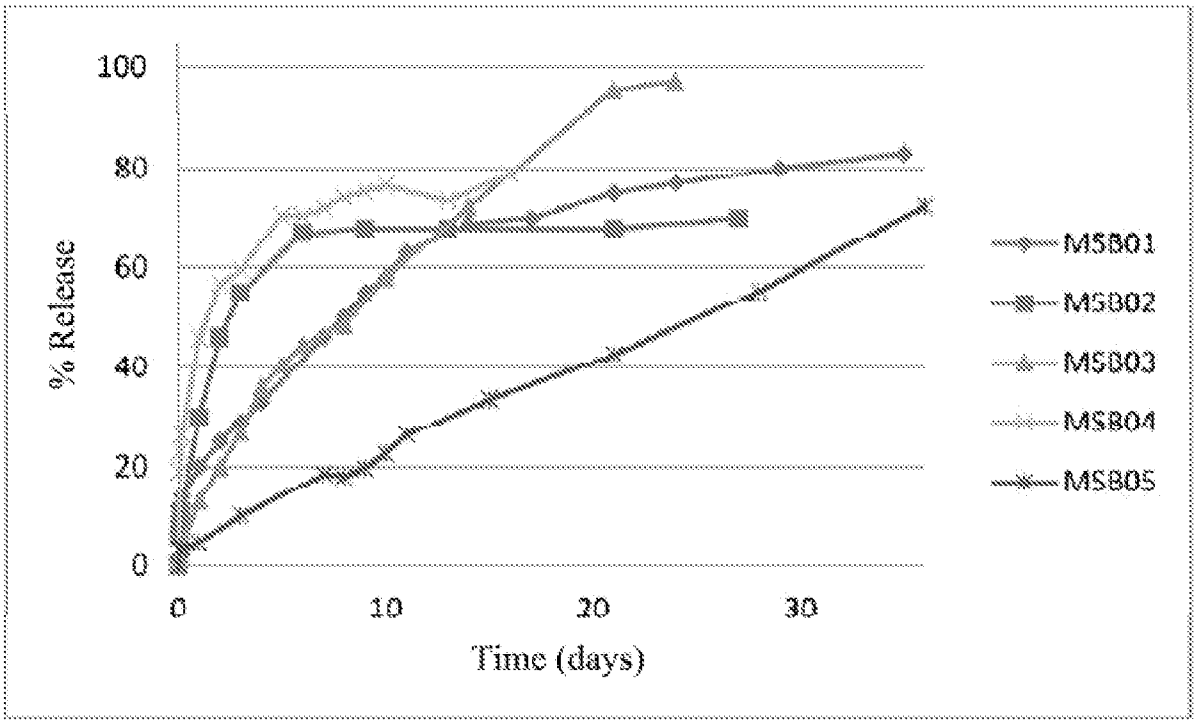

100
80
60
40
20
0
% Release
0
10
20
30
Time (days)
MSB01
MSB02
MSB03
MSB04
MSB05

FIG. 28

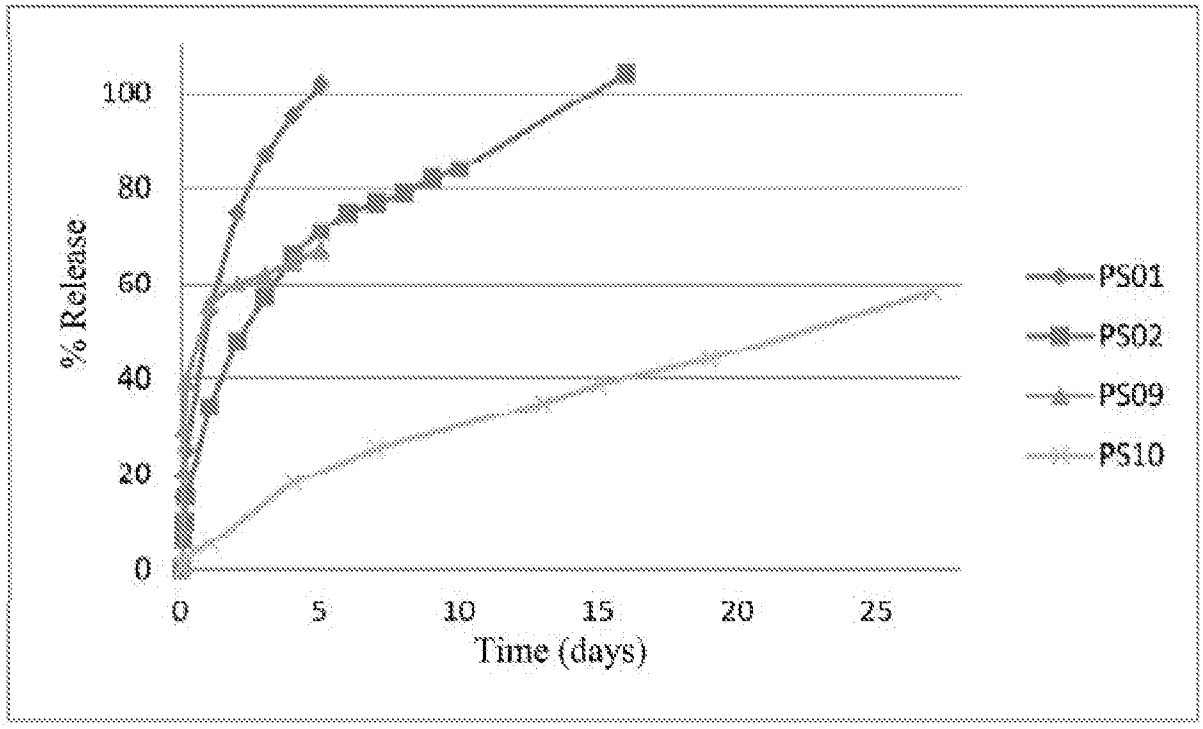

100
80
60
40
20
0
% Release
0
5
10
15
20
25
Time (days)
PS01
PS02
PS09
PS10

FIG. 29

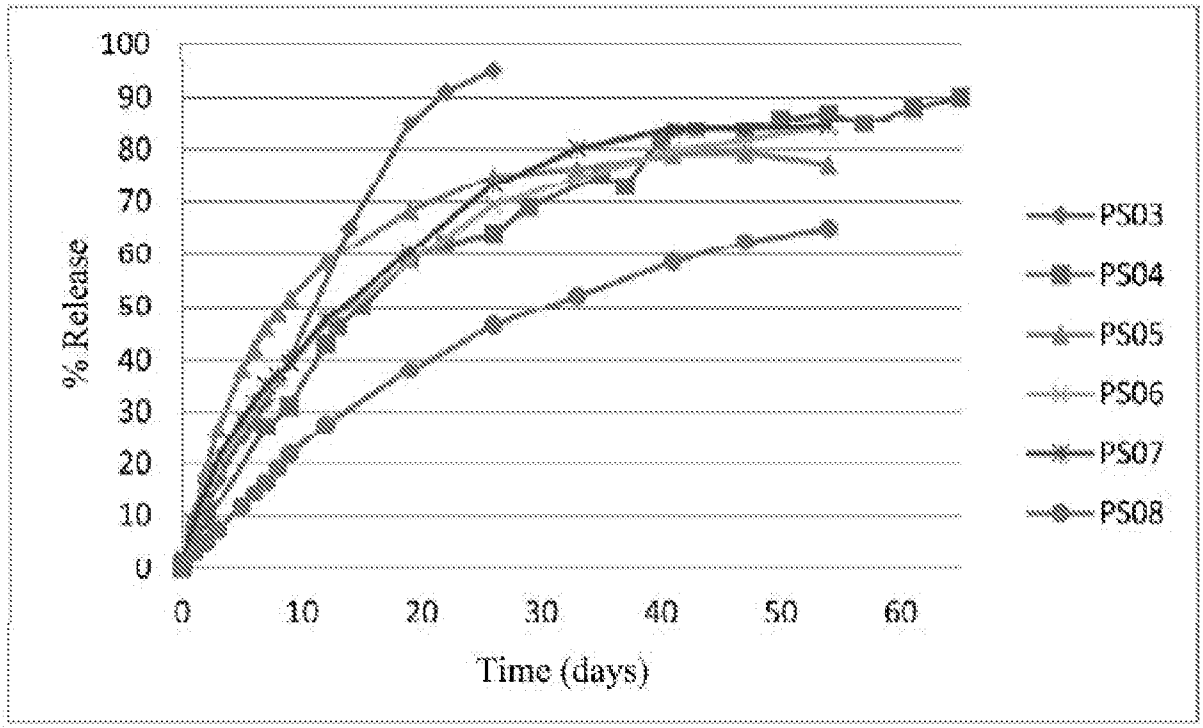

100
90
80
70
60
50
40
30
20
10
0
% Release
0
10
20
30
40
50
60
Time (days)
PS03
PS04
PS05
PS06
PS07
PS08

FIG. 30

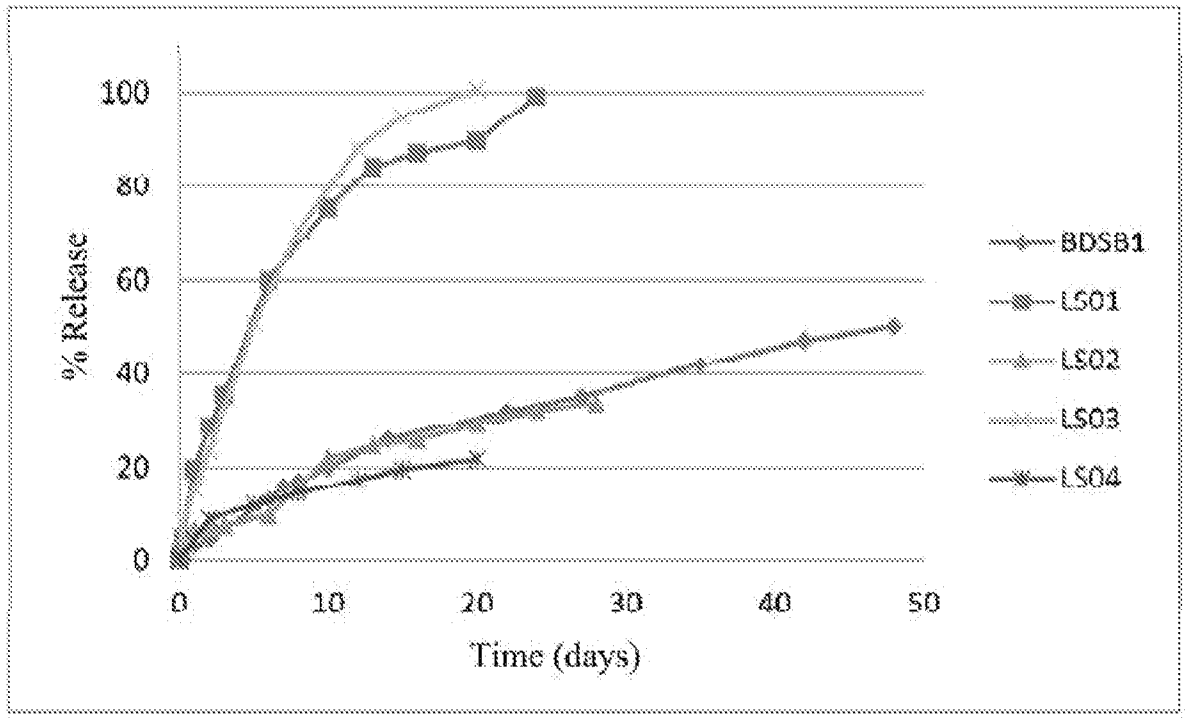

100
80
60
40
20
0
% Release
0
10
20
30
40
50
Time (days)
BDSB1
LS01
LS02
LS03
LS04

FIG. 31

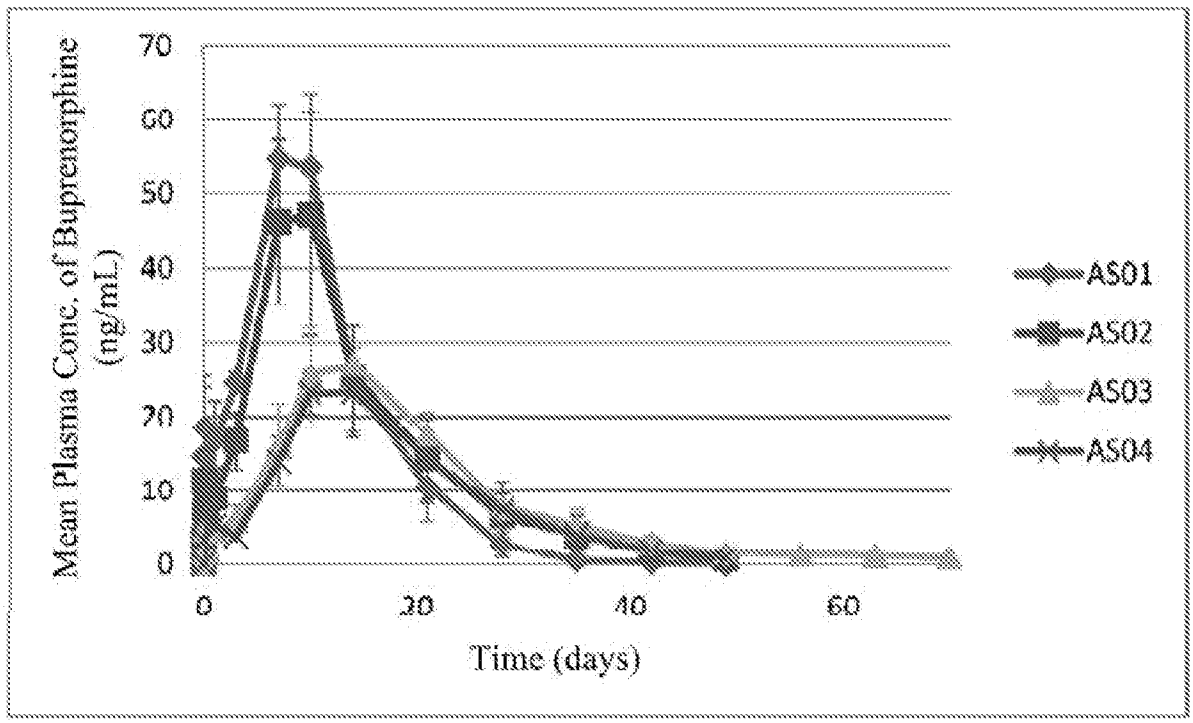

70
60
50
40
30
20
10
0
Mean Plasma Conc. of Buprenorphine (ng/mL)
0
20
40
60
Time (days)
AS01
AS02
AS03
AS04

FIG. 32

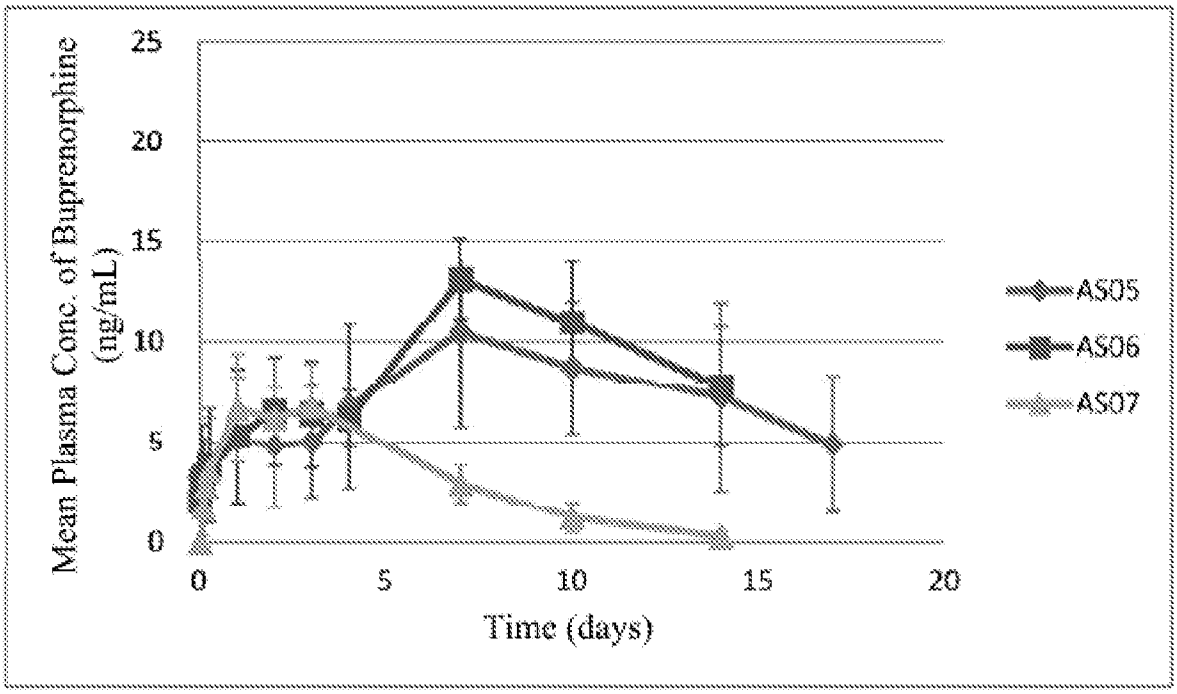

Mean Plasma Conc. of Buprenorphine (ng/mL)
25
20
15
10
5
0
0
5
10
15
20
Time (days)
AS05
AS06
AS07

FIG. 33

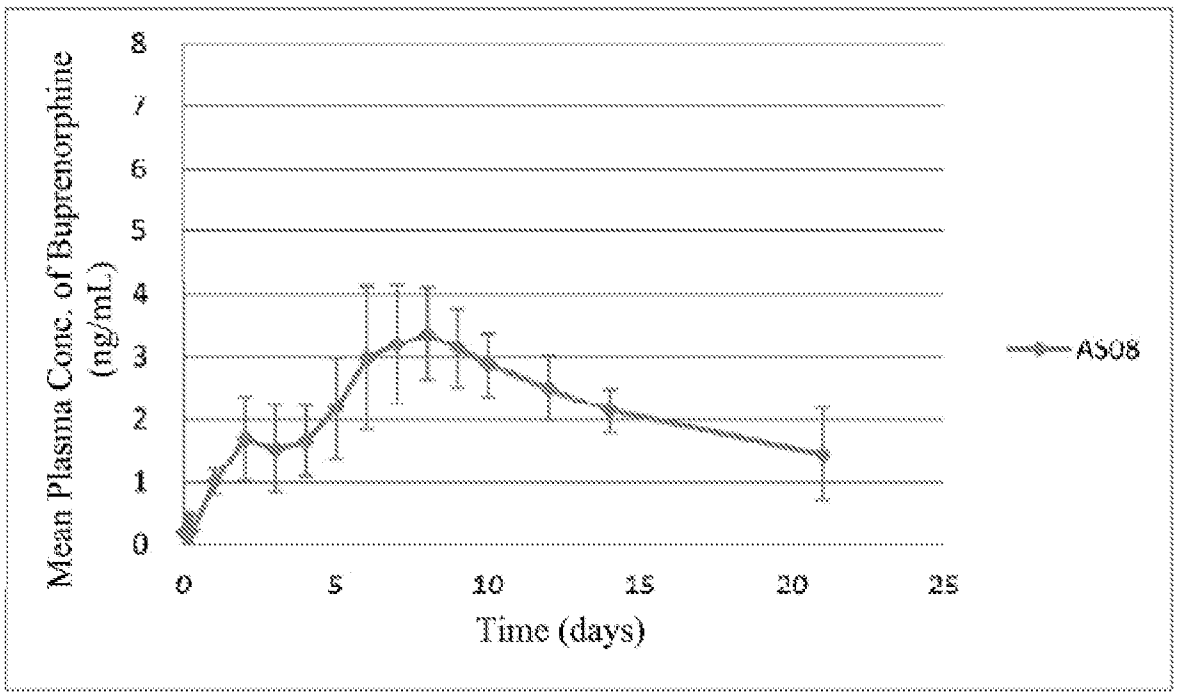

Mean Plasma Conc. of Buprenorphine (ng/mL)
8
7
6
5
4
3
2
1
0
0
5
10
15
20
25
Time (days)
AS08

FIG. 34

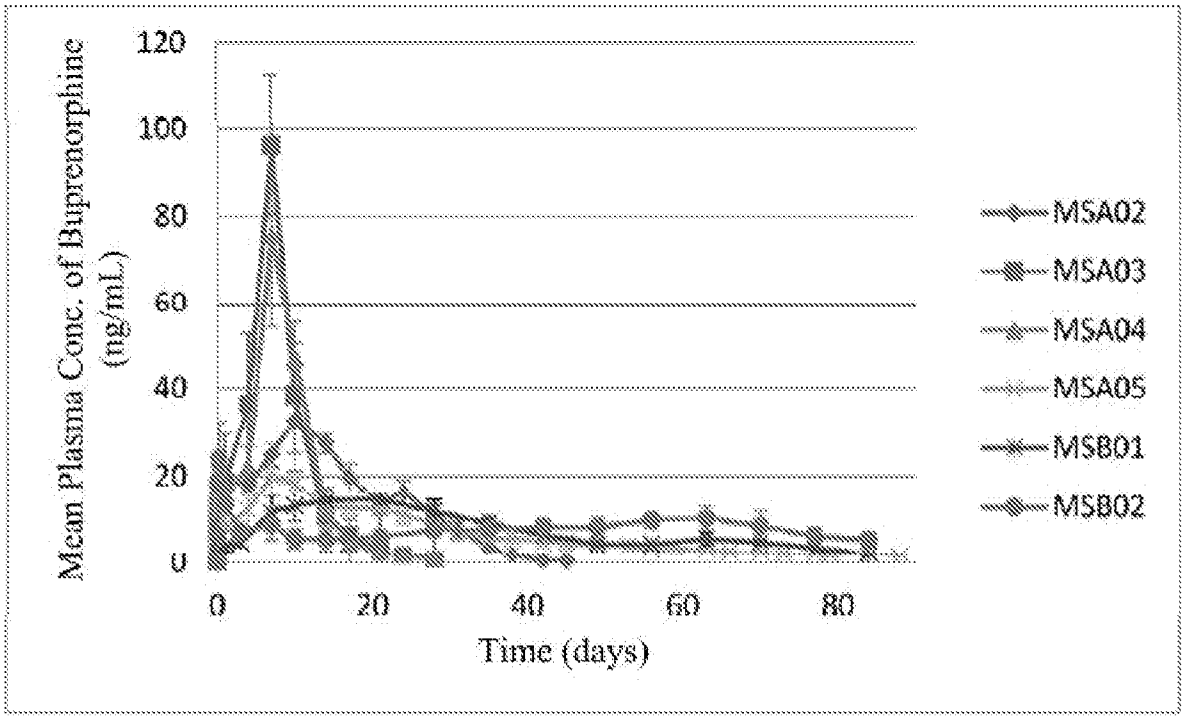

Mean Plasma Conc. of Buprenorphine (ng/mL)
120
100
80
60
40
20
0
0
20
40
60
80
Time (days)
MSA02
MSA03
MSA04
MSA05
MSB01
MSB02

FIG. 35

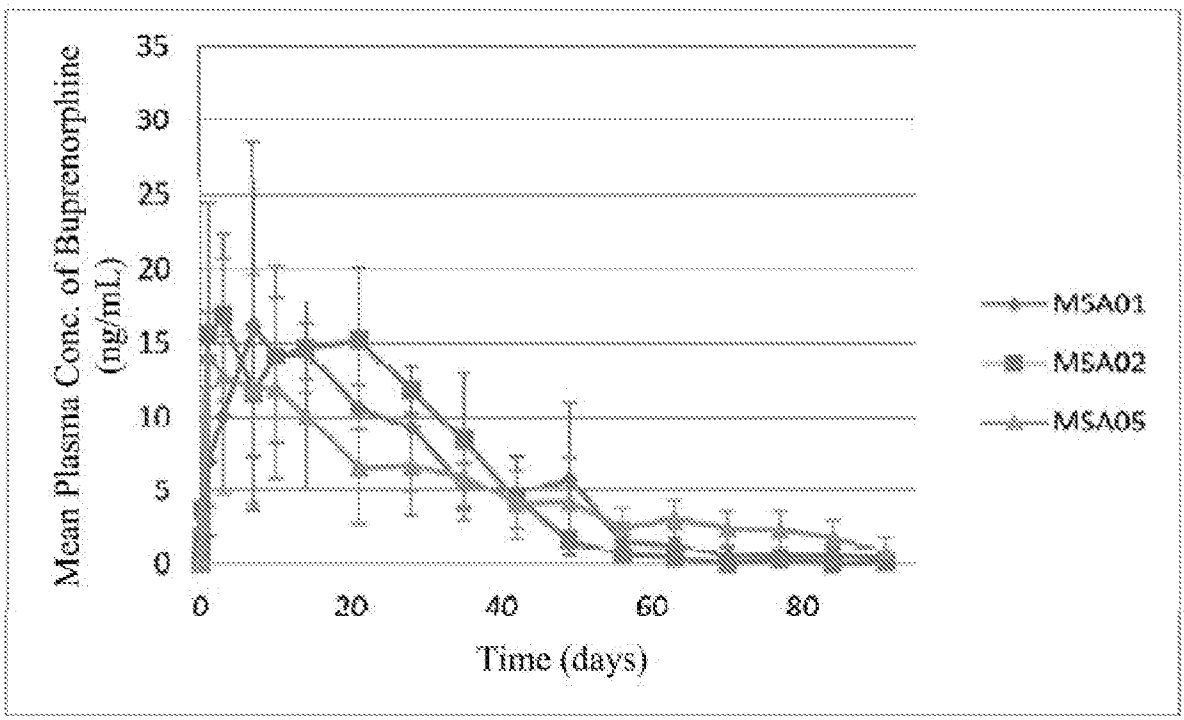

Mean Plasma Conc. of Buprenorphine (ng/mL)
35
30
25
20
15
10
5
0
0
20
40
60
80
Time (days)
MSA01
MSA02
MSA05

FIG. 36

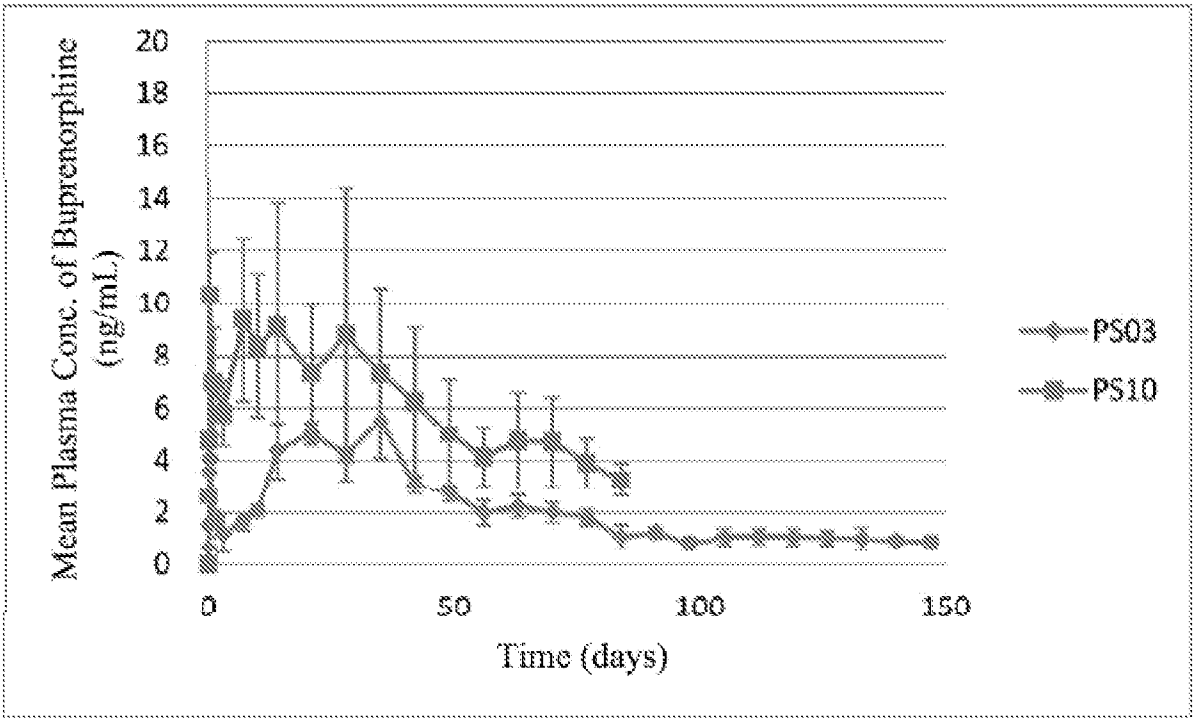

Mean Plasma Conc. of Buprenorphine (ng/mL)
20
18
16
14
12
10
8
6
4
2
0
0
50
100
150
Time (days)
PS03
PS10

FIG. 37

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2019/086449

A. CLASSIFICATION OF SUBJECT MATTER

C07D 489/12(2006.01)i; A61K 31/485(2006.01)i; A61P 1/10(2006.01)i; A61P 29/00(2006.01)i; A61P 25/30(2006.01)i

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)

C07D489/-;A61K31/-;A61P1/-

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)

DWPI;CNABS,CNKI,STN:buprenorphine, acyl,thebaine,opioid,alkaloid,μ-receptor agonist,crystalline,

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2016142877 A1 (RHODES TECH ET AL.) 15 September 2016 (2016-09-15) see page 42	1-13
X	AUDRA L. et al. "A solubility and related physicochemical property composition of burenorphine and its 3-alkyl esters" *Pharmaceutical Research,* Vol. 12, No. 10, 31 December 1995 (1995-12-31), pages 1526-1529	1-13
X	HIROFUMI I et al. "Transdermal Prodrug concepts:permeation of burenorphine and its alkyl esters through hairless mouse skin and influence of vehicles" *Biol. Pharm. Bull.,* Vol. 19, No. 2, 31 December 1996 (1996-12-31), pages 263-267	1-13
X	AUDRA L. et al. "permeation of burenorphine and its 3-alkyl-esters prodrugs through human skin" *Pharmaceutical Research,* Vol. 13, No. 10, 31 December 1996 (1996-12-31), pages 1519-1523	1-13

☐ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

* Special categories of cited documents:

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

"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	Date of mailing of the international search report
03 July 2019	**15 August 2019**
Name and mailing address of the ISA/CN **National Intellectual Property Administration, PRC** **6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing 100088** **China** Facsimile No. **(86-10)62019451**	Authorized officer **WANG Ying** Telephone No. **(86-10)62089793**

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2019/086449

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

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

1. ☑ Claims Nos.: **14**
because they relate to subject matter not required to be searched by this Authority, namely:

[1] Claim 14 is directed to a method for the treatment of the human/animal body .Thus, the subject-matter of claim 14 is not required to be searched by this Authority. (Rule 39.1(iv) PCT).

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

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

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2019/086449

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)	Publication date (day/month/year)
WO 2016142877 A1	15 September 2016	NZ 735736 A	22 February 2019
		US 10278967 B2	07 May 2019
		JP 2018507882 A	22 March 2018
		AR 103902 A1	14 June 2017
		CN 107660207 A	02 February 2018
		AU 2016230750 B2	30 May 2019
		EP 3283490 A1	21 February 2018
		BR 112017019357 A2	05 June 2018
		PH 12017501641 A1	12 February 2018
		AU 2019203308 A1	30 May 2019
		US 2018235955 A1	23 August 2018
		US 9926329 B2	27 March 2018
		TW 201639856 A	16 November 2016
		US 2017197975 A1	13 July 2017
		AU 2016230750 A1	12 October 2017
		MX 2017011606 A	26 October 2017
		EA 201792014 A1	31 January 2018
		KR 20170137738 A	13 December 2017
		CA 2977732 A1	15 September 2016
		SG 11201707350T A	30 October 2017
		IL 254384 D0	30 November 2017
		US 2018162866 A1	14 June 2018