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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 September 2015 (24.09.2015)

WIPO | PCT

(10) International Publication Number
WO 2015/143253 A1

(51) International Patent Classification:
C07D 489/08 (2006.01) *A61P 25/04* (2006.01)
A61K 31/485 (2006.01)

(21) International Application Number:
PCT/US2015/021627

(22) International Filing Date:
20 March 2015 (20.03.2015)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
14/221,456 21 March 2014 (21.03.2014) US

(71) Applicant: **JOHNSON MATTHEY PUBLIC LIMITED COMPANY** [GB/GB]; 5th Floor, 25 Farringdon Street, London EC4A 4AB (GB).

(72) Inventor; and
(71) Applicant : **SINGH, Aniruddh** [IN/US]; 63 Essex St., Apt. 5206, Carteret, New Jersey 07008 (US).

(72) Inventor: **MIRMEHRABI, Mahmoud**; 5885 Spring Garden Road, Halifax, Nova Scotia B3H 1Y3 (CA).

(74) Agent: **MCCASTLE, Shanay**; Johnson Matthey Inc., 435 Devon Park Drive, Suite 600, Wayne, Pennsylvania 19087 (US).

(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, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, 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).

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

(54) **Title**: CRYSTALLE FORMS OF OXYMORPHONE HYDROCHLORIDE

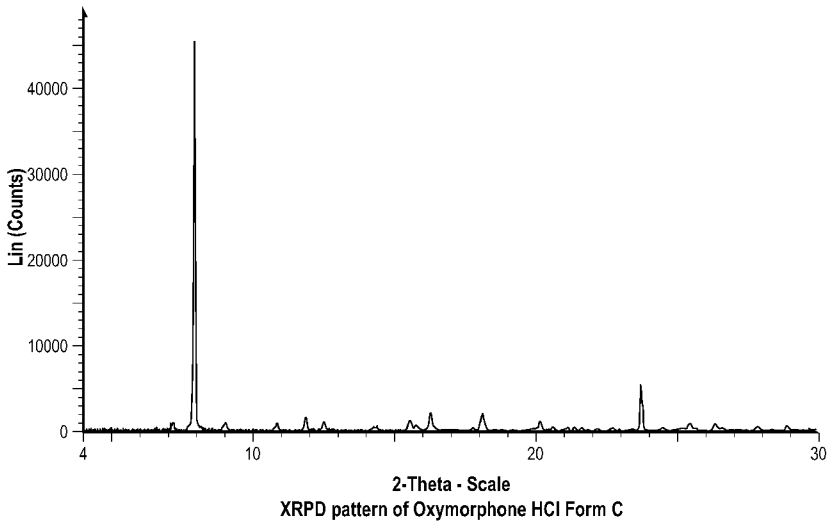


FIG. 3

(57) **Abstract**: The present disclosure is directed to crystalline forms of oxymorphone hydrochloride and compositions comprising any of the crystalline forms of oxymorphone hydrochloride. Also provided are processes for the preparation of crystalline forms of oxymorphone hydrochloride.

WO 2015/143253 A1

CRYSTALLE FORMS OF OXYMORPHONE HYDROCHLORIDE

FIELD OF THE INVENTION

The present disclosure is directed to crystalline forms of oxymorphone hydrochloride. The disclosure further relates to processes for making the crystalline forms of oxymorphone hydrochloride identified herein.

BACKGROUND OF THE INVENTION

Oxymorphone, generally administered in the form of its hydrochloride salt, is a potent semi-synthetic opiate analgesic. Oxymorphone hydrochloride is indicated for the relief of moderate to severe pain and has been approved for use in the United States since 1959. Oxymorphone hydrochloride is also indicated as a pre-operative medication to alleviate apprehension, maintain anesthesia and as an obstetric analgesic. Additionally, oxymorphone hydrochloride may be used to alleviate pain in patients with dyspnea associated with acute left ventricular failure and pulmonary edema. It can be administered as an injectable solution, suppository, tablet or extended release tablet.

Some crystalline forms of oxymorphone hydrochloride are known. US 8,563,571 describes oxymorphone hydrochloride crystalline Form A as a commercially produced form of oxymorphone hydrochloride. US 8,563,571 also describes oxymorphone hydrochloride crystalline Form B. Other crystalline forms, including mixtures of forms, of oxymorphone hydrochloride are described in US 7,851,482, US 8,563,571 and WO 2012/163796.

SUMMARY OF THE INVENTION

The present disclosure is directed to six novel crystalline forms of oxymorphone hydrochloride. These forms are identified herein as Forms C, D, E, F, G and H. The disclosure also provides processes for making the crystalline forms of oxymorphone hydrochloride identified herein.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is an X-ray powder diffractogram of oxymorphone hydrochloride crystalline Form A, expressed in terms of °2θ.

FIG. 2 is an X-ray powder diffractogram of oxymorphone hydrochloride crystalline Form B, expressed in terms of °2θ.

FIG. 3 is an X-ray powder diffractogram of oxymorphone hydrochloride crystalline Form C, expressed in terms of °2θ.

FIG. 4 is an X-ray powder diffractogram of oxymorphone hydrochloride crystalline Form D, expressed in terms of °2θ.

FIG. 5 is an X-ray powder diffractogram of oxymorphone hydrochloride crystalline Form E, expressed in terms of °2θ.

FIG. 6 is an X-ray powder diffractogram of oxymorphone hydrochloride crystalline Form F, expressed in terms of °2θ.

FIG. 7 is an X-ray powder diffractogram of oxymorphone hydrochloride crystalline Form G, expressed in terms of °2θ.

FIG. 8 is an X-ray powder diffractogram of oxymorphone hydrochloride crystalline Form H, expressed in terms of °2θ.

FIG. 9 is a measured differential scanning calorimetry thermogram for oxymorphone hydrochloride Form D.

FIG. 10 is a measured differential scanning calorimetry thermogram for oxymorphone hydrochloride Form E.

FIG. 11 is a measured differential scanning calorimetry thermogram for oxymorphone hydrochloride Form F.

FIG. 12 is a measured differential scanning calorimetry thermogram for oxymorphone hydrochloride Form G.

FIG. 13 is a measured differential scanning calorimetry thermogram for oxymorphone hydrochloride Form H.

FIG. 14 is a thermal gravimetric analysis thermogram for oxymorphone hydrochloride Form D.

FIG. 15 is a thermal gravimetric analysis thermogram for oxymorphone hydrochloride Form E.

FIG. 16 is a thermal gravimetric analysis thermogram for oxymorphone hydrochloride Form F.

DETAILED DESCRIPTION OF THE INVENTION

The present disclosure is directed to six novel crystalline forms of oxymorphone hydrochloride, as herein described in detail. More particularly, the present disclosure is directed to novel crystalline Forms C, D, E, F, G and H of oxymorphone hydrochloride.

The novel crystalline forms of oxymorphone hydrochloride of the present disclosure may be prepared directly or indirectly from oxymorphone freebase and/or may be interconverted from other crystalline forms of oxymorphone hydrochloride. Examples 1-12 herein provide embodiments of the preparation of the crystalline forms of oxymorphone hydrochloride described in the present disclosure.

The novel crystalline forms of oxymorphone hydrochloride described herein may be characterized by one or more of their characteristic physical properties including, but not limited to, X-ray powder diffraction peaks, differential scanning calorimetry, thermal gravimetric analyses and water content (as measured by Karl-Fischer titration).

X-ray powder diffraction analysis on representative samples of the crystalline forms of oxymorphone hydrochloride as herein described is performed using a Bruker D8 Advance instrument equipped with a Cu Kα radiation source (1.54° Angstrom), a 9-position sample holder and a LYNXEYE™ Super Speed Detector. Samples are placed on zero-background, silicon plate holders.

One skilled in the art would recognize that the °2θ values and the relative intensity values are generated by performing a peak search on the measured data and the *d*-spacing values are calculated by the instrument from the °2θ values using Bragg's equation. One skilled in the art would further recognize that the relative

intensity for the measured peaks may vary as a result of sample preparation, orientation and instrument used, for example. A variation of about ± 0.2 is not atypical in obtainable 2θ values.

Oxymorphone hydrochloride crystalline Form A is a sesquihydrate and, as disclosed in US 8,563,571, is a commercially available form of oxymorphone hydrochloride. FIG. 1 is a representative X-ray powder diffractogram for a representative sample of oxymorphone hydrochloride Form A made according to Examples 1-3.

Oxymorphone hydrochloride crystalline Form C is a unique crystalline phase. Oxymorphone Form C may be characterized as a white to off-white powder. Form C is further characterized by its X-ray powder diffraction pattern peaks and/or *d*-spacing values, as listed in Table 1 below. FIG. 3 is a representative X-ray powder diffractogram for a representative sample of oxymorphone hydrochloride Form C made according to Example 4.

Table 1- XRPD peak list of Form C

Angle, 2θ	*d*-spacing	Intensity, %
7.10	12.441	2
7.87	11.224	100
8.97	9.849	2.2
10.78	8.198	1.7
11.84	7.471	3.7
12.47	7.092	2.3
14.30	6.190	0.9
15.52	5.704	2.8
16.27	5.445	4.9
17.76	4.991	1.2
18.09	4.899	4.6
20.14	4.406	2.4
20.62	4.304	1.1
21.10	4.206	1.1
21.37	4.155	1.2
21.65	4.101	1
22.18	4.004	0.8
22.73	3.909	1.1
23.73	3.747	12.1
23.39	3.800	0.9

24.49	3.631	1.2
25.45	3.497	2.1
26.59	3.350	0.9
26.38	3.376	2
27.86	3.199	1.1
28.90	3.087	1.4

Oxymorphone hydrochloride crystalline Form D is a unique crystalline phase. Oxymorphone Form D may be characterized as a white to off-white powder. Form D is further characterized by its X-ray powder diffraction pattern peaks and/or *d*-spacing values, as listed in Table 2 below. FIG. 4 is a representative X-ray powder diffractogram for a representative sample of oxymorphone hydrochloride Form D made according to Examples 5 and 6.

Table 2- XRPD peak list of Form D

Angle, 2θ	*d*-spacing	Intensity, %
9.40	9.400	100
9.58	9.223	12.5
10.29	8.592	48.5
12.39	7.136	8.5
12.56	7.040	11.6
13.14	6.733	25.8
15.58	5.683	9.6
16.41	5.398	1.4
16.74	5.293	5.1
17.39	5.097	17.5
18.37	4.826	2.4
18.83	4.709	12
19.21	4.618	4.6
19.69	4.506	17.8
20.18	4.397	0.5
20.64	4.299	7.4
21.31	4.166	2.6
22.32	3.981	1.7
22.60	3.931	2
23.21	3.829	3.4
23.80	3.735	13.5
24.70	3.601	4.1
25.05	3.552	20.5
25.35	3.510	6.6
26.66	3.342	3.7
26.94	3.307	15.1
27.28	3.267	3.6
28.36	3.144	7.6

28.76	3.102	3.9
28.98	3.079	1.9
29.35	3.040	2
30.05	2.972	1.1
30.51	2.927	1.3
31.21	2.864	3.7
31.70	2.820	1.7
32.35	2.766	1.2
33.12	2.703	0.3
33.68	2.659	0.9
34.55	2.594	4.1
35.08	2.556	0.8
35.59	2.520	1.6
36.39	2.467	0.9
36.81	2.440	1.7
37.51	2.396	1.2
38.13	2.358	1.3
38.45	2.339	0.9
39.16	2.299	1.3
39.40	2.285	0.9
39.90	2.258	1.1

Oxymorphone hydrochloride crystalline Form E is a unique crystalline phase. Oxymorphone Form E may be characterized as a white to off-white powder. Form E is further characterized by its X-ray powder diffraction pattern peaks and/or *d*-spacing values, as listed in Table 3 below. FIG. 5 is a representative X-ray powder diffractogram for a representative sample of oxymorphone hydrochloride Form E made according to Examples 7, 8 and 9.

Table 3- XRPD peak list of Form E

Angle, 2θ	*d*-spacing	Intensity, %
9.21	9.600	100
12.69	6.968	83.9
13.82	6.401	2.4
14.73	6.009	13.1
15.44	5.736	38.3
16.24	5.453	19.7
17.14	5.168	5.1
18.47	4.800	12.6
19.02	4.663	4.7
19.27	4.603	2.7
19.93	4.451	18.9
20.54	4.320	7.4
21.67	4.098	8.4
23.30	3.815	1.5

23.80	3.736	1.1
24.33	3.655	1.4
24.57	3.621	11.9
24.85	3.581	0.9
25.36	3.509	2.1
25.51	3.489	2.8
26.48	3.363	3.3
27.83	3.203	6.1
28.06	3.177	2.1
28.78	3.100	1.7
28.97	3.080	2.7
29.79	2.997	1.8
30.19	2.958	2.1
31.14	2.870	3.5
31.54	2.834	1.7
31.82	2.810	5
32.68	2.738	0.5
33.33	2.686	2.5
33.65	2.661	0.8
34.63	2.589	4.3
36.57	2.455	1.7

Oxymorphone hydrochloride crystalline Form F is a unique crystalline phase. Oxymorphone Form F may be characterized as a white to off-white powder. Form F is further characterized by its X-ray powder diffraction pattern peaks and/or *d*-spacing values, as listed in Table 4 below. FIG. 6 is a representative X-ray powder diffractogram for a representative sample of oxymorphone hydrochloride Form F made according to Example 10.

Table 4- XRPD peak list of Form F

Angle, 2θ	*d*-spacing	Intensity, %
6.42	13.747	5.5
6.65	13.272	20.5
8.20	10.768	23.7
8.94	9.883	16.6
9.20	9.607	94.6
10.42	8.487	32.2
11.47	7.710	61.8
11.80	7.492	91.7
12.88	6.867	3.3
13.36	6.621	12.7
13.85	6.388	1.7
14.36	6.161	0.9
15.35	5.768	1.9
15.70	5.640	14.1

16.04	5.521	100
17.38	5.097	6.2
18.10	4.897	11.8
18.53	4.785	24.5
19.24	4.610	1
19.97	4.442	33.5
20.38	4.354	2.4
20.93	4.241	28.7
21.35	4.159	11.7
21.70	4.093	7.9
23.10	3.848	7.8
23.75	3.743	8.5
24.09	3.691	10.8
24.59	3.618	1
25.21	3.530	13.6
25.45	3.498	17.1
25.86	3.442	10
26.96	3.304	7.5
27.39	3.254	1.5
27.96	3.189	11.7
29.12	3.064	6.9
29.95	2.981	15.6
30.63	2.916	2
31.26	2.859	1.3
31.51	2.837	1.4
31.88	2.805	1.2
32.39	2.762	8.9
33.38	2.683	3.2
34.66	2.586	2.4
35.25	2.544	3.8
36.11	2.486	3.5
36.47	2.462	1.3
37.80	2.378	2.5
38.32	2.347	1.7

Oxymorphone hydrochloride crystalline Form G is a unique crystalline phase. Oxymorphone Form G may be characterized as a white to off-white powder. Form G is further characterized by its X-ray powder diffraction pattern peaks and/or *d*-spacing values, as listed in Table 5 below. FIG. 7 is a representative X-ray powder diffraction pattern for a representative sample of oxymorphone hydrochloride Form G made according to Example 11.

Table 5- XRPD peak list of Form G

Angle, 2θ	*d*-spacing	Intensity, %
8.22	10.748	3

8.63	10.244	2.5
9.65	9.160	55.9
10.73	8.238	2.4
11.71	7.550	4.6
12.68	6.977	40.5
14.24	6.214	12.7
14.80	5.980	1.2
16.16	5.480	100
17.20	5.151	34.3
19.29	4.599	6.8
19.82	4.476	14.1
21.18	4.192	16.8
22.31	3.981	1.9
22.76	3.904	3.1
23.83	3.732	2
24.99	3.560	1.4
26.50	3.361	7.3
26.80	3.324	5.7
27.52	3.239	0.9
29.04	3.073	3.9
30.12	2.965	11
31.11	2.872	1.2
34.16	2.623	3.1
35.58	2.521	1.3

Oxymorphone hydrochloride crystalline Form H is a unique crystalline phase. Oxymorphone Form H may be characterized as a white to off-white powder. Form H is further characterized by its X-ray powder diffraction pattern peaks and/or *d*-spacing values, as listed in Table 6 below. FIG. 8 is a representative X-ray powder diffraction pattern for a representative sample of oxymorphone hydrochloride Form H made according to Example 12.

Table 6- XRPD peak list of Form H

Angle, 2θ	*d*-spacing	Intensity, %
6.50	13.588	0.4
7.95	11.106	100
8.47	10.429	0.8
9.04	9.774	34.3
9.80	9.016	0.6
10.21	8.661	0.7
10.68	8.280	0.8
11.57	7.641	4.1
11.88	7.443	0.7
12.09	7.316	4.7
12.98	6.816	1.2

13.28	6.660	0.3
14.03	6.308	0.5
14.72	6.012	0.9
15.41	5.746	1
15.77	5.617	4.7
16.22	5.460	1.5
17.22	5.144	1.1
17.48	5.069	0.3
17.91	4.949	0.6
18.16	4.882	3.2
18.80	4.715	0.4
19.13	4.637	1
19.90	4.459	1.7
20.46	4.338	1.1
21.38	4.153	1
21.80	4.075	0.5
22.43	3.961	0.4
23.22	3.828	1
23.87	3.725	31.1
24.60	3.616	1.8
25.16	3.537	1.1
25.45	3.497	0.9
26.26	3.391	0.7
26.66	3.342	0.4
27.26	3.268	0.9
27.83	3.203	0.7
28.88	3.089	0.6
29.58	3.018	0.7

Differential scanning calorimetry is performed using a TA Instruments Q10 DSC. Typically, samples are placed in unsealed, covered hermetic alodined aluminum sample pans and scanned from about 30 °C to about 300 °C at a rate of about 10°C/min under a nitrogen purge of about 50mL/min.

Differential scanning calorimetry is performed on representative samples of oxymorphone hydrochloride Form D, E, F, G and H, as shown in FIG. 9, 10, 11, 12 and 13, respectively. Two thermal events may be observed in the differential scanning calorimetry thermogram for Form D at about 93 °C and about 149°C. One thermal event at a peak of about 286 °C may be observed in the differential scanning calorimetry thermogram for Form E. Two thermal events may be observed in the differential scanning calorimetry thermogram for Form F at about 122 °C and about 225°C. Multiple thermal events may be observed in the differential scanning calorimetry thermogram for Form G, one peak occurring at about 105 °C. Multiple

thermal events may be observed in the differential scanning calorimetry thermogram for Form H, one peak occurring at about 96°C.

Thermal gravimetric analyses are performed using a TA Instruments TGA Q500. Typically samples are placed in an open, pre-tared aluminum sample pan and scanned from about 30 °C to about 300 °C at a rate of about 10°C/min using a nitrogen purge at about 60 mL/min.

Thermal gravimetric analysis is performed on representative samples of oxymorphone hydrochloride Form D, E, and F, as shown in FIG. 14, 15, and 16, respectively. Thermal gravimetric analysis data of Form D shows a weight loss of about 5.8% between about room temperature and about 85 °C as a result of desolvation. Thermal gravimetric analysis data of Form E shows a weight loss of about 0.2% up to about 180 °C which confirms that Form E is an anhydrous solid. Thermal gravimetric analysis data of Form F shows a weight loss of about 6.5% between about room temperature and about 100 °C as a result of dehydration.

Any of the oxymorphone hydrochloride Forms C, D, E, F, G and H disclosed herein can be incorporated into pharmaceutical dosage forms, e.g., by admixtures of any one or more of oxymorphone hydrochloride Forms C, D, E, F, G and H with conventional excipients, i.e., pharmaceutically acceptable organic or inorganic carrier substances. For oral formulations, the dosage forms can provide a sustained release of the active component. Suitable pharmaceutically acceptable carriers include but are not limited to, alcohols, gum arabic, vegetable oils, benzyl alcohols, polyethylene glycols, gelate, carbohydrates such as lactose, amylose or starch, magnesium stearate, talc, silicic acid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxy-methylcellulose, polyvinylpyrrolidone, etc. The pharmaceutical preparations can be sterilized and if desired mixed with auxiliary agents, e.g., lubricants, disintegrants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure buffers, colouring, flavouring and/or aromatic substances and the like. The compositions intended for oral use may be prepared according to any method known in the art and such compositions may contain one or more agents selected from the group consisting of inert, non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets. Such excipients include, for example an inert diluent such as

lactose; granulating and disintegrating agents such as cornstarch; binding agents such as starch; and lubricating agents such as magnesium stearate. The tablets may be uncoated or they may be coated by known techniques for elegance or to delay release of the active ingredients. Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert diluent. The oral dosage forms of the present invention may be in the form of tablets (sustained release and/or immediate release), troches, lozenges, powders or granules, hard or soft capsules, microparticles (e.g., microcapsules, microspheres and the like), buccal tablets, solutions, suspensions, etc.

In certain embodiments, the present disclosure provides for a method of treating pain by administering to a human patient the dosage forms described herein.

When the dosage form is oral, the dosage form of the present invention contains from about 1 mg to about 40 mg of any one or more of oxymorphone hydrochloride Forms C, D, E, F, G and H. Particularly preferred dosages are about 5 mg, about 10 mg, about 20 mg or about 40 mg however other dosages may be used as well. Oxymorphone hydrochloride Forms C, D, E, F, G and H can also be formulated with suitable pharmaceutically acceptable excipients to provide a sustained release dosage form. Such formulations can be prepared in accordance with US 7,851,482, US 7,276,250, US 2003/129234 A1 and US 2003/157167 A1.

Oxymorphone hydrochloride Forms C, D, E, F, G and H can be formulated as a sustained release oral formulation in any suitable tablet, coated tablet or multiparticulate formulation known to those skilled in the art. The sustained release dosage form may include a sustained release material that is incorporated into a matrix along with the oxymorphone salt thereof.

The sustained release dosage form may optionally comprise particles containing oxymorphone hydrochloride Forms C, D, E, F, G and H. In certain embodiments, the particles have a diameter from about 0.1 mm to about 2.5 mm, preferably from about 0.5 mm to about 2 mm. Preferably, the particles are film coated with a material that permits release of the active at a sustained rate in an aqueous medium. The film coat is chosen so as to achieve, in combination with the other stated properties, desired release properties. The sustained release coating

formulations of the present invention should preferably be capable of producing a strong, continuous film that is smooth and elegant, capable of supporting pigments and other coating additives, non-toxic, inert, and tack-free.

Coated Beads

In certain embodiments of the present invention a hydrophobic material is used to coat inert pharmaceutical beads such as nu pariel 18/20 beads, and a plurality of the resultant solid sustained release beads may thereafter be placed in a gelatin capsule in an amount sufficient to provide an effective sustained release dose when ingested and contacted by an environmental fluid, e.g., gastric fluid or dissolution media.

The sustained release bead formulations of the present invention slowly release the active component of the present invention, e.g., when ingested and exposed to gastric fluids, and then to intestinal fluids. The sustained release profile of the formulations of the invention can be altered, for example, by varying the amount of overcoating with the hydrophobic material, altering the manner in which a plasticiser is added to the hydrophobic material, by varying the amount of plasticiser relative to hydrophobic material, by the inclusion of additional ingredients or excipients, by altering the method of manufacture, etc. The dissolution profile of the ultimate product may also be modified, for example, by increasing or decreasing the thickness of the retardant coating.

Spheroids or beads coated with the agent(s) of the present are prepared, e.g., by dissolving the agent(s) in water and then spraying the solution onto a substrate, for example, nu pariel 18/20 beads, using a Wuster insert. Optionally, additional ingredients are also added prior to coating the beads in order to assist the binding of the active to the beads, and/or to color the solution, etc. For example, a product that includes hydroxypropylmethylcellulose, etc with or without colorant (e.g., Opadry ™, commercially available from Colorcon, Inc.) may be added to the solution and the solution mixed (e.g., for about 1 hour) prior to application of the same onto the beads. The resultant coated substrate, in these example beads, may then be optionally overcoated with a barrier agent, to separate the active component(s) from the hydrophobic sustained release coating. An example of a suitable barrier agent is one

which comprises hydroxypropylmethylcellulose. However, any film-former known in the art may be used. It is preferred that the barrier agent does not affect the dissolution rate of the final product.

The beads may then be overcoated with an aqueous dispersion of the hydrophobic material. The aqueous dispersion of hydrophobic material preferably further includes an effective amount of plasticiser, e.g. triethyl citrate. Pre-formulated aqueous dispersions of ethylcellulose, such as Aquacoat™ or Surelease™, may be used. If Surelease™ is used, it is not necessary to separately add a plasticiser. Alternatively, pre-formulated aqueous dispersions of acrylic polymers such as Eudragit™ can be used.

The coating solutions of the present invention preferably contain, in addition to the film-former, plasticiser, and solvent system (i.e., water), a colorant to provide elegance and product distinction. Colour may be added to the solution of the therapeutically active agent instead, or in addition to the aqueous dispersion of hydrophobic material. For example, colour may be added to Aquacoat™ via the use of alcohol or propylene glycol based colour dispersions, milled aluminium lakes and opacifiers such as titanium dioxide by adding colour with shear to water soluble polymer solution and then using low shear to the plasticised Aquacoat™. Alternatively, any suitable method of providing colour to the formulations of the present invention may be used. Suitable ingredients for providing colour to the formulation when an aqueous dispersion of an acrylic polymer is used include titanium dioxide and colour pigments, such as iron oxide pigments. The incorporation of pigments, may, however, increase the retard effect of the coating.

Plasticised hydrophobic material may be applied onto the substrate comprising the agent(s) by spraying using any suitable spray equipment known in the art. In a preferred method, a Wurster fluidised-bed system is used in which an air jet, injected from underneath, fluidises the core material and effects drying while the acrylic polymer coating is sprayed on. A sufficient amount of the hydrophobic material to obtain a predetermined sustained release of the agent(s) when the coated substrate is exposed to aqueous solutions, e.g. gastric fluid, may be applied. After coating with the hydrophobic material, a further overcoat of a film-former, such as Opadry™, is

optionally applied to the beads. This overcoat is provided, if at all, in order to substantially reduce agglomeration of the beads.

The release of the agent(s) from the sustained release formulation of the present invention can be further influenced, i.e., adjusted to a desired rate, by the addition of one or more release-modifying agents, or by providing one or more passageways through the coating. The ratio of hydrophobic material to water soluble material is determined by, among other factors, the release rate required and the solubility characteristics of the materials selected.

The release-modifying agents, which function as pore-formers may be organic or inorganic, and include materials that can be dissolved, extracted or leached from the coating in an environment of use. The pore-formers may comprise one or more hydrophilic materials such as hydroxypropylmethylcellulose.

The sustained release coatings of the present invention can also include erosion-promoting agents such as starch and gums.

The sustained release coatings of the present invention can also include materials useful for making microporous lamina in the environment of use, such as polycarbonates comprised of linear polyesters of carbonic acid in which carbonate groups reoccur in the polymer chain.

The release-modifying agent may also comprise a semi-permeable polymer.

In certain preferred embodiments, the release-modifying agent is selected from hydroxypropylmethylcellulose, lactose, metal stearates, and mixtures of any of the foregoing.

The sustained release coatings of the present invention may also include an exit means comprising at least one passageway, orifice, or the like. The passageway may be formed by such methods as those disclosed in US 3,845,770, US 3,916,899, US 4,063,064 and US 4,088,864.

Matrix Formulations

In other embodiments of the present invention, the sustained release formulation is achieved via a matrix optionally having a sustained release coating as set forth herein. The materials suitable for inclusion in a sustained release matrix may depend on the method used to form the matrix.

For example, a matrix in addition to the any one or more of oxymorphone hydrochloride Forms C, D, E, F, G and H may include: hydrophilic and/or hydrophobic materials, such as gums, cellulose ethers, acrylic resins, protein derived materials. The list is not meant to be exclusive, any pharmaceutically acceptable hydrophobic material or hydrophilic material which is capable of imparting sustained release of the agent(s) and which melts (or softens to the extent necessary to be extruded) may be used in accordance with the present invention.

Digestible, long chain (C_8-C_{50}, especially C_{12}-C_{40}), substituted or unsubstituted hydrocarbons, such as fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral and vegetable oils and waxes, and stearyl alcohol; and polyalkylene glycols. Of these polymers, acrylic polymers, especially Eudragit™. RSPO-the cellulose ethers, especially hydroxyalkylcelluloses and carboxyalkylcelluloses, are preferred. The oral dosage form may contain between 1% and 80% (by weight) of at least one hydrophilic or hydrophobic material.

When the hydrophobic material is a hydrocarbon, the hydrocarbon preferably has a melting point of between 25 °C and 90 °C. Of the long chain hydrocarbon materials, fatty (aliphatic) alcohols are preferred. The oral dosage form may contain up to 60% (by weight) of at least one digestible, long chain hydrocarbon.

Preferably, the oral dosage form contains up to 60% (by weight) of at least one polyalkylene glycol.

The hydrophobic material is preferably selected from the group consisting of alkylcelluloses, acrylic and methacrylic acid polymers and copolymers, shellac, zein, hydrogenated castor oil, hydrogenated vegetable oil, or mixtures thereof. In certain preferred embodiments of the present invention, the hydrophobic material is a pharmaceutically acceptable acrylic polymer, including but not limited to acrylic acid and methacrylic acid copolymers, methyl methacrylate, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, aminoalkyl

methacrylate copolymer, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamine copolymer, poly(methyl methacrylate), poly(methacrylic acid)(anhydride), polymethacrylate, polyacrylamide, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers. In other embodiments, the hydrophobic material is selected from materials such as hydroxyalkylcelluloses such as hydroxypropylmethylcellulose and mixtures of the foregoing.

Preferred hydrophobic materials are water-insoluble with more or less pronounced hydrophilic and/or hydrophobic trends. Preferably, the hydrophobic materials useful in the invention have a melting point from about 25 °C to about 200 °C, preferably from about 45 °C to about 90 °C. Specifically, the hydrophobic material may comprise natural or synthetic waxes, fatty alcohols (such as lauryl, myristyl, stearyl, cetyl or preferably cetostearyl alcohol), fatty acids, including but not limited to fatty acid esters, fatty acid glycerides (mono-, di-, and tri-glycerides), hydrogenated fats, hydrocarbons, normal waxes, stearic aid, stearyl alcohol and hydrophobic and hydrophilic materials having hydrocarbon backbones. Suitable waxes include, for example, beeswax, glycowax, castor wax and carnauba wax. For the purposes of the present invention, a wax-like substance is defined as any material that is normally solid at room temperature and has a melting point of from about 25 °C to about 100 °C.

Suitable hydrophobic materials which may be used in accordance with the present invention include digestible, long chain (C_8-C_{50}, especially C_{12}-C_{40}), substituted or unsubstituted hydrocarbons, such as fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral and vegetable oils and natural and synthetic waxes. Hydrocarbons having a melting point of between 25 °C and 90 °C are preferred. Of the long chain hydrocarbon materials, fatty (aliphatic) alcohols are preferred in certain embodiments. The oral dosage form may contain up to 60% (by weight) of at least one digestible, long chain hydrocarbon.

Preferably, a combination of two or more hydrophobic materials are included in the matrix formulations. If an additional hydrophobic material is included, it is preferably selected from natural and synthetic waxes, fatty acids, fatty alcohols, and mixtures of the same. Examples include beeswax, carnauba wax, stearic acid and stearyl alcohol. This list is not meant to be exclusive.

One particular suitable matrix comprises at least one water soluble hydroxyalkyl cellulose, at least one C_{12}-C_{36}, preferably C_{14}-C_{22}, aliphatic alcohol and, optionally, at least one polyalkylene glycol. The at least one hydroxyalkyl cellulose is preferably a hydroxy (C_1 to C_6) alkyl cellulose, such as hydroxypropylcellulose, hydroxypropyl-methylcellulose and, especially, hydroxyethylcellulose. The amount of the at least one hydroxyalkyl cellulose in the present oral dosage form will be determined, inter alia, by the precise rate of oxymorphone hydrochloride release required. The at least one aliphatic alcohol may be, for example, lauryl alcohol, myristyl alcohol or stearyl alcohol. In particularly preferred embodiments of the present oral dosage form, however, the at least one aliphatic alcohol is cetyl alcohol or cetostearyl alcohol. The amount of the at least one aliphatic alcohol in the present oral dosage form will be determined, as above, by the precise rate of opioidoxycmorphone release required. It will also depend on whether at least one polyalkylene glycol is present in or absent from the oral dosage form. In the absence of at least one polyalkylene glycol, the oral dosage form preferably contains between 20% and 50% (by wt) of the at least one aliphatic alcohol. When at least one polyalkylene glycol is present in the oral dosage form, then the combined weight of the at least one aliphatic alcohol and the at least one polyalkylene glycol preferably constitutes between 20% and 50% (by wt) of the total dosage.

In one embodiment, the ratio of, e.g., the at least one hydroxyalkyl cellulose or acrylic resin to the at least one aliphatic alcohol/polyalkylene glycol determines, to a (w/w) of the at least one hydroxyalkyl cellulose to the at least one aliphatic alcohol/ polyalkylene glycol of between 1:2 and 1:4 is preferred, with a ratio of between 1:3 and 1:4 being particularly preferred.

The at least one polyalkylene glycol may be, for example, polypropylene glycol or, preferably, polyethylene glycol. The number average molecular weight of the at least one polyalkylene glycol is preferably between 1,000 and 15,000 especially between 1,500 and 12,000.

Another suitable sustained release matrix would comprise an alkylcellulose (especially ethyl cellulose), a C_{12} to C_{36} aliphatic alcohol and, optionally, a polyalkylene glycol.

In another preferred embodiment, the matrix includes a pharmaceutically acceptable combination of at least two hydrophobic materials.

In addition to the above ingredients, a sustained release matrix may also contain suitable quantities of other materials, e.g. diluents, lubricants, binders, granulating aids, colorants, flavorants and glidants that are conventional in the pharmaceutical art.

Matrix--Particulates

In order to facilitate the preparation of a solid, sustained release, oral dosage form according to this invention, any method of preparing a matrix formulation known to those skilled in the art may be used. For example incorporation in the matrix may be effected, for example, by (a) forming granules comprising at least one water soluble hydroxyalkyl cellulose, and any one or more of oxymorphone hydrochloride Forms C, D, E, F, G and H; (b) mixing the hydroxyalkyl cellulose containing granules with at least one C_{12} to C_{36} aliphatic alcohol; and (c) optionally, compressing and shaping the granules. Preferably, the granules are formed by wet granulating the hydroxalkyl cellulose granules with water.

In yet other alternative embodiments, a spheronising agent, together with the active component can be spheronised to form spheroids. Microcrystalline cellulose is a preferred spheronising agent. A suitable microcrystalline cellulose is, for example, the material sold as Avicel PH 101 (Trade Mark, FMC Corporation). In such embodiments, in addition to the active ingredient and spheronising agent, the spheroids may also contain a binder. Suitable binders, such as low viscosity, water soluble polymers, will be well known to those skilled in the pharmaceutical art. However, water soluble hydroxy lower alkyl cellulose, such as hydroxypropyl-cellulose, are preferred. Additionally (or alternatively) the spheroids may contain a water insoluble polymer, especially an acrylic polymer, an acrylic copolymer, such as a methacrylic acid-ethyl acrylate copolymer, or ethyl cellulose. In such embodiments, the sustained release coating will generally include a hydrophobic material such as (a) a wax, either alone or in admixture with a fatty alcohol; or (b) shellac or zein.

Melt Extrusion Matrix

Sustained release matrices can also be prepared via melt-granulation or melt-extrusion techniques. Generally, melt-granulation techniques involve melting a normally solid hydrophobic material, e.g. a wax, and incorporating a powdered drug therein. To obtain a sustained release dosage form, it may be necessary to incorporate an additional hydrophobic substance, e.g. ethylcellulose or a water-insoluble acrylic polymer, into the molten wax hydrophobic material. Examples of sustained release formulations prepared via melt-granulation techniques are found in US 4,861,598.

The additional hydrophobic material may comprise one or more water-insoluble wax-like thermoplastic substances possibly mixed with one or more wax-like thermoplastic substances being less hydrophobic than said one or more water-insoluble wax-like substances. In order to achieve constant release, the individual wax-like substances in the formulation should be substantially non-degradable and insoluble in gastrointestinal fluids during the initial release phases. Useful water-insoluble wax-like substances may be those with a water-solubility that is lower than about 1:5,000 (w/w).

In addition to the above ingredients, a sustained release matrix may also contain suitable quantities of other materials, e.g., diluents, lubricants, binders, granulating aids, colourants, flavourants and glidants that are conventional in the pharmaceutical art. The quantities of these additional materials will be sufficient to provide the desired effect to the desired formulation.

In addition to the above ingredients, a sustained release matrix incorporating melt-extruded multiparticulates may also contain suitable quantities of other materials, e.g. diluents, lubricants, binders, granulating aids, colourants, flavourants and glidants that are conventional in the pharmaceutical art in amounts up to about 50% by weight of the particulate if desired.

Specific examples of pharmaceutically acceptable carriers and excipients that may be used to formulate oral dosage forms are described in the Handbook of Pharmaceutical Excipients, American Pharmaceutical Association (1986).

Melt Extrusion Multiparticulates

The preparation of a suitable melt-extruded matrix according to the present invention may, for example, include the steps of blending any one or more of oxymorphone hydrochloride Forms C, D, E, F, G and H together with at least one hydrophobic material and preferably the additional hydrophobic material to obtain a homogeneous mixture. The homogeneous mixture is then heated to a temperature sufficient to at least soften the mixture sufficiently to extrude the same. The resulting homogeneous mixture is then extruded to form strands. The extrudate is preferably cooled and cut into multiparticulates by any means known in the art. The strands are cooled and cut into multiparticulates. The multiparticulates are then divided into unit doses. The extrudate preferably has a diameter of from about 0.1 mm to about 5 mm and provides sustained release of the therapeutically active agent for a time period of from about 8 hours to about 24 hours.

An optional process for preparing the melt extrusions of the present invention includes directly metering into an extruder a hydrophobic material, any one or more of oxymorphone hydrochloride Forms C, D, E, F, G and H, and an optional binder; heating the homogenous mixture; extruding the homogenous mixture to thereby form strands; cooling the strands containing the homogeneous mixture; cutting the strands into particles having a size from about 0.1 mm to about 12 mm; and dividing said particles into unit doses. In this aspect of the invention, a relatively continuous manufacturing procedure is realized.

The diameter of the extruder aperture or exit port can also be adjusted to vary the thickness of the extruded strands. Furthermore, the exit part of the extruder need not be round; it can be oblong, rectangular, etc. The exiting strands can be reduced to particles using a hot wire cutter, guillotine, etc.

The melt extruded multiparticulate system can be, for example, in the form of granules, spheroids or pellets depending upon the extruder exit orifice. For the purposes of the present invention, the terms "melt-extruded multiparticulate(s)" and "melt-extruded multiparticulate system(s)" and "melt-extruded particles" shall refer to a plurality of units, preferably within a range of similar size and/or shape and containing one or more active agents and one or more excipients, preferably including a hydrophobic material as described herein. In this regard, the melt-extruded multiparticulates will be of a range of from about 0.1 mm to about 12 mm in length

and have a diameter of from about 0.1 mm to about 5 mm. In addition, it is to be understood that the melt-extruded multiparticulates can be any geometrical shape within this size range. Alternatively, the extrudate may simply be cut into desired lengths and divided into unit doses of the therapeutically active agent without the need of a spheronisation step.

In one preferred embodiment, oral dosage forms are prepared to include an effective amount of melt-extruded multiparticulates within a capsule. For example, a plurality of the melt-extruded multiparticulates may be placed in a gelatin capsule in an amount sufficient to provide an effective sustained release dose when ingested and contacted by gastric fluid.

In another preferred embodiment, a suitable amount of the multiparticulate extrudate is compressed into an oral tablet using conventional tabletting equipment using standard techniques. Techniques and compositions for making tablets (compressed and moulded), capsules (hard and soft gelatin) and pills are also described in Remington's Pharmaceutical Sciences, (Arthur Osol, editor), 1553-1593 (1980).

In yet another preferred embodiment, the extrudate can be shaped into tablets as set forth in US 4,957,681, described in additional detail above.

Optionally, the sustained release melt-extruded multiparticulate systems or tablets can be coated, or the gelatin capsule containing the multiparticulates can be further coated, with a sustained release coating such as the sustained release coatings described above. Such coatings preferably include a sufficient amount of hydrophobic material to obtain a weight gain level from about 2% to about 30%, although the overcoat may be greater depending upon the desired release rate, among other things.

The melt-extruded unit dosage forms of the present invention may further include combinations of melt-extruded particles before being encapsulated. Furthermore, the unit dosage forms can also include an amount of an immediate release agent for prompt release. The immediate release agent may be incorporated, e.g., as separate pellets within a gelatin capsule, or may be coated on the surface of the multiparticulates after preparation of the dosage forms (e.g., sustained release

coating or matrix-based). The unit dosage forms of the present invention may also contain a combination of sustained release beads and matrix multiparticulates to achieve a desired effect.

The sustained release formulations of the present invention preferably slowly release the agent(s), e.g. when ingested and exposed to gastric fluids, and then to intestinal fluids. The sustained release profile of the melt-extruded formulations of the invention can be altered, for example, by varying the amount of retardant, i.e., hydrophobic material, by varying the amount of plasticiser relative to hydrophobic material, by the inclusion of additional ingredients or excipients, by altering the method of manufacture, etc.

In other embodiments of the invention, the melt extruded material is prepared without the inclusion of any one or more of oxymorphone hydrochloride Forms C, D, E, F, G and H, which can be added thereafter to the extrudate. Such formulations typically will have the agents blended together with the extruded matrix material, and then the mixture would be tableted in order to provide a slow release formulation.

Coatings

The dosage forms of the present invention may optionally be coated with one or more materials suitable for the regulation of release or for the protection of the formulation. In one embodiment, coatings are provided to permit either pH-dependent or pH-independent release. A pH-dependent coating serves to release the active in desired areas of the gastro-intestinal (GI) tract, e.g. the stomach or small intestine, such that an absorption profile is provided which is capable of providing at least about eight hours and preferably about twelve hours to up to about twenty-four hours of analgesia to a patient. When a pH-independent coating is desired, the coating is designed to achieve optimal release regardless of pH-changes in the environmental fluid, e.g., the GI tract. It is also possible to formulate compositions that release a portion of the dose in one desired area of the GI tract, e.g., the stomach, and release the remainder of the dose in another area of the GI tract, e.g., the small intestine.

Formulations according to the invention that utilize pH-dependent coatings to obtain formulations may also impart a repeat-action effect whereby unprotected drug

is coated over the enteric coat and is released in the stomach, while the remainder, being protected by the enteric coating, is released further down the gastrointestinal tract. Coatings which are pH-dependent may be used in accordance with the present invention include shellac, cellulose acetate phthalate (CAP), polyvinyl acetate phthalate (PVAP), hydroxypropylmethylcellulose phthalate, and methacrylic acid ester copolymers, zein, and the like.

In certain preferred embodiments, the substrate (e.g., tablet core bead, matrix particle) containing any one or more of oxymorphone hydrochloride Forms C, D, E, F, G and H thereof is coated with a hydrophobic material selected from (i) an alkylcellulose; (ii) an acrylic polymer; or (iii) mixtures thereof. The coating may be applied in the form of an organic or aqueous solution or dispersion. The coating may be applied to obtain a weight gain from about 2% to about 25% of the substrate in order to obtain a desired sustained release profile. Coatings derived from aqueous dispersions are described in detail US 5,273,760, US 5,286,493, US 5,324,351, US 5,356,467, and US 5,472,712.

Alkylcellulose Polymers

Cellulosic materials and polymers, including alkylcelluloses, provide hydrophobic materials well suited for coating the beads according to the invention. Simply by way of example, one preferred alkylcellulosic polymer is ethylcellulose, although the artisan will appreciate that other cellulose and/or alkylcellulose polymers may be readily employed, singly or in any combination, as all or part of a hydrophobic coating according to the invention.

Acrylic Polymers

In other preferred embodiments of the present invention, the hydrophobic material comprising the sustained release coating is a pharmaceutically acceptable acrylic polymer, including but not limited to acrylic acid and methacrylic acid copolymers, methyl methacrylate copolymers, ethoxyethyl methacrylates, cyanoethyl methacrylate, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamide copolymer, poly(methyl methacrylate), polymethacrylate, poly(methyl methacrylate) copolymer, polyacrylamide, aminoalkyl methacrylate copolymer, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers.

In certain preferred embodiments, the acrylic polymer is comprised of one or more ammonio methacrylate copolymers. Ammonio methacrylate copolymers are well known in the art, and are described as fully polymerised copolymers of acrylic and methacrylic acid esters with a low content of quaternary ammonium groups.

In order to obtain a desirable dissolution profile, it may be necessary to incorporate two or more ammonio methacrylate copolymers having differing physical properties, such as different molar ratios of the quaternary ammonium groups to the neutral (meth)acrylic esters.

Certain methacrylic acid ester-type polymers are useful for preparing pH-dependent coatings, which may be used in accordance with the present invention. For example, there are a family of copolymers synthesized from diethylaminoethyl methacrylate and other neutral methacrylic esters, also known as methacrylic acid copolymer or polymeric methacrylates, commercially available as Eudragit™ from Rohm Tech, Inc. There are several different types of Eudragit™, for example Eudragit™ E is an example of a methacrylic acid copolymer that swells and dissolves in acidic media. Eudragit™ L is a methacrylic acid copolymer which does not swell at about pH<5.7 and is soluble at about pH>6. Eudragit™ S does not swell at about pH<6.5 and is soluble at about pH>7. Eudragit™ RL and Eudragit™ RS are water swellable, and the amount of water absorbed by these polymers is pH-dependent, however, dosage forms coated with Eudragit™ RL and RS are pH-independent.

In certain preferred embodiments, the acrylic coating comprises a mixture of two acrylic resin lacquers commercially available from Rohm Pharma under the Tradenames Eudragit™ RL30D and Eudragit™ RS30D, respectively. Eudragit™ RL30D and Eudragit™ RS30D are copolymers of acrylic and methacrylic esters with a low content of quaternary ammonium groups, the molar ratio of ammonium groups to the remaining neutral (meth)acrylic esters being 1:20 in Eudragit™ RL30D and 1:40 in Eudragit™ RS30D. The mean molecular weight is about 150,000. The code designations RL (high permeability) and RS (low permeability) refer to the permeability properties of these agents. Eudragit™ RL/RS mixtures are insoluble in water and in digestive fluids. However, coatings formed from the same are swellable and permeable in aqueous solutions and digestive fluids.

The Eudragit™ RL/RS dispersions of the present invention may be mixed together in any desired ratio in order to ultimately obtain a sustained release formulation having a desirable dissolution profile. Desirable sustained release formulations may be obtained, for instance, from a retardant coating derived from 100% Eudragit™ RL, 50% Eudragit™ RL and 50% Eudragit™ RS, or 10% Eudragit™ RL and 90% Eudragit™ RS. Of course, one skilled in the art will recognize that other acrylic polymers may also be used, such as, for example, Eudragit™ L.

Plasticisers

In embodiments of the present invention where the coating comprises an aqueous dispersion of a hydrophobic material, the inclusion of an effective amount of a plasticiser in the aqueous dispersion of hydrophobic material will further improve the physical properties of the sustained release coating. For example, because ethyl-cellulose has a relatively high glass transition temperature and does not form flexible films under normal coating conditions, it is preferable to incorporate a plasticiser into an ethylcellulose coating containing sustained release coating before using the same as a coating material. Generally, the amount of plasticiser included in a coating solution is based on the concentration of the film-former, e.g., most often from about 1wt% to about 50wt% of the film-former. Concentration of the plasticiser, however, can only be properly determined after careful experimentation with the particular coating solution and method of application.

Examples of suitable plasticisers for ethylcellulose include water insoluble plasticisers such as dibutyl sebacate, diethyl phthalate, triethyl citrate, tributyl citrate, and triacetin, although it is possible that other water-insoluble plasticisers (such as acetylated monoglycerides, phthalate esters, castor oil, etc.) may be used. Triethyl citrate is an especially preferred plasticiser for the aqueous dispersions of ethyl cellulose of the present invention.

Examples of suitable plasticisers for the acrylic polymers of the present invention include, but are not limited to citric acid esters such as triethyl citrate, tributyl citrate, dibutyl phthalate, and possibly 1,2-propylene glycol. Other plasticisers that have proved to be suitable for enhancing the elasticity of the films formed from acrylic films such as Eudragit™ RL/RS lacquer solutions include polyethylene glycols,

propylene glycol, diethyl phthalate, castor oil, and triacetin. Triethyl citrate is an especially preferred plasticiser for the aqueous dispersions of ethyl cellulose of the present invention.

The addition of a small amount of talc may also help reduce the tendency of the aqueous dispersion to stick during processing, and may act as a polishing agent.

Sustained Release Osmotic Dosage Form

Sustained release dosage forms according to the present invention may also be prepared as osmotic dosage formulations. The osmotic dosage forms preferably include a bilayer core comprising a drug layer (containing any one or more of oxymorphone hydrochloride Forms C, D, E, F, G and H) and a delivery or push layer, wherein the bilayer core is surrounded by a semipermeable wall and optionally having at least one passageway disposed therein.

The expression "passageway" as used for the purpose of this invention, includes aperture, orifice, bore, pore, porous element through which any one or more of oxymorphone hydrochloride Forms C, D, E, F, G and H can be pumped, diffuse or migrate through a fibre, capillary tube, porous overlay, porous insert, microporous member, or porous composition. The passageway can also include a compound that erodes or is leached from the wall in the fluid environment of use to produce at least one passageway. Representative compounds for forming a passageway include erodable poly(glycolic) acid, or poly(lactic) acid in the wall; a gelatinous filament; a water-removable poly(vinyl alcohol); leachable compounds such as fluid-removable pore-forming polysaccharides, acids, salts or oxides. A passageway can be formed by leaching a compound from the wall, such as sorbitol, sucrose, lactose, maltose, or fructose, to form a sustained-release dimensional pore-passageway. The dosage form can be manufactured with one or more passageways in spaced-apart relation on one or more surfaces of the dosage form. A passageway and equipment for forming a passageway are disclosed in US 3,845,770, US 3,916,899, US 4,063,064 and US 4,088,864. Passageways comprising sustained-release dimensions sized, shaped and adapted as a releasing-pore formed by aqueous leaching to provide a releasing-pore of a sustained-release rate are disclosed in US 4,200,098 and US 4,285,987.

In certain embodiments the drug layer may also comprise at least one polymer hydrogel. The polymer hydrogel may have an average molecular weight of between about 500 and about 6,000,000. Examples of polymer hydrogels include but are not limited to a maltodextrin polymer comprising the formula $(C_6H_{12}O_5)_nH_2O$, wherein n is 3 to 7,500, and the maltodextrin polymer comprises a 500 to 1,250,000 number-average molecular weight; a poly(alkylene oxide) represented by, e.g., a poly(ethylene oxide) and a poly(propylene oxide) having a 50,000 to 750,000 weight-average molecular weight, and more specifically represented by a poly(ethylene oxide) of at least one of 100,000, 200,000, 300,000 or 400,000 weight-average molecular weights; an alkali carboxyalkylcellulose, wherein the alkali is sodium or potassium, the alkyl is methyl, ethyl, propyl, or butyl of 10,000 to 175,000 weight-average molecular weight; and a copolymer of ethylene-acrylic acid, including methacrylic and ethacrylic acid of 10,000 to 500,000 number-average molecular weight.

In certain embodiments of the present invention, the delivery or push layer comprises an osmopolymer. Examples of an osmopolymer include but are not limited to a member selected from the group consisting of a polyalkylene oxide and a carboxyalkylcellulose. The polyalkylene oxide possesses a 1,000,000 to 10,000,000 weight-average molecular weight. The polyalkylene oxide may be a member selected from the group consisting of polymethylene oxide, polyethylene oxide, polypropylene oxide, polyethylene oxide having a 1,000,000 average molecular weight, polyethylene oxide comprising a 5,000,000 average molecular weight, polyethylene oxide comprising a 7,000,000 average molecular weight, cross-linked polymethylene oxide possessing a 1,000,000 average molecular weight, and polypropylene oxide of 1,200,000 average molecular weight. Typical osmopolymer carboxyalkylcellulose comprises a member selected from the group consisting of alkali carboxyalkyl-cellulose, sodium carboxymethylcellulose, potassium carboxymethylcellulose, sodium carboxyethylcellulose, lithium carboxymethylcellulose, sodium carboxyethyl-cellulose, carboxyalkylhydroxyalkylcellulose, carboxymethylhydroxyethyl cellulose, carboxyethylhydroxyethylcellulose and carboxymethylhydroxypropylcellulose. The osmopolymers used for the displacement layer exhibit an osmotic pressure gradient across the semipermeable wall. The osmopolymers imbibe fluid into dosage form, thereby swelling and expanding as an osmotic hydrogel (also known as an osmogel),

whereby they push any one or more of oxymorphone hydrochloride Forms C, D, E, F, G and H thereof from the osmotic dosage form.

The push layer may also include one or more osmotically effective compounds also known as osmagents and as osmotically effective solutes. They imbibe an environmental fluid, for example, from the gastrointestinal tract, into dosage form and contribute to the delivery kinetics of the displacement layer. Examples of osmotically active compounds comprise a member selected from the group consisting of osmotic salts and osmotic carbohydrates. Examples of specific osmagents include but are not limited to sodium chloride, potassium chloride, magnesium sulphate, lithium phosphate, lithium chloride, sodium phosphate, potassium sulphate, sodium sulphate, potassium phosphate, glucose, fructose and maltose.

The push layer may optionally include a hydroxypropylalkylcellulose possessing a 9,000 to 450,000 number-average molecular weight. The hydroxypropylalkyl-cellulose is represented by a member selected from the group consisting of hydroxypropylmethylcellulose, hydroxypropylethylcellulose, hydroxypropylisopropyl cellulose, hydroxypropylbutylcellulose, and hydroxypropylpentylcellulose.

The push layer optionally may comprise a non-toxic colourant or dye. Examples of colourants or dyes include but are not limited to Food and Drug Administration Colourants (FD&C), such as FD&C No.1 blue dye, FD&C No.4 red dye, red ferric oxide, yellow ferric oxide, titanium dioxide, carbon black, and indigo.

The push layer may also optionally comprise an antioxidant to inhibit the oxidation of ingredients. Some examples of antioxidants include but are not limited to a member selected from the group consisting of ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, a mixture of 2 and 3 tertiary-butyl-4-hydroxyanisole, butylated hydroxytoluene, sodium isoascorbate, dihydroguaretic acid, potassium sorbate, sodium bisulfate, sodium metabisulfate, sorbic acid, potassium ascorbate, vitamin E, 4-chloro-2,6-ditertiary butylphenol, alphatocopherol, and propylgallate.

In certain alternative embodiments, the dosage form comprises a homogenous core comprising any one or more of oxymorphone hydrochloride Forms C, D, E, F, G and H, a pharmaceutically acceptable polymer (e.g., polyethylene oxide), optionally a disintegrant (e.g., polyvinylpyrrolidone), optionally an absorption enhancer (e.g., a

fatty acid, a surfactant, a chelating agent, a bile salt, etc). The homogenous core is surrounded by a semipermeable wall having a passageway (as defined above) for the release of any one or more of oxymorphone hydrochloride Forms C, D, E, F, G and H.

In certain embodiments, the semipermeable wall comprises a member selected from the group consisting of a cellulose ester polymer, a cellulose ether polymer and a cellulose ester-ether polymer. Representative wall polymers comprise a member selected from the group consisting of cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, mono-, di- and tricellulose alkenylates, and mono-, di- and tricellulose alkinylates. The poly(cellulose) used for the present invention comprises a number-average molecular weight of 20,000 to 7,500,000.

Additional semipermeable polymers for the purpose of this invention comprise acetaldehyde dimethycellulose acetate, cellulose acetate ethylcarbamate, cellulose acetate methylcarbamate, cellulose diacetate, propylcarbamate, cellulose acetate diethylaminoacetate; semipermeable polyamide; semipermeable polyurethane; semipermeable sulfonated polystyrene; semipermeable cross-linked polymer formed by the coprecipitation of a polyanion and a polycation, semipermeable crosslinked polystyrenes, semipermeable cross-linked poly(sodium styrene sulfonate), semipermeable crosslinked poly(vinylbenzyltrimethyl ammonium chloride) and semipermeable polymers possessing a fluid permeability of 2.5×10^{-8} to 2.5×10^{-2} (cm^2/hr atm) expressed per atmosphere of hydrostatic or osmotic pressure difference across the semipermeable wall. Other polymers useful in the present invention are known in the art including those in Handbook of Common Polymers, Scott, J. R. and W. J. Roff, 1971, CRC Press, Cleveland, Ohio.

In certain embodiments, preferably the semipermeable wall is nontoxic, inert, and it maintains its physical and chemical integrity during the dispensing life of the drug. In certain embodiments, the dosage form comprises a binder. An example of a binder includes, but is not limited to a therapeutically acceptable vinyl polymer having a 5,000 to 350,000 viscosity-average molecular weight, represented by a member selected from the group consisting of poly-n-vinylamide, poly-n-vinylacetamide, poly(vinyl pyrrolidone), also known as poly-n-vinylpyrrolidone, poly-n-vinylcaprolactone, poly-n-vinyl-5-methyl-2-pyrrolidone, and poly-n-vinyl-pyrrolidone

copolymers with a member selected from the group consisting of vinyl acetate, vinyl alcohol, vinyl chloride, vinyl fluoride, vinyl butyrate, vinyl laureate, and vinyl stearate. Other binders include for example, acacia, starch, gelatin, and hydroxypropylalkylcellulose of 9,200 to 250,000 average molecular weight.

In certain embodiments, the dosage form comprises a lubricant, which may be used during the manufacture of the dosage form to prevent sticking to die wall or punch faces. Examples of lubricants include but are not limited to magnesium stearate, sodium stearate, stearic acid, calcium stearate, magnesium oleate, oleic acid, potassium oleate, caprylic acid, sodium stearyl fumarate, and magnesium palmitate.

In certain preferred embodiments, the present invention includes a therapeutic composition comprising an amount of any one or more oxymorphone hydrochloride Forms C, D, E, F, G and H equivalent to 10 to 40 mg oxymorphone hydrochloride, 25 mg to 500 mg of poly(alkylene oxide) having a 150,000 to 500,000 average molecular weight, 1 mg to 50 mg of polyvinylpyrrolidone having a 40,000 average molecular weight, and 0 mg to about 7.5 mg of a lubricant.

Suppositories

The sustained release formulations of the present invention may be formulated as a pharmaceutical suppository for rectal administration comprising a suitable suppository base, and any one or more of oxymorphone hydrochloride Forms C, D, E, F, G and H. Preparation of sustained release suppository formulations is described in, e.g., US 5,215,758.

Prior to absorption, the drug must be in solution. In the case of suppositories, solution must be preceded by dissolution of the suppository base, or the melting of the base and subsequent partition of the drug from the suppository base into the rectal fluid. The absorption of the drug into the body may be altered by the suppository base. Thus, the particular suppository base to be used in conjunction with a particular drug must be chosen giving consideration to the physical properties of the drug. For example, lipid-soluble drugs will not partition readily into the rectal fluid, but drugs that are only slightly soluble in the lipid base will partition readily into the rectal fluid.

Among the different factors affecting the dissolution time (or release rate) of the drugs are the surface area of the drug substance presented to the dissolution solvent medium, the pH of the solution, the solubility of the substance in the specific solvent medium, and the driving forces of the saturation concentration of dissolved materials in the solvent medium. Generally, factors affecting the absorption of drugs from suppositories administered rectally include suppository vehicle, absorption site pH, drug pKa, degree of ionisation, and lipid solubility.

The suppository base chosen should be compatible with the active of the present invention. Further, the suppository base is preferably non-toxic and non-irritating to mucous membranes, melts or dissolves in rectal fluids, and is stable during storage.

In certain preferred embodiments of the present invention for both water-soluble and water-insoluble drugs, the suppository base comprises a fatty acid wax selected from the group consisting of mono-, di- and triglycerides of saturated, natural fatty acids of the chain length C_{12} to C_{18}.

In preparing the suppositories of the present invention other excipients may be used. For example, a wax may be used to form the proper shape for administration via the rectal route. This system can also be used without wax, but with the addition of diluent filled in a gelatin capsule for both rectal and oral administration.

Examples of suitable commercially available mono-, di- and triglycerides include saturated natural fatty acids of the 12-18 carbon atom chain sold under the trade name Novata ™ (types AB, AB, B, BC, BD, BBC, E, BCF, C, D and 299), manufactured by Henkel, and Witepsol ™ (types H5, H12, H15, H175, H185, H19, H32, H35, H39, H42, W25, W31, W35, W45, S55, S58, E75, E76 and E85), manufactured by Dynamit Nobel.

Other pharmaceutically acceptable suppository bases may be substituted in whole or in part for the above-mentioned mono-, di- and triglycerides. The amount of base in the suppository is determined by the size (i.e. actual weight) of the dosage form, the amount of base (e.g., alginate) and drug used. Generally, the amount of suppository base is from about 20% to about 90% by weight of the total weight of the

suppository. Preferably, the amount of suppository base in the suppository is from about 65% to about 80%, by weight of the total weight of the suppository.

Oxymorphone hydrochloride Forms C, D, E, F, G, and H can also be formulated with suitable pharmaceutically acceptable excipients to provide an abuse-proof dosage form. As described in US 8,114,383, opiates, which are highly active in combating severe to very severe pain, are frequently used by abusers to induce a state of narcosis or euphoria. In order to make abuse possible, dosage forms such as tablets or capsules are comminuted, for example ground in a mortar, by the abuser, the active ingredient is extracted from the resultant solution, optionally after being filtered through cotton wool or cellulose wadding, and is administered parenterally, in particular intravenously. An additional phenomenon of this kind of administration, in comparison with abusive oral administration, is a further accelerated increase in active ingredient levels giving the abuser the desired effect, namely the "kick" or "rush." This kick is also obtained if the powdered dosage form is administered nasally, i.e. sniffed.

Oxymorphone hydrochloride Forms C, D, E, F, G, and H can be formulated as an abuse-proofed, thermoformed dosage form containing, in addition to any one or more oxymorphone hydrochloride Forms C, D, E, F, G, and H, at least one synthetic or natural polymer. The use of polymers having a minimum breaking strength (e.g. 500N) means that pulverisation of the dosage form is considerably more difficult using conventional means, so considerably complicating or preventing the subsequent abuse. At least one polymer selected from the group consisting of polymethylene oxide, polyethylene oxide, polypropylene oxide, polyethylene, polypropylene, polyvinyl chloride, polycarbonate, polystyrene, polyacrylate, copolymers thereof, and mixtures of at least two of the stated polymers is preferably used for this purpose. Such formulations can be prepared in accordance with US 8,114,383.

In order to achieve an adequate breaking strength of the abuse-proofed dosage form, it is possible to also use at least one natural or synthetic wax with a breaking strength of at least 500 N. Carnauba wax and beeswax are particularly preferred. Carnauba wax is very particularly preferred.

The abuse-proofed dosage forms, which comprise, apart from any one or more of oxymorphone Form C, D, E, F, G and H, at least one hardening polymer and

optionally at least one wax, may also comprise one or more of the following components (a)-(f) as auxiliary substances:

(a) at least one substance which irritates the nasal passages and/or pharynx,

(b) at least one viscosity-increasing agent, which, with the assistance of a necessary minimum quantity of an aqueous liquid, forms a gel with the extract obtained from the dosage form, which gel preferably remains visually distinguishable when introduced into a further quantity of an aqueous liquid,

(c) at least one antagonist for each of the active ingredients with abuse potential,

(d) at least one emetic,

(e) at least one dye as an aversive agent,

(f) at least one bitter substance.

Components (a) to (f) are additionally each individually suitable for abuse-proofing the dosage form. Accordingly, component (a) is preferably suitable for proofing the dosage form against nasal, oral and/or parenteral, preferably intravenous, abuse, component (b) is preferably suitable for proofing against parenteral, particularly preferably intravenous and/or nasal abuse, component (c) is preferably suitable for proofing against nasal and/or parenteral, particularly preferably intravenous, abuse, component (d) is preferably suitable for proofing against parenteral, particularly preferably intravenous, and/or oral and/or nasal abuse, component (e) is suitable as a visual deterrent against oral or parenteral abuse and component (f) is suitable for proofing against oral or nasal abuse. Combined use according to the invention of at least one of the above-stated components makes it possible still more effectively to prevent abuse of dosage forms according to the invention.

In another embodiment, the dosage form according to the invention may comprise the addition of a swellable agent in order to prevent abuse. When water is added to extract the active ingredient, this agent swells and ensures that the filtrate separated from the gel contains only a small quantity of active ingredients. Such formulations can be prepared in accordance with US 4,070,494.

In another embodiment, the dosage form according the invention may comprise a multilayer tablet in order to prevent abuse. The tablet contains the active ingredient and at least one gel former, each in different layers. Such formulations can be prepared in accordance with US 6,309,668.

EXAMPLES

The invention is illustrated by the following examples.

The following examples are set forth to aid in the understanding of the invention, and are not intended and should not be construed to limit in any way the invention set forth in the claims which follow thereafter.

Example 1

Preparation of Form A

About 8 mg of oxymorphone freebase is added with stirring to a reaction vessel containing about 7.2 g of water, about 5.28 g of concentrated hydrochloric acid and about 22.08 g of 1-propanol. The mixture is heated to about 65 °C. Stirring is continued for about 30 minutes. The mixture is vacuum distilled to about 3.5 vol. with respect to freebase. 1-propanol is added to the mixture, with stirring, to about 9 vol. with respect to freebase. Stirring is continued for about 30 minutes and the temperature remains at about 65 °C. The mixture is cooled slowly to about 50 °C and further cooled to about 2 to 5 °C over about 1-3 hours. Stirring is continued and the temperature remains at about 2 to 5 °C for about 2 additional hours. A slurry is formed and filtered. The vessel is washed with about 1 vol. of 1-propanol with respect to freebase. The wash liquor is used to wash the resulting solids. The resulting solids are collected and dried in an oven at a temperature less than 45 °C. The solids are collected from the oven, analyzed by X-ray powder diffraction and determined to be oxymorphone hydrochloride Form A.

Example 2

Preparation of Form A

About 8 mg of oxymorphone freebase is added with stirring to a reaction vessel containing about 7.2 g of water, about 5.28 g of concentrated hydrochloric acid and about 22.08 g of ethanol. The mixture is heated to about 65 °C. Stirring is continued for about 30 minutes. The mixture is vacuum distilled to about 3.5 vol. with respect to freebase. N-propanol is added to the mixture, with stirring, to about 9 vol. with respect to freebase. Stirring is continued for about 1 hour and the temperature remains at about 65 °C. The mixture is cooled to about 2 to 5 °C and stirring is continued at that temperature for about 12 to 24 hours. A slurry is formed and filtered. The resulting solids are collected and dried in an oven at about 40 °C for about 12 to 24 hours. The solids are collected from the oven, analyzed by X-ray powder diffraction and determined to be oxymorphone hydrochloride Form A.

Example 3

Preparation of Form A

About 8 mg of oxymorphone freebase is added with stirring to a reaction vessel containing about 7.2 g of water, about 5.28 g of concentrated hydrochloric acid and about 22.08 g of n-propanol. The mixture is heated to about 65 °C. Stirring is continued for about 30 minutes. The mixture is vacuum distilled to about 3.5 vol. with respect to freebase. N-propanol is added to the mixture, with stirring, to about 9 vol. with respect to freebase. The mixture is vacuum distilled to about 4 vol. with respect to freebase. N-propanol is added to the mixture, with stirring, to about 9 vol. with respect to freebase. Stirring is continued for about 30 minutes and the temperature remains at about 65 °C. The mixture is cooled to about 50 °C over about 1 hour and further cooled to about 2 to 5 °C over about 2.5 hours. Stirring is continued and the temperature remains at about 2 to 5 °C for about 2 additional hours. A slurry is formed and filtered. The vessel is washed with about 1 vol. of n-propanol with respect to freebase. The wash liquor is used to wash the resulting solids. The solids are dried in an oven at about 40 °C for about 12 to 24 hours. The solids are collected from the oven, analyzed by X-ray powder diffraction and determined to be oxymorphone hydrochloride Form A.

Example 4

Preparation of Form C

About 30 mg of oxymorphone hydrochloride Form A is added, with stirring, to a reaction vessel containing about 0.5 mL of ACS grade acetone. Stirring is continued for at least about 48 hours and the temperature remains at about 15 °C. A slurry is formed and centrifuged. The resulting supernatant is removed and white to off-white solids are collected. The solids are analyzed by X-ray powder diffraction and determined to be oxymorphone hydrochloride Form C.

Example 5

Preparation of Form D

About 30 mg of oxymorphone hydrochloride Form A is added, with stirring, to a reaction vessel containing about 0.5 mL of ethanol:water (about 90:10). Stirring is continued for at least about 48 hours and the temperature remains at about 15 °C. A slurry is formed and centrifuged. The resulting supernatant is removed and white to off-white solids are collected. The solids are analyzed by X-ray powder diffraction and determined to be oxymorphone hydrochloride Form D.

Example 6

Preparation of Form D

About 30 mg of oxymorphone hydrochloride Form A is added, with stirring, to a reaction vessel containing about 0.5 mL of ethanol:water (about 95:5). Stirring is continued for at least about 48 hours and the temperature remains at about 15 °C. A slurry is formed and centrifuged. The resulting supernatant is removed and white to off-white solids are collected. The solids are analyzed by X-ray powder diffraction and determined to be oxymorphone hydrochloride Form D.

Example 7

Preparation of Form E

About 30 mg of oxymorphone hydrochloride Form A is added, with stirring, to a reaction vessel containing about 0.5 mL of ethyl acetate. Stirring is continued for at least about 48 hours and the temperature remains at about 45 °C. A slurry is formed and centrifuged. The resulting supernatant is removed and white to off-white solids

are collected. The solids are analyzed by X-ray powder diffraction and determined to be oxymorphone hydrochloride Form E.

Example 8

Preparation of Form E

About 30 mg of oxymorphone hydrochloride Form A is added, with stirring, to a reaction vessel containing about 0.5 mL of ACS grade acetone. Stirring is continued for at least about 2 days and the temperature remains at about 45 °C. A slurry is formed and centrifuged. The resulting supernatant is removed and white to off-white solids are collected. The solids are analyzed by X-ray powder diffraction and determined to be oxymorphone hydrochloride Form E.

Example 9

Preparation of Form E

About 30 mg of oxymorphone hydrochloride Form A is added, with stirring, to a reaction vessel containing about 0.5 mL of acetonitrile. Stirring is continued for at least about 48 hours and the temperature remains at about 45 °C. Slurry is formed and centrifuged. The resulting supernatant is removed and white to off-white solids are collected. The solids are analyzed by X-ray powder diffraction and determined to be oxymorphone hydrochloride Form E.

Example 10

Preparation of Form F

About 100 mg of oxymorphone hydrochloride Form A is dried in a vacuum oven for at least about 72 hours while the temperature remains at about 50 °C. White to off-white solids are collected. The solids are analyzed by X-ray powder diffraction and determined to be oxymorphone hydrochloride Form F.

Example 11

Preparation of Form G

About 100 mg of oxymorphone hydrochloride Form B, as characterized by its X-ray powder diffraction pattern in FIG. 2, is dried in a vacuum oven for at least about 24 hours whilst the temperature remains at about 50 °C. White to off-white solids are collected. The solids are analyzed by X-ray powder diffraction and determined to be oxymorphone hydrochloride Form G.

Example 12

Preparation of Form H

About 4 g of oxymorphone freebase is added, with stirring, to a reaction vessel followed by the addition of about 3.6 mL water, about 2.64 g concentrated hydrochloric acid and about 11.04 g ethanol. The stirring is continued and the temperature remains at about 65 °C. About 6.1 g of the solvent mixture is vacuum distilled before about 12.9 g of ethanol is added. About 8.8 g of solvent mixture is removed and about 8.8 g of ethanol is added. White to off-white solids are formed. The solids are analyzed by X-ray powder diffraction and determined to be oxymorphone hydrochloride Form H.

What is claimed is:

1. A form of oxymorphone hydrochloride selected from the group consisting of Form C, Form D, Form E, Form F, Form G and Form H; wherein:

Form C has an X-ray powder diffraction pattern comprising peaks, in terms of 2-theta, at about 7.87 and about 23.73;

Form D has an X-ray powder diffraction pattern comprising peaks, in terms of 2-theta, at about 9.4 and about 10.29;

Form E has an X-ray powder diffraction pattern comprising peaks, in terms of 2-theta, at about 9.21 and about 12.69;

Form F has an X-ray powder diffraction pattern comprising peaks, in terms of 2-theta, at about 9.2, about 11.8 and about 16.04;

Form G has an X-ray powder diffraction pattern comprising peaks, in terms of 2-theta, at about 9.65 and about 16.16; and

Form H has an X-ray powder diffraction pattern comprising peaks, in terms of 2-theta, at about 7.95 and about 9.04.

2. A form of oxymorphone hydrochloride according to claim 1, wherein:

Form C has an X-ray powder diffraction pattern further comprising peaks, in terms of 2-theta, at about 16.27 and about 18.09;

Form D has an X-ray powder diffraction pattern further comprising peaks, in terms of 2-theta, at about 13.14, about 17.39, about 19.69 and about 25.05;

Form E has an X-ray powder diffraction pattern further comprising peaks, in terms of 2-theta, at about 15.44, about 16.24 and about 19.93;

Form F has an X-ray powder diffraction pattern further comprising peaks, in terms of 2-theta, at about 11.47, about 19.97 and about 20.93;

Form G has an X-ray powder diffraction pattern further comprising peaks, in terms of 2-theta, at about 12.68 and about 17.2; and

Form H has an X-ray powder diffraction pattern further comprising a peak, in terms of 2-theta, at about 23.87.

3. A form of oxymorphone hydrochloride selected from the group consisting of Form C, Form D, Form E, Form F, Form G and Form H; wherein:

Form C has an X-ray powder diffraction pattern substantially as shown in FIG. 3;

Form D has an X-ray powder diffraction pattern substantially as shown in FIG. 4;

Form E has an X-ray powder diffraction pattern substantially as shown in FIG. 5;

Form F has an X-ray powder diffraction pattern substantially as shown in FIG. 6;

Form G has an X-ray powder diffraction pattern substantially as shown in FIG. 7; and

Form H has an X-ray powder diffraction pattern substantially as shown in FIG. 8.

4. A form of oxymorphone hydrochloride selected from the group consisting of Form C, Form D, Form E, Form F, Form G and Form H; wherein:

Form C has an X-ray powder diffraction pattern comprising peaks at *d*-spacing, in terms of Angstroms, of about 11.224 and about 3.747;

Form D has an X-ray powder diffraction pattern comprising peaks at *d*-spacing, in terms of Angstroms, of about 9.400 and about 8.592;

Form E has an X-ray powder diffraction pattern comprising peaks at *d*-spacing, in terms of Angstroms, of about 9.600 and about 6.968;

Form F has an X-ray powder diffraction pattern comprising peaks at *d*-spacing, in terms of Angstroms, of about 9.607, about 7.492 and about 5.521;

Form G has an X-ray powder diffraction pattern comprising peaks at *d*-spacing, in terms of Angstroms, of about 9.160 and about 5.480; and

Form H has an X-ray powder diffraction pattern comprising peaks at *d*-spacing, in terms of Angstroms, of about 11.106 and about 9.774.

5. A form of oxymorphone hydrochloride according to claim 4, wherein:

Form C has an X-ray powder diffraction pattern further comprising peaks at *d*-spacing, in terms of Angstroms, of about 5.445 and about 4.899;

Form D has an X-ray powder diffraction pattern further comprising peaks at *d*-spacing, in terms of Angstroms, of about 6.733, about 5.097, about 4.506 and about 3.552;

Form E has an X-ray powder diffraction pattern further comprising peaks at *d*-spacing, in terms of Angstroms, of about 5.736, about 5.453 and about 4.451;

Form F has an X-ray powder diffraction pattern further comprising peaks at *d*-spacing, in terms of Angstroms, of about 7.710, about 4.442 and about 4.241;

Form G has an X-ray powder diffraction pattern further comprising peaks at *d*-spacing, in terms of Angstroms, of about 6.977 and about 5.151; and

Form H has an X-ray powder diffraction pattern comprising further a peak at *d*-spacing, in terms of Angstroms, of about 3.725.

6. A form of oxymorphone hydrochloride according to claim 1, wherein, as measured by differential scanning calorimetry:

Form D is characterized by an endotherm at about 93°C;

Form E is characterized by an endotherm at about 286°C;

Form F is characterized by an endotherm at about 122°C;

Form G is characterized by an endotherm at about 105°C; and

Form H is characterized by an endotherm at about 96°C.

7. A form of oxymorphone hydrochloride according to claim 1, wherein:

Form D is characterized by a differential scanning calorimetry pattern substantially as shown in FIG. 9;

Form E is characterized by a differential scanning calorimetry pattern substantially as shown in FIG. 10;

Form F is characterized by a differential scanning calorimetry pattern substantially as shown in FIG. 11;

Form G is characterized by a differential scanning calorimetry pattern substantially as shown in FIG. 12; and

Form H is characterized by a differential scanning calorimetry pattern substantially as shown in FIG. 13.

8. A form of oxymorphone hydrochloride according to claim 1, wherein:

Form D is characterized by a thermal gravimetric analysis pattern substantially as shown in FIG. 14;

Form E is characterized by a thermal gravimetric analysis pattern substantially as shown in FIG. 15; and

Form F is characterized by a thermal gravimetric analysis pattern substantially as shown in FIG. 16.

9. A pharmaceutical formulation comprising at least one pharmaceutically acceptable excipient and oxymorphone hydrochloride according to claim 1.

10. A pharmaceutical formulation according to claim 9, wherein the formulation is a tamper resistant or abuse proof dosage form.

11. The pharmaceutical formulation according to claim 9, wherein the formulation is an extended release or sustained release dosage form.

12. A method of treating pain comprising administering a pharmaceutical formulation according to claim 9 to a patient in need thereof.

13. A method of making oxymorphone hydrochloride Form C according to claim 1, comprising exposing a starting material comprising oxymorphone hydrochloride Form A to acetone at a temperature in the range of about 0 to 20 °C for a time sufficient to yield oxymorphone hydrochloride Form C.

14. A method of making oxymorphone hydrochloride Form D according to claim 1, comprising exposing a starting material comprising oxymorphone hydrochloride Form A to a mixture of ethanol and water at a temperature in the range of about 0 to 20 °C for a time sufficient to yield oxymorphone hydrochloride Form D.

15. A method of making oxymorphone hydrochloride Form E according to claim 1, comprising exposing a starting material comprising oxymorphone hydrochloride

Form A to ethyl acetate at a temperature in the range of about 40 to 55 °C for a time sufficient to yield oxymorphone hydrochloride Form E.

16. A method of making oxymorphone hydrochloride Form E according to claim 1, comprising exposing a starting material comprising oxymorphone hydrochloride Form A to acetone at a temperature in the range of about 40 to 55 °C for a time sufficient to yield oxymorphone hydrochloride Form E.

17. A method of making oxymorphone hydrochloride Form E according to claim 1, comprising exposing a starting material comprising oxymorphone hydrochloride Form A to acetronitrile at a temperature in the range of about 40 to 55 °C for a time sufficient to yield oxymorphone hydrochloride Form E.

18. A method of making oxymorphone hydrochloride Form F according to claim 1, comprising drying a starting material comprising oxymorphone hydrochloride Form A at a temperature in the range of about 45 to 65 °C for a time sufficient to yield oxymorphone hydrochloride Form F.

19. A method of making oxymorphone hydrochloride Form G according to claim 1, comprising drying a starting material comprising oxymorphone hydrochloride Form B at a temperature in the range of about 45 to 65 °C for a time sufficient to yield oxymorphone hydrochloride Form G.

20. A method of making oxymorphone hydrochloride Form H according to claim 1, comprising the steps of:

dissolving oxymorphone freebase in a mixture comprising water, ethanol and hydrochloric acid at a temperature in the range of about 60 to 70 °C;

removing a portion of the solvent;

adding ethanol to the mixture;

removing an additional portion of the solvent; and

adding additional ethanol to the mixture to yield oxymorphone hydrochloride Form H.

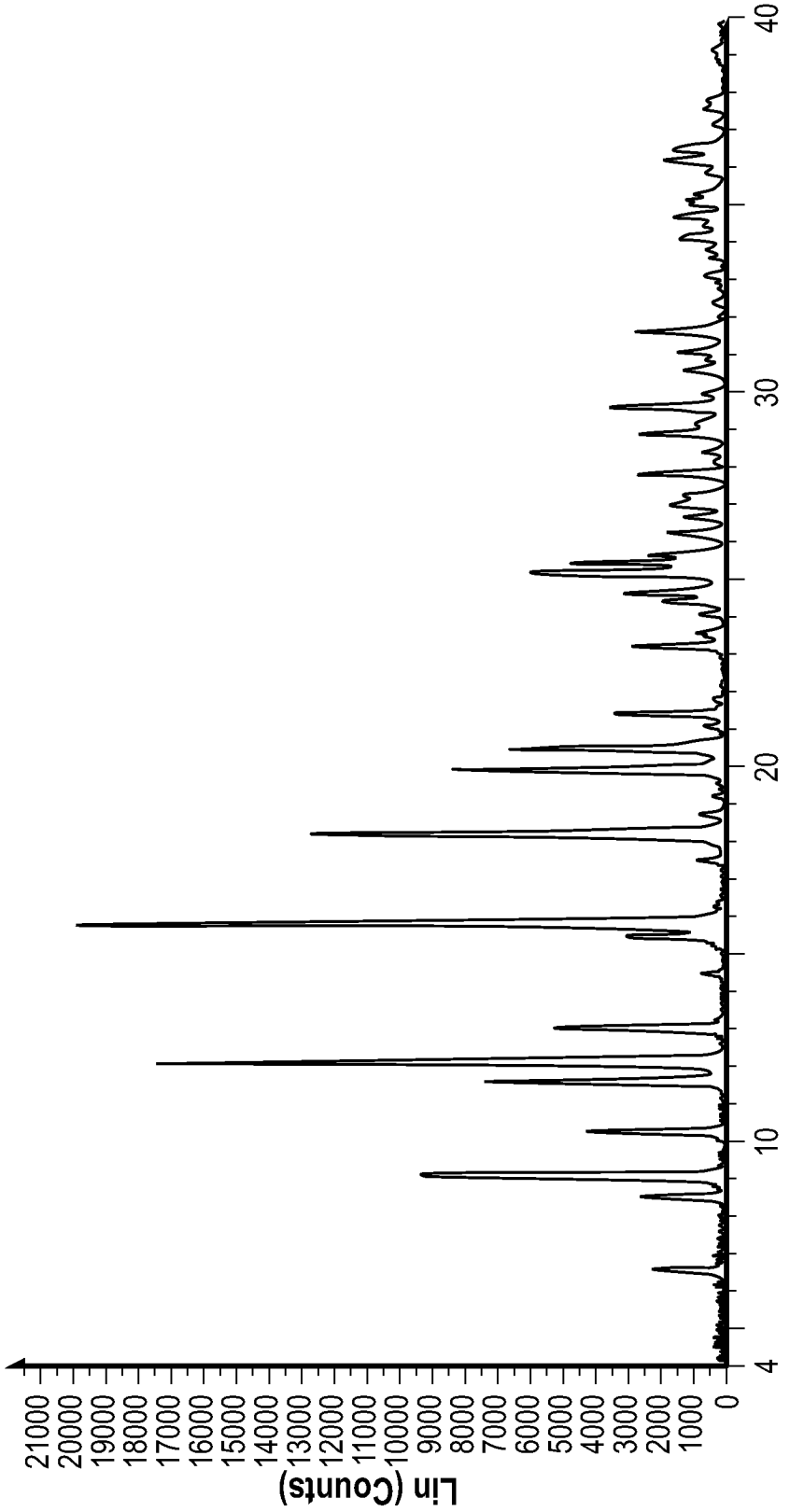

Lin (Counts)
0
1000
2000
3000
4000
5000
6000
7000
8000
9000
10000
11000
12000
13000
14000
15000
16000
17000
18000
19000
20000
21000
4
10
20
30
40
2-Theta - Scale
XRPD pattern of Oxymorphone HCl Form A

FIG. 1

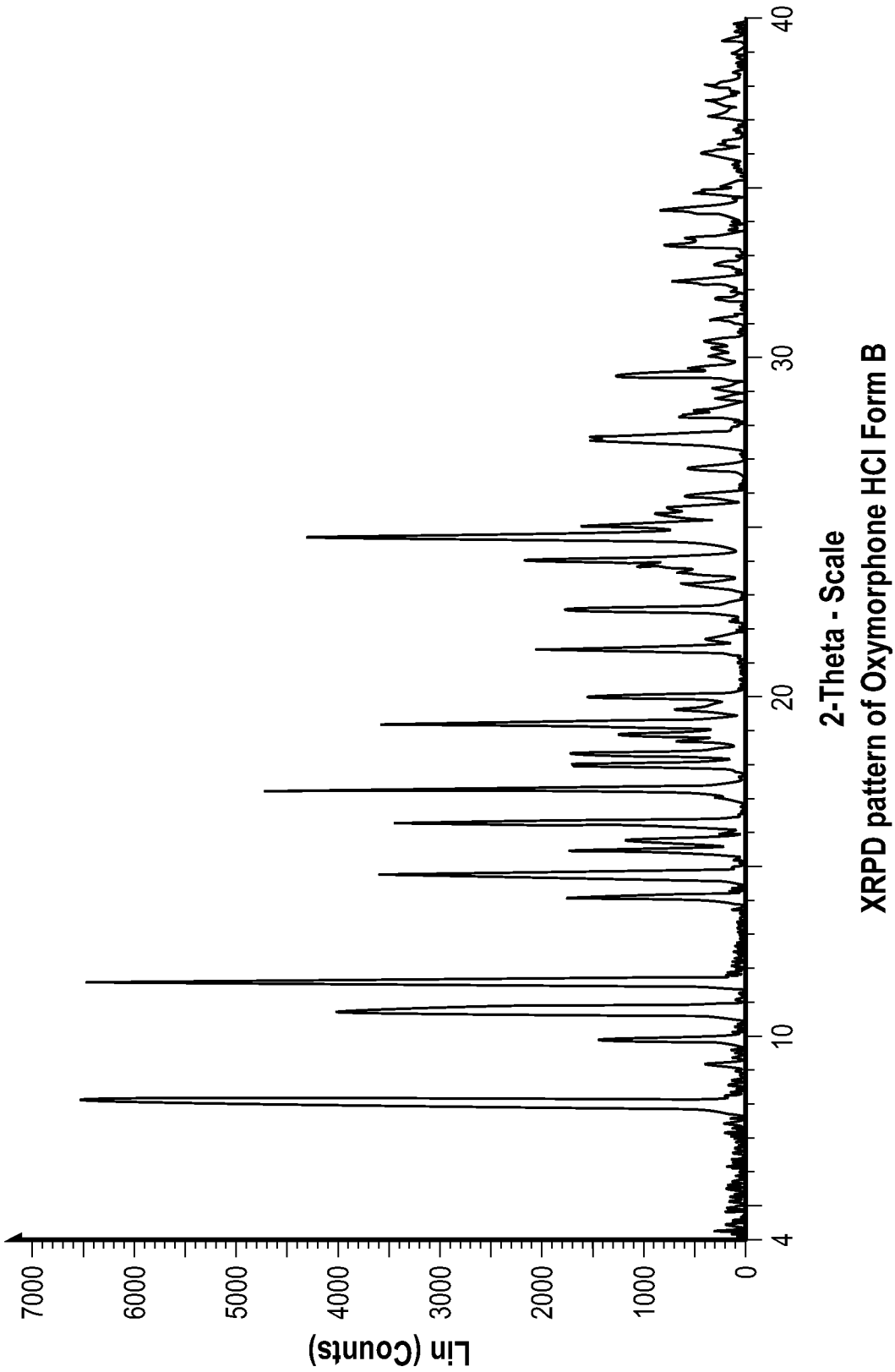

Lin (Counts)
7000
6000
5000
4000
3000
2000
1000
0
4
10
20
30
40
2-Theta - Scale
XRPD pattern of Oxymorphone HCl Form B

FIG. 2

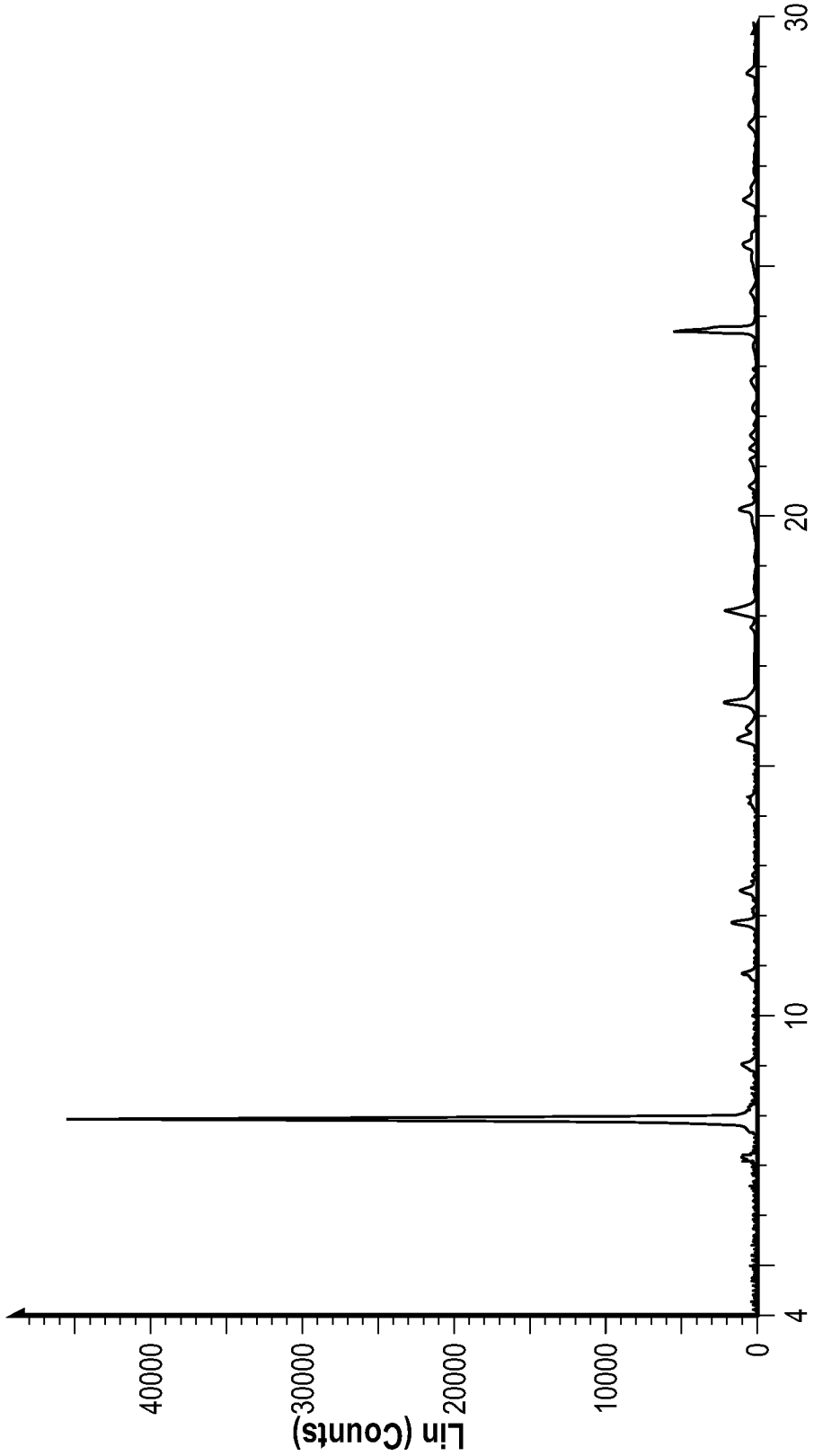

Lin (Counts)
40000
30000
20000
10000
0
4
10
20
30
2-Theta - Scale
XRPD pattern of Oxymorphone HCl Form C

FIG. 3

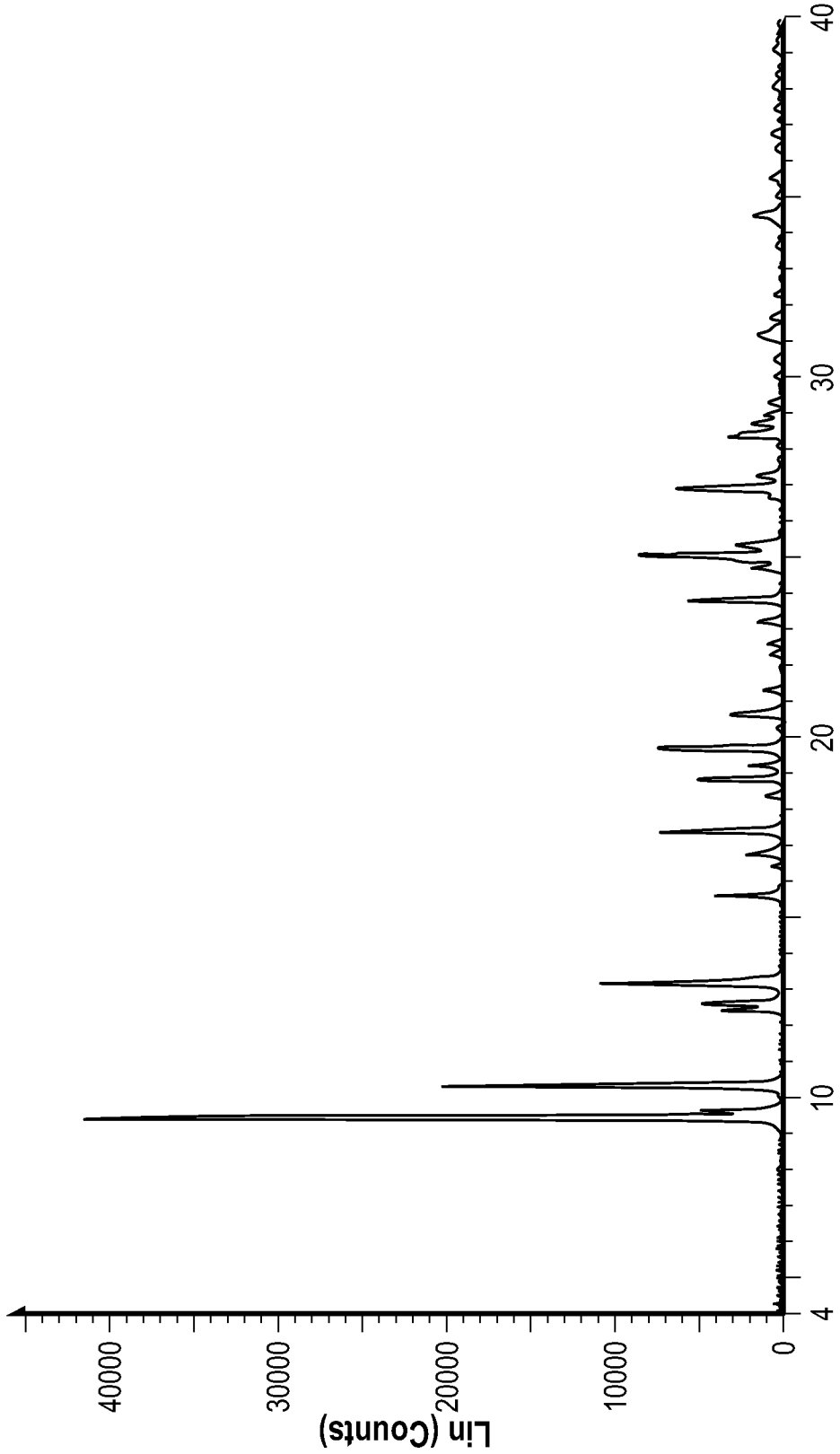

Lin (Counts)
40000
30000
20000
10000
0
4
10
20
30
40
2-Theta - Scale
XRPD pattern of Oxymorphone HCl Form D

FIG. 4

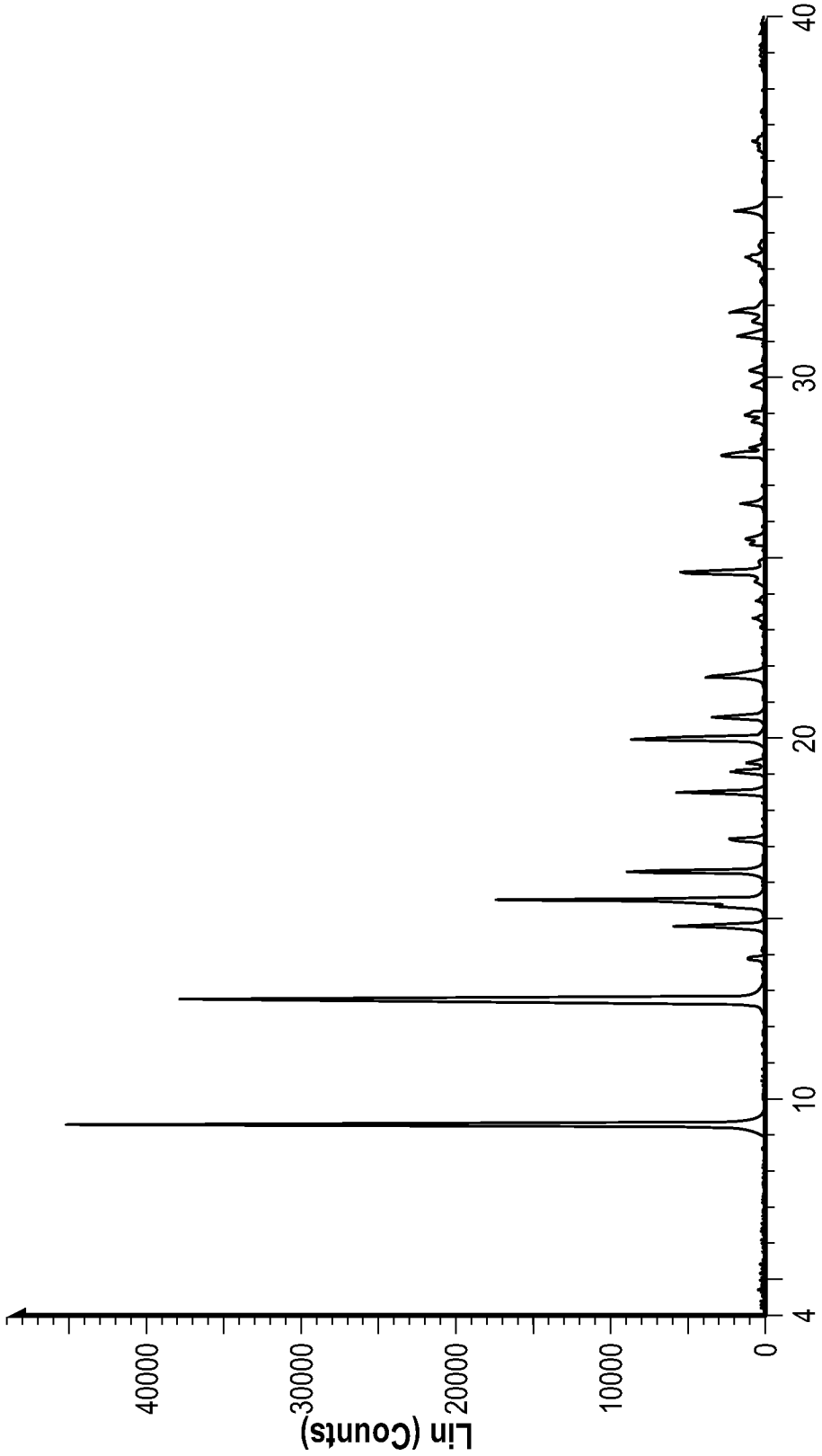

Lin (Counts)
40000
30000
20000
10000
0
4
10
20
30
40
2-Theta - Scale
XRPD pattern of Oxymorphone HCl Form E

FIG. 5

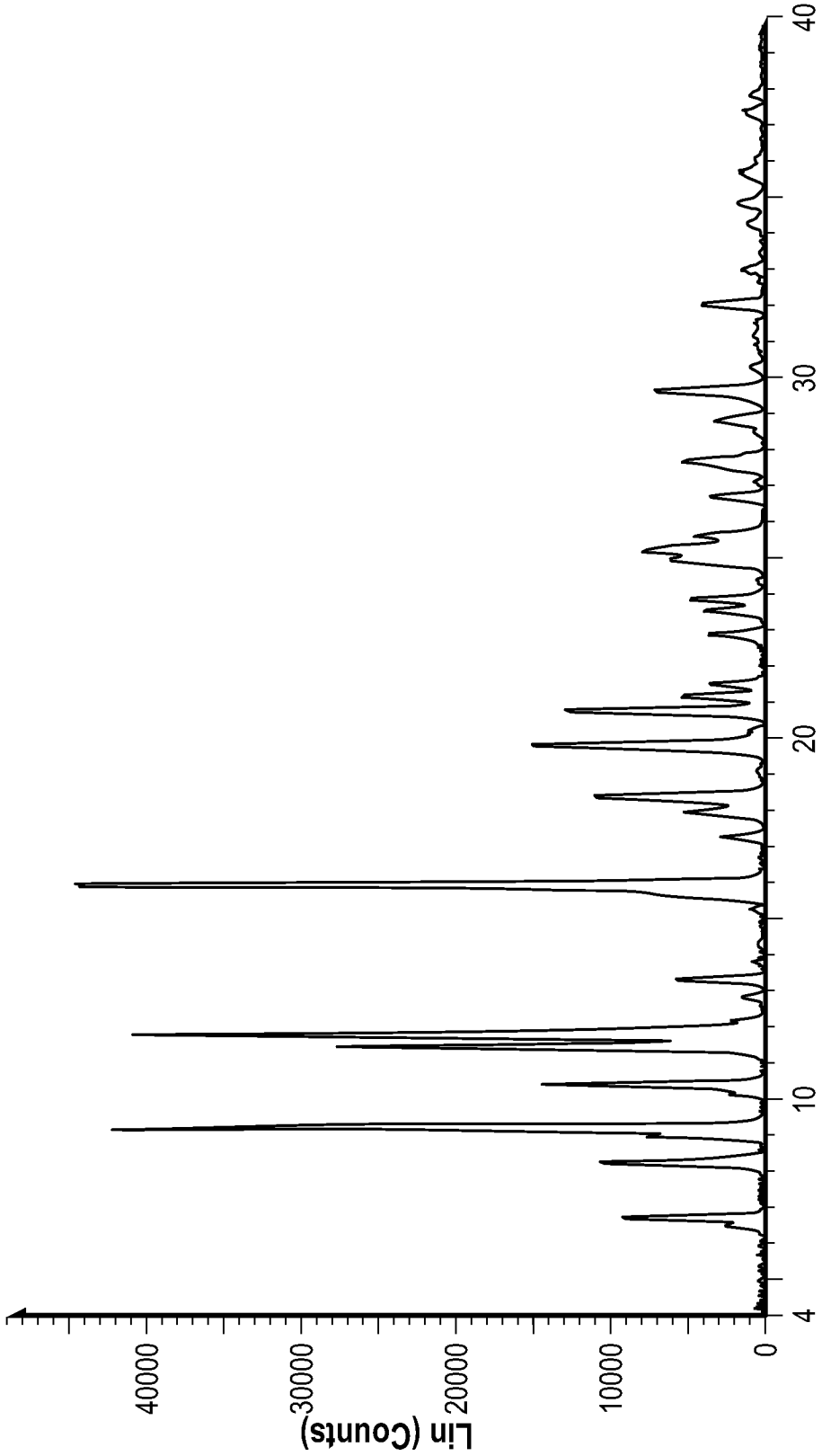
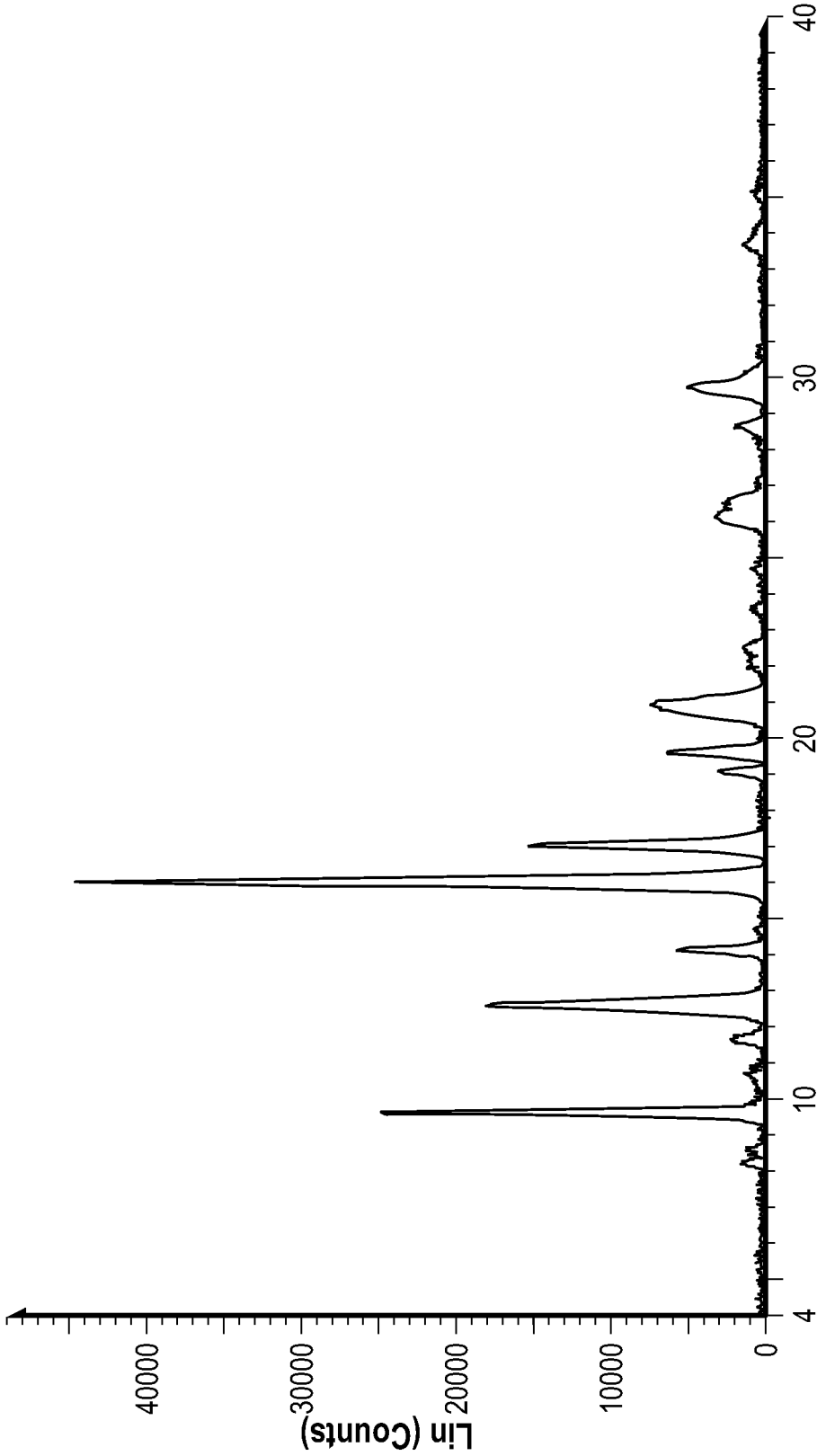

Lin (Counts)
0
10000
20000
30000
40000
4
10
20
30
40
2-Theta - Scale
XRPD pattern of Oxymorphone HCl Form F

FIG. 6



XRPD pattern of Oxymorphone HCl Form G

FIG. 7

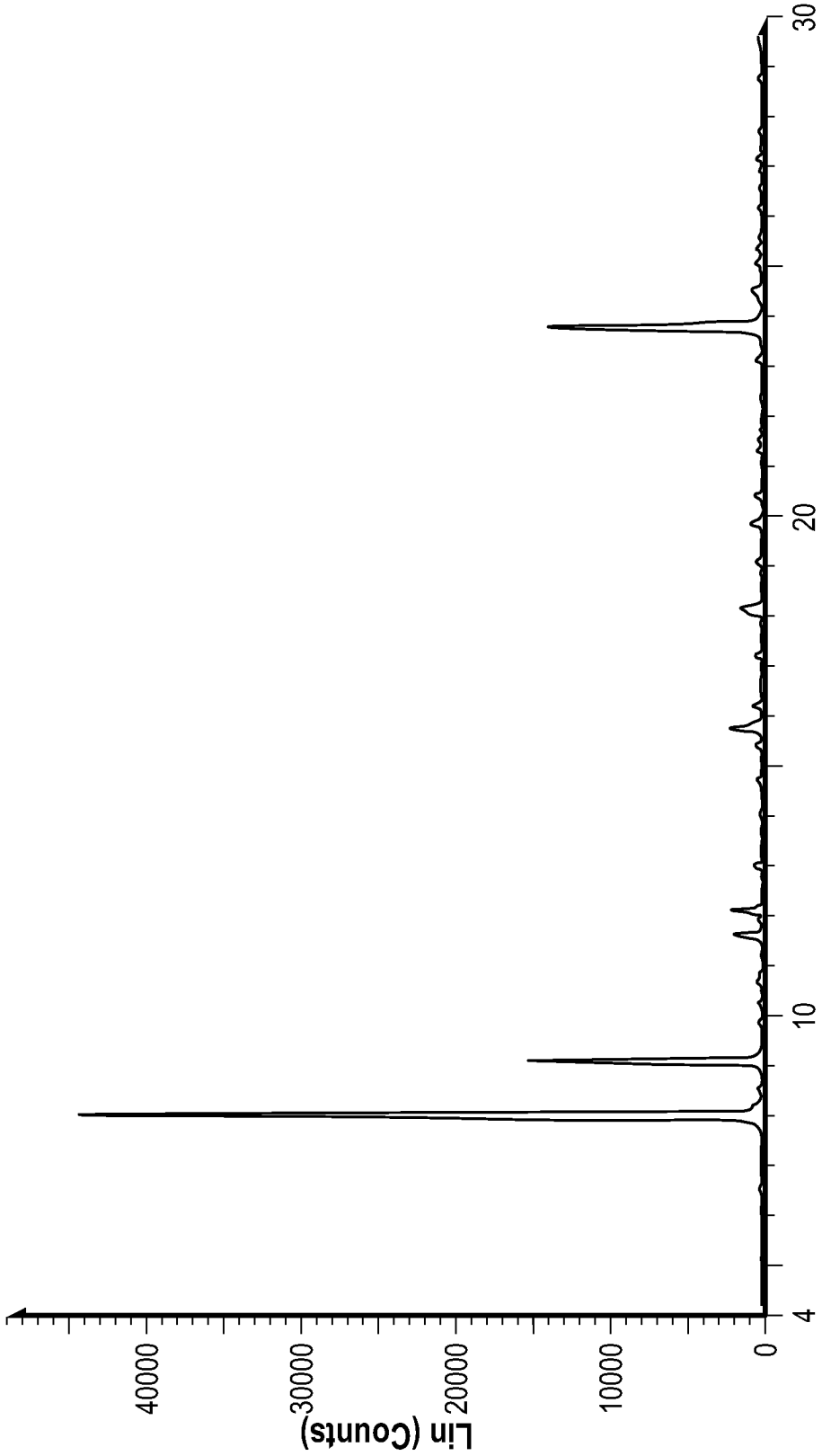
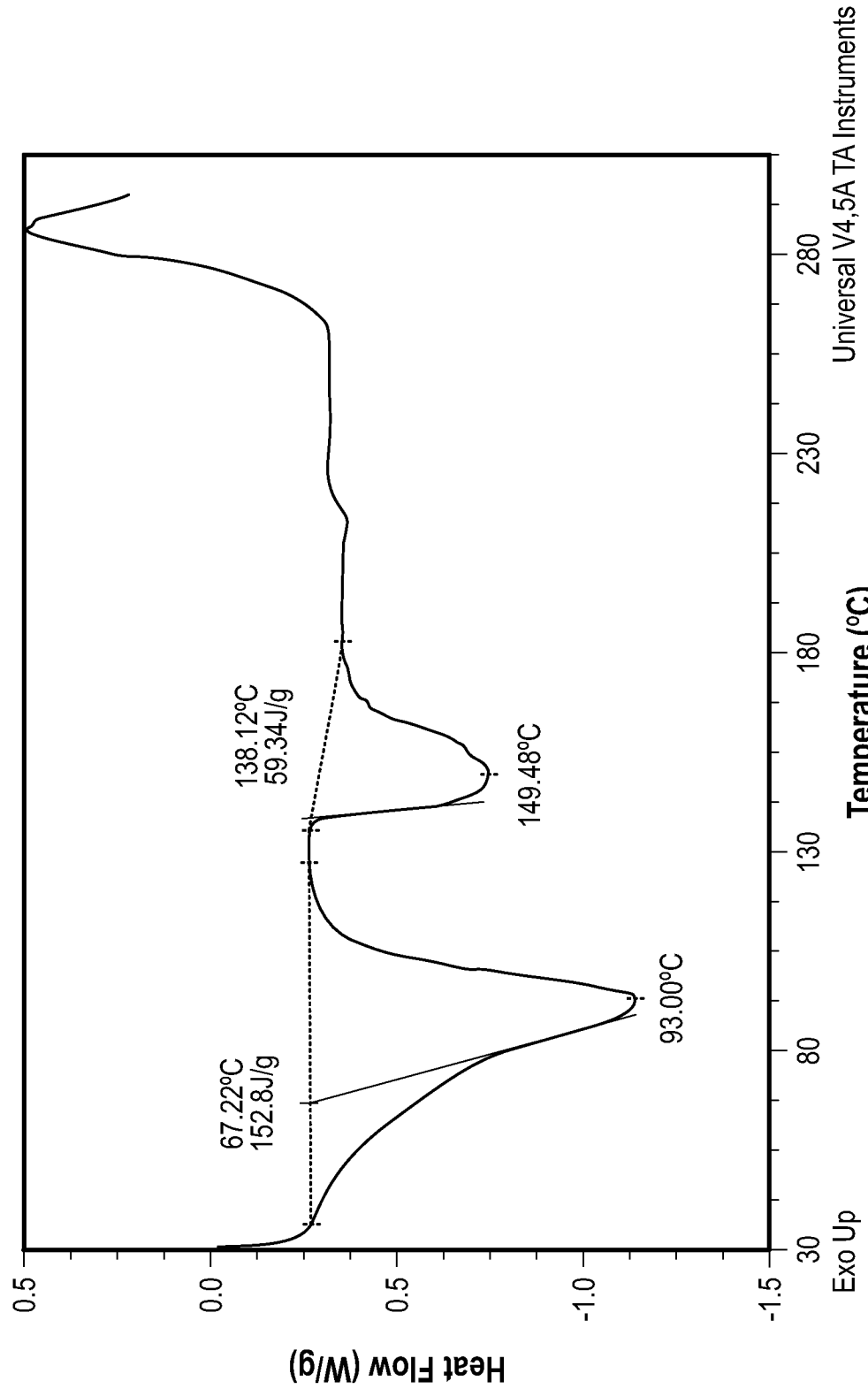

Lin (Counts)
40000
30000
20000
10000
0
4
10
20
30
2-Theta - Scale
XRPD pattern of Oxymorphone HCl Form H

FIG. 8



DSC thermogram of Oxymorphone HCl Form D

FIG. 9

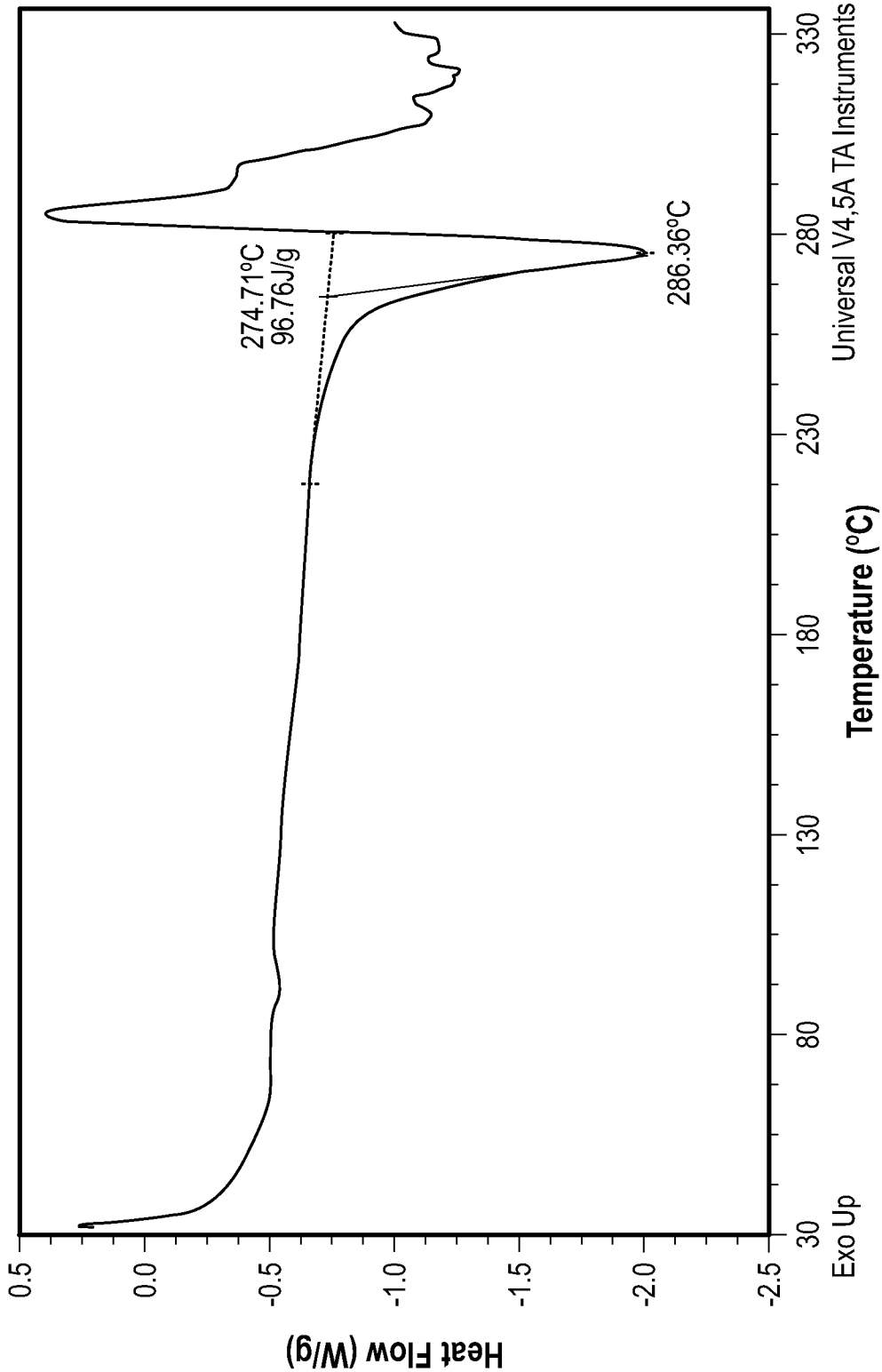
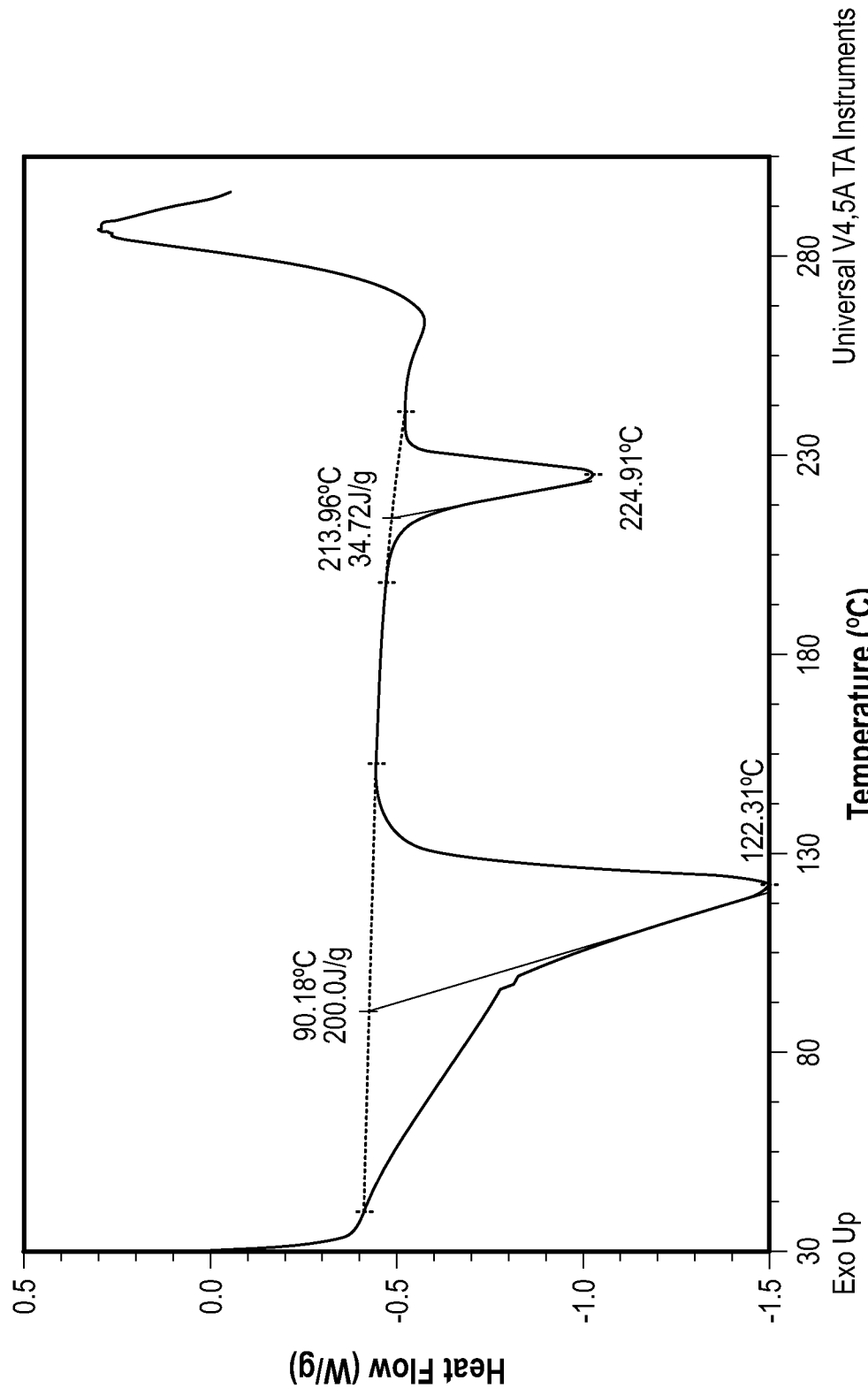

Heat Flow (W/g)
0.5
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
Exo Up
30
80
130
180
230
280
330
Temperature (°C)
Universal V4,5A TA Instruments
274.71°C
96.76J/g
286.36°C
DSC thermogram of Oxymorphone HCl Form E

FIG. 10



DSC thermogram of Oxymorphone HCl Form F

FIG. 11

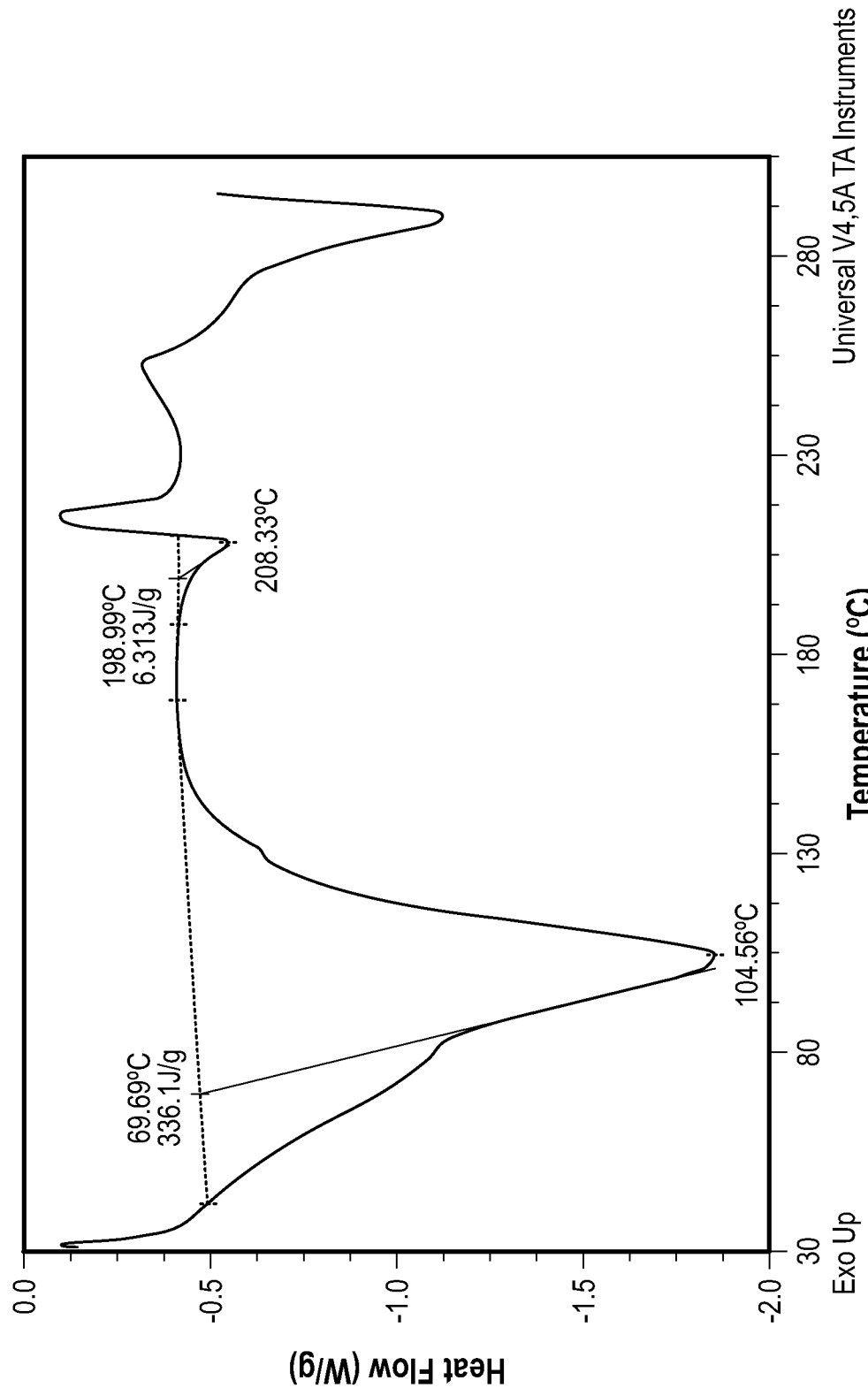

Heat Flow (W/g)
0.0
-0.5
-1.0
-1.5
-2.0
Exo Up
30
80
130
180
230
280
Temperature (°C)
Universal V4,5A TA Instruments
69.69°C
336.1J/g
104.56°C
198.99°C
6.313J/g
208.33°C
DSC thermogram of Oxymorphone HCl Form G

FIG. 12

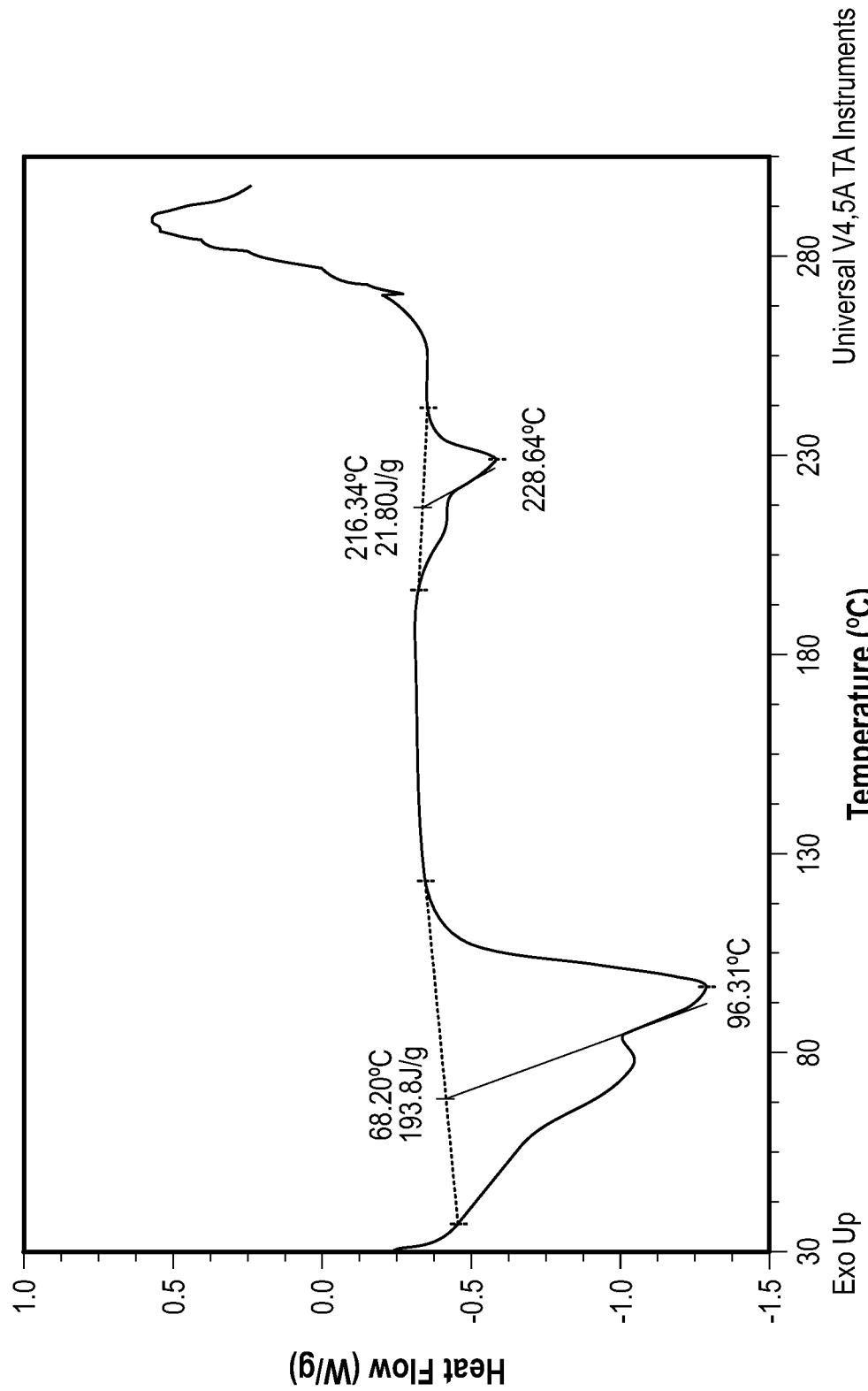
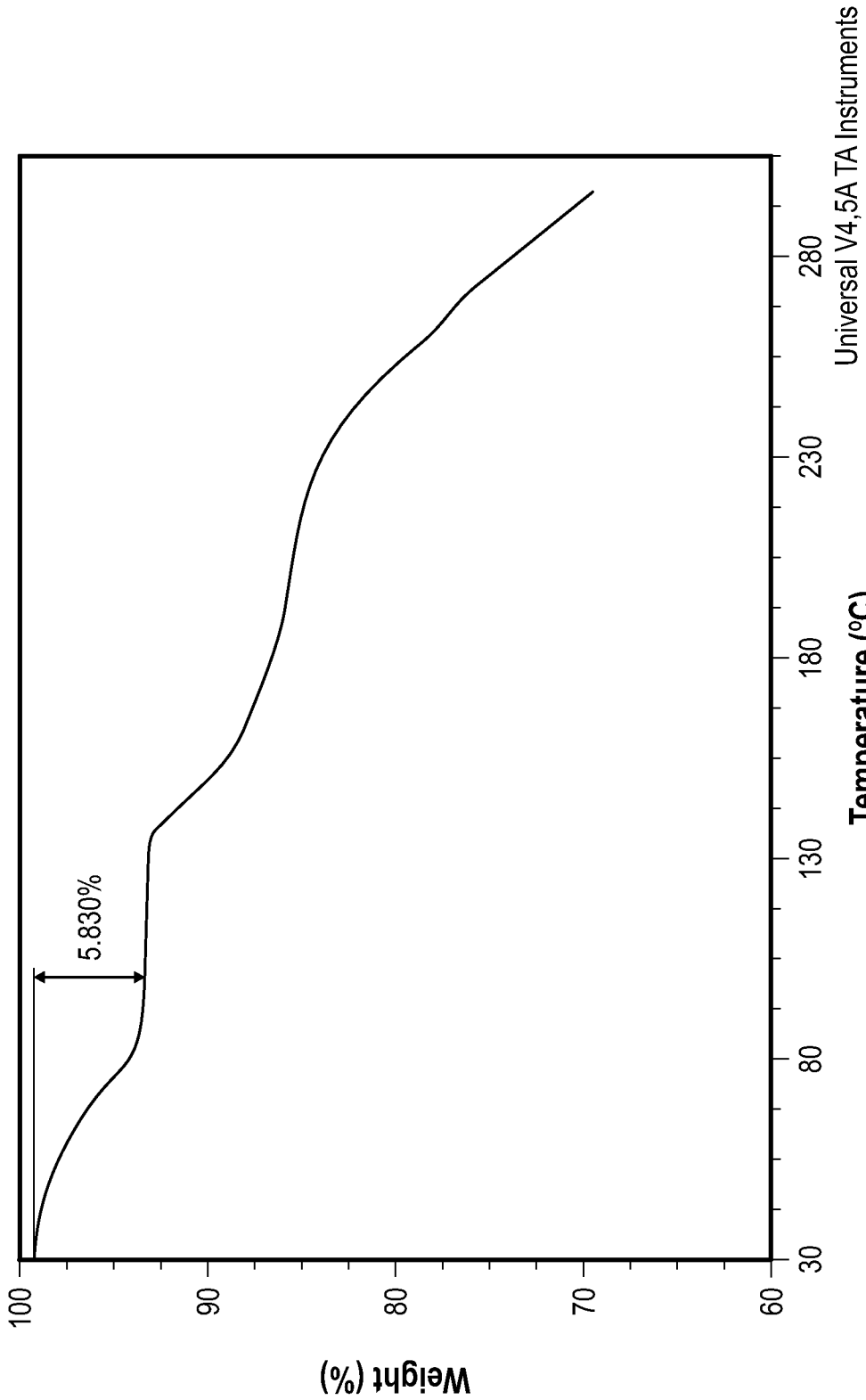
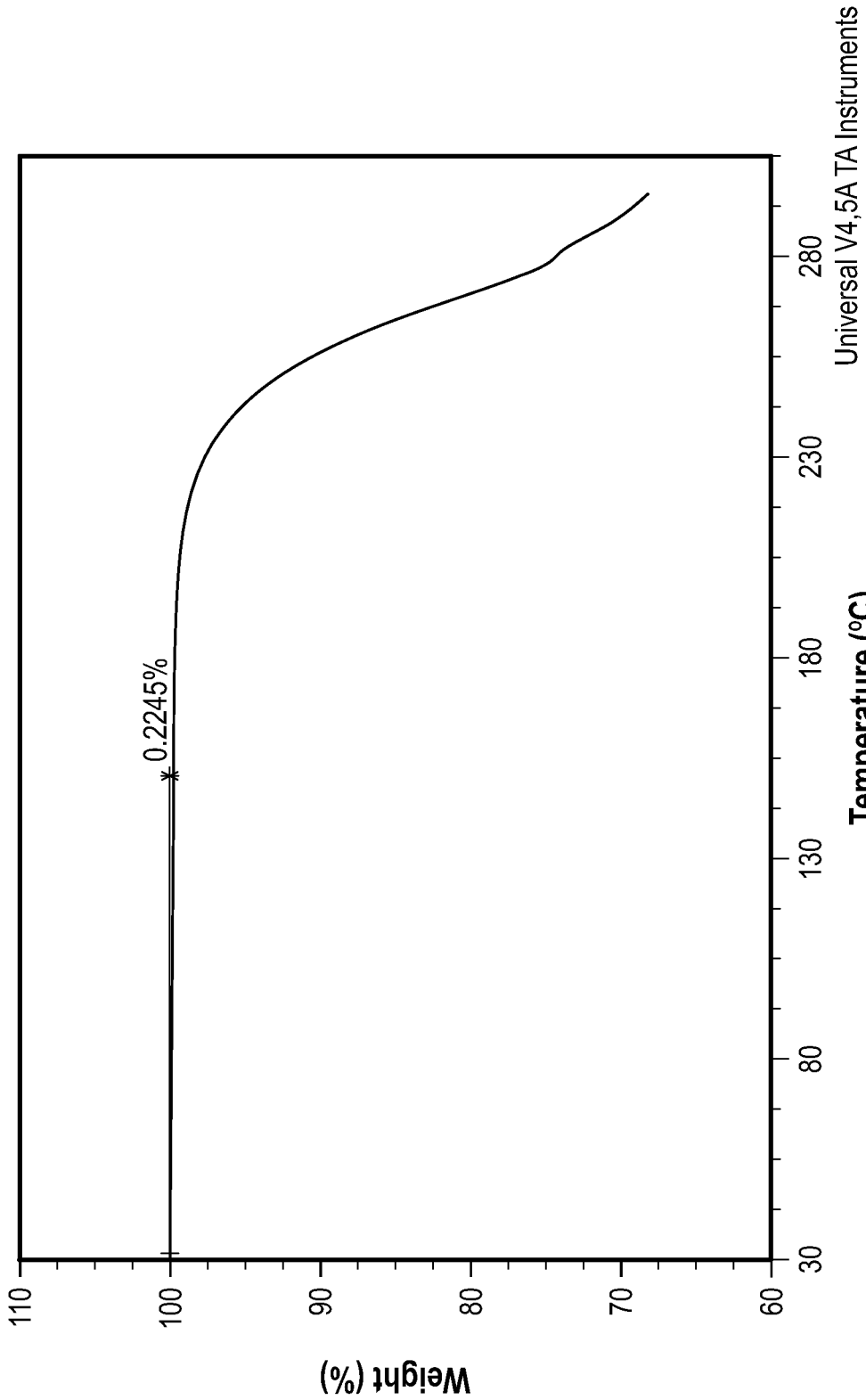

Heat Flow (W/g)
1.0
0.5
0.0
-0.5
-1.0
-1.5
Exo Up
30
80
130
180
230
280
Temperature (°C)
Universal V4.5A TA Instruments
68.20°C
193.8J/g
96.31°C
216.34°C
21.80J/g
228.64°C
DSC thermogram of Oxymorphone HCl Form H

FIG. 13



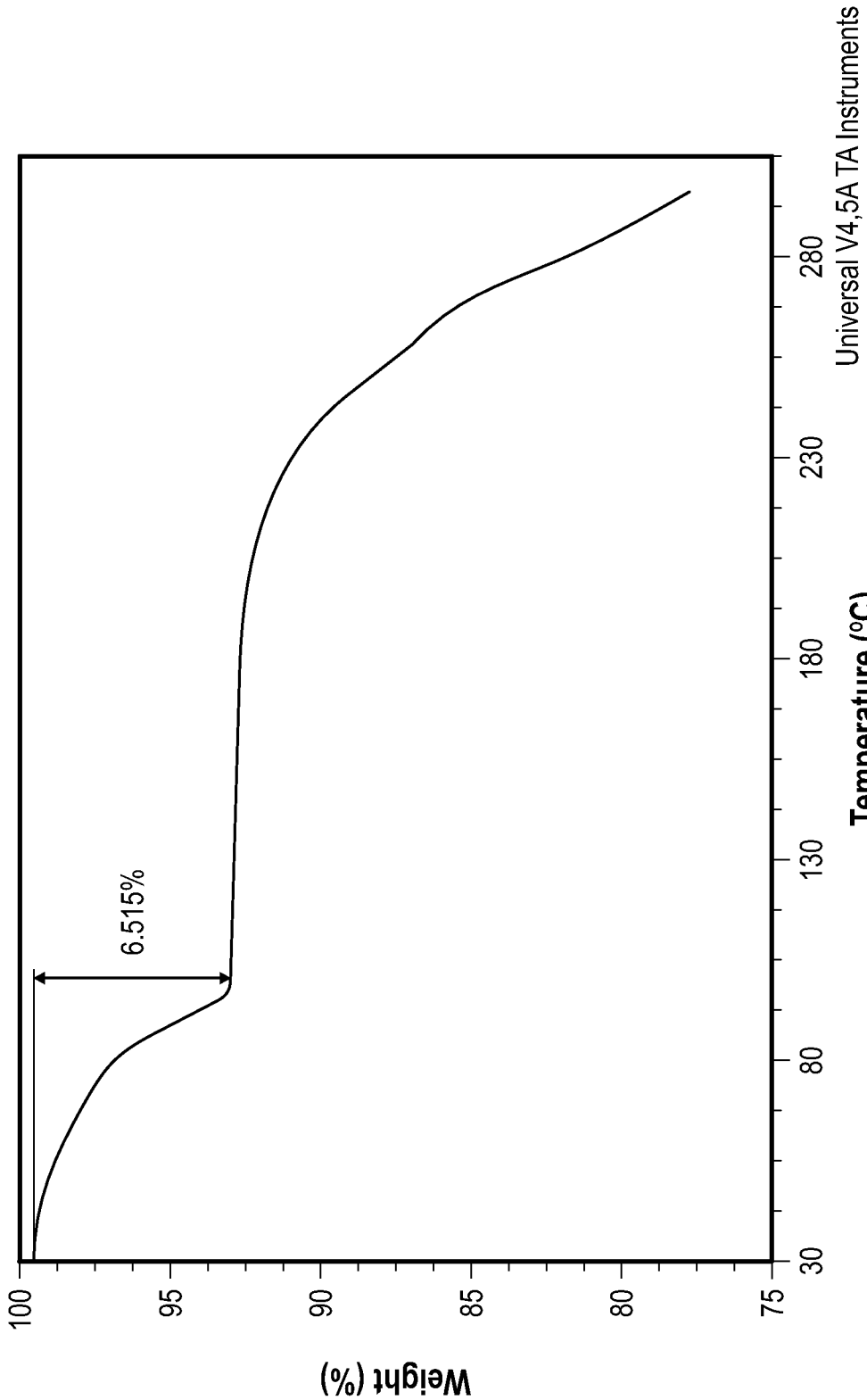
TGA thermogram of Oxymorphone HCl Form D

FIG. 14



TGA thermogram of Oxymorphone HCl Form E

FIG. 15



TGA thermogram of Oxymorphone HCl Form F

FIG. 16

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/021627

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D489/08 A61K31/485 A61P25/04
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 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, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2012/163796 A1 (GRUENENTHAL GMBH [DE]; FISCHER ANDREAS [DE]; PETERS-GROTH DAGMAR [DE];) 6 December 2012 (2012-12-06) the whole document page 4 - page 5; tables 1, 3	1-20
X	US 2012/022093 A1 (GUSHURST KAREN S [US] ET AL) 26 January 2012 (2012-01-26) the whole document tables A1,B1,D1	1-20
X	WO 2008/072018 A1 (JOHNSON MATTHEY PLC [GB]; DUNG JEN-SEN [US]; KESKENY ERNO M [US]; MENC) 19 June 2008 (2008-06-19) the whole document	1-20

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 May 2015	29/05/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Goss, Ilaria

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2015/021627

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2012163796 A1	06-12-2012	CA 2837233 A1	06-12-2012
		EP 2714695 A1	09-04-2014
		US 2014088132 A1	27-03-2014
		WO 2012163796 A1	06-12-2012
US 2012022093 A1	26-01-2012	NONE	
WO 2008072018 A1	19-06-2008	AU 2007331223 A1	19-06-2008
		BR PI0720232 A2	24-12-2013
		CA 2672644 A1	19-06-2008
		CN 101652371 A	17-02-2010
		CN 102391271 A	28-03-2012
		EP 2102213 A1	23-09-2009
		JP 4786748 B2	05-10-2011
		JP 2010513260 A	30-04-2010
		JP 2011201906 A	13-10-2011
		RU 2009126774 A	20-01-2011
		US 2008146601 A1	19-06-2008
		WO 2008072018 A1	19-06-2008
		ZA 200904317 A	25-08-2010