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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
18 September 2014 (18.09.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/143935 A4

(51) International Patent Classification:
A61K 31/55 (2006.01)

(21) International Application Number:
PCT/US2014/028125

(22) International Filing Date:
14 March 2014 (14.03.2014)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/791,726 15 March 2013 (15.03.2013) US

(71) Applicant: **APRECIA PHARMACEUTICALS COMPANY** [US/US]; 2010 Cabot Blvd. West, Suite F, Langhorne, PA 19047 (US).

(72) Inventors: **JACOB, Jules**; 1008 N. Elbow LN, Yardley, PA 19067 (US). **CAPUTO, Kelly**; 610 Atkinson Lane, Langhorne, PA 19047 (US). **GUILLOT, Micael**; 2132 Bustard RD, Lansdale, PA 19446 (US). **SULTZBAUGH, Kenneth, J.**; 1341 Tilton RD, Bridgewater, NJ 08807 (US). **WEST, Thomas, G.**; 13135 East Run Dr., Lawrenceville, NJ 08648 (US).

(74) Agent: **MATOS, Rick**; Innovar, L.L.C., P.O. Box 250647, Plano, TX 75025-0647 (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, LT, 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, 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))*

— *with amended claims and statement (Art. 19(1))*

Date of publication of the amended claims and statement: 20 November 2014

WO 2014/143935 A4

(54) Title: RAPIDLY DISPERSIBLE DOSAGE FORM OF OXCARBAZEPINE

(57) Abstract: A high dose orodispersible dosage form of oxcarbazepine is provided. Drug-containing particles of oxcarbazepine are included within a porous bound matrix. The dosage form disperses in saliva or water in less than 15 sec and it has sufficient hardness to withstand handling and storage. It can be used to treat diseases or disorders that are therapeutically responsive to oxcarbazepine or a derivative thereof.

AMENDED CLAIMS

received by the International Bureau on 25 September 2014 (25.09.2014)

1) A rapidly dispersible solid dosage form comprising a porous non-compressed three-dimensionally printed bound matrix comprising :

drug-containing particles having an effective particle size and comprising a first grade of oxcarbazepine (OXC) particles having a first native particle size, a second grade of OXC particles having a second native particle size, at least one disintegrant, at least one surfactant, and at least one binder;

at least one disintegrant; and

at least one binder; wherein

the dosage form disperses in 15 sec or less when placed in 15 ml of aqueous fluid; and

the ratio of effective particle size to first native particle size is >1:1 to 5:1, and the ratio of effective particle size to second native particle size is 20:1 to 50:1.

2) A rapidly dispersible three-dimensionally printed porous non-compressed bound matrix comprising:

a first grade of OXC particles having a first native particle size, a second grade of OXC particles having a second native particle size, at least one sweetener, at least one binder, at least one disintegrant, at least one surfactant, and at least one glidant; wherein .

the matrix comprises particles bound by binder;

the matrix disperses in less than 15 sec in a volume of 15 ml of aqueous fluid;

the OXC particles are included in drug-containing particles having an effective particle size and comprising the OXC particles and at least one pharmaceutical excipient as carrier;

the content of OXC in the matrix ranges from 35-60 % wt based upon the total weight of the matrix; and

the ratio of effective particle size to first native particle size is >1:1 to 5:1, and the ratio of effective particle size to second native particle size is 20:1 to 50:1.

3) The invention according to any one of the above claims, wherein: a) OXC particles possess a bi-modal or multi-modal particle size distribution; b) the drug-

containing particles possess a mono-modal, bi-modal or multi-modal particle size distribution; or c) a combination of one or more of the above.

4) The invention according to claim 1 or 2, wherein: a) the at least one surfactant is present in an amount ranging from 0.5- 7.0% wt based upon the final weight of the dosage form; b) the at least one sweetener is present in an amount ranging from 0.01-2.0% based upon the final weight of the dosage form; c) the at least one binder is present in an amount ranging from 5-15% based upon the final weight of the dosage form; d) the at least one disintegrant is present in an amount ranging from 10-30% based upon the final weight of the dosage form; and/or e) the at least one glidant is present in an amount ranging from 0-2% based upon the final weight of the dosage form.

5) The invention according to claim 1 or 2, wherein: a) the hardness of the matrix ranges from about 1 to about 7 kiloponds (kp), about 1 to about 3 kp; b) the matrix disperses in 10 sec or less when placed in 15 ml of water or in saliva; c) binder is introduced into the matrix by way of printing fluid used to form the matrix; d) binder is introduced into the matrix by way of bulk powder used to form the matrix; e) the matrix comprises about 150 mg to about 600 mg of OXC; and/or f) the matrix comprises 10 to 40 three-dimensionally printed incremental layers.

6) The invention according to claim 1 or 2, wherein the drug-containing particles further comprise sweetener and/or flavorant.

7) The invention according to claim 1 or 2, wherein: a) the content of drug-containing particles in the matrix generally ranges from 55-85% wt, 60-80% wt or 65-70% wt based upon the total weight of matrix in the final dosage form; b) the content of native particles of OXC in the drug-containing particles ranges from 55-85% wt, 60-80% wt or 65-70% wt, based upon the final weight of the drug-containing particles; c) the content of disintegrant in the drug-containing particles ranges from 0-30%, 1-15%, or 2-5 % wt, based upon the final weight of the drug-containing particles; d) the content of binder in the drug-containing particles ranges from 0-10%, 1-7%, or 2-5% wt, based upon the final weight of the drug-containing particles; e) the content of surfactant in the drug-containing particles ranges from 0-10%, 1-5%, or 1.4-4.2 % wt, based upon the final

weight of the drug-containing particles; and/or f) the drug-containing particles are manufactured by wet granulation.

8) The invention according to claim 1 or 2, wherein the matrix comprises about 150 to about 1200 mg, about 150 mg, about 300 mg, about 450 mg, about 600 mg, about 750 mg, about 900 mg, about 1050 mg or about 1200 of OXC.

9) The invention according to claim 1 or 2, wherein the dosage form has been prepared by a three-dimensional printing process employing printing fluid, drug-containing particles and bulk powder of the following compositions:

Printing fluid

Water (% wt)	80-95 or	80-90
Glycerin (% wt)	0.5-20 or	2-7
Alcohol (% wt)	0.1-20 or	1-10
Surfactant (% wt)	0.01-10 or	1-5
Sweetener (% wt)	0-10 or	1-5
Binder (% wt)	0-10	

OXC Drug-containing particles:

OXC (% wt)	55-75 or	60-70
Disintegrant (% wt)	15-45 or	30-40
Binder (% wt)	0-10 or	2-5
Surfactant (% wt)	0-10 or	1-5

Bulk powder:

OXC containing particles (% wt)	55-65 or	55-65
Disintegrant (% wt)	2-15 or	3-12
Binder (% wt)	20-45 or	20-35
Glidant (%wt)	0.1-1.5 or	0.2-0.7.

10) The invention according to claim 1 or 2, wherein the dosage form has the following composition:

Oxcarbazepine (% wt)	30-40	35-45
Disintegrant (% wt)	15-30	15-25
Binder (% wt)	30-55	30-50
Glidant (% wt)	0-5	>0-5
Glycerin (% wt)	>0-20	>0-5
Surfactant (% wt)	0-5	>0-5
Sweetener (% wt)	0-5	>0-5

11) The invention according to claim 1, wherein the dosage form is shaped as a wafer, cylinder, ring, donut, tube, cube, spheroid, ellipsoid or rectangular box.

12) The invention according to claim 1 or 2, wherein: a) the binder is selected from the group consisting of polyvinylpyrrolidone (povidone), mannitol, hydroxypropylcellulose, and a combination thereof; b) the disintegrant is selected from the group consisting of microcrystalline cellulose, a combination of two grades of microcrystalline celluse, croscarmellose, and a combination thereof; or b) a combination of the above.

13) A method of treating a disease, condition or disorder that is therapeutically responsive to oxcarbazepine comprising administering the dosage form of claim 1 or the matrix of claim 2 one to three times daily to a subject in need thereof throughout a treatment period.

14) The invention according to claim 5, wherein the thickness (height) of an incremental layer ranges from 0.006 to 0.014 inches or 0.008 to 0.012 inches.

15) A rapidly dispersible solid matrix comprising a porous three-dimensionally printed bound matrix comprising:

drug-containing particles comprising at least one disintegrant, at least one binder, at least one surfactant and native particles of drug, wherein the drug-containing particles have an effective particle size and the native particles of drug have a native

particle size, and the ratio of effective particle size to native particle size of >1:1 to 200:1;

at least one disintegrant; and

at least one binder;

wherein the hardness of the matrix ranges from about 1 to about 7 kiloponds.

16) The matrix of claim 15, wherein the matrix disperses in 15 sec or less when placed in 15 ml of aqueous fluid.

17) The matrix of claim 15, wherein the average native particle size is such that 90%-100% of the drug is <10 microns, and the ratio of effective particle size to native particle size is in the range of 10:1 to 200:1.

18) The matrix of claim 15, wherein the average native particle size is such that not more than 20% of the drug is <32 microns, 40-70% of the drug is <63 microns, 70-95% of the drug is <125 microns, and 100% of the drug is <250 microns, and the ratio of effective particle size to native particle size is in the range of >1:1 to about 10:1.

19) The matrix of claim 15, wherein the native particles of drug have an average, mean or median native particle size in the range of about 1 to about 90 microns, about 1 to about 75 microns, about 1 to about 50 microns, about 1 to about 30 microns, about 1 to about 15 microns, about 1 to about 10 microns, about 2 to about 14 microns, about 10 to about 80 microns, about 20 to about 70 microns, about 20 to about 60 microns or about 30 to about 50 microns.

20) The matrix of claim 17, 18 or 19, wherein the drug-containing particles have an average, mean or median effective particle size in the range of about 50 to about 400 microns, about 50 to about 300 microns, about 50 to about 250 microns, about 60 to about 250 microns, about 60 to about 100 microns, or about 75 to about 250 microns.

21) The matrix of claim 15, 16, 17, 18 or 19, wherein the drug is poorly water soluble.

22) The matrix of claim 21, wherein the drug is OXC.

STATEMENT UNDER ARTICLE 19 (1)

Claims now require non-compressed matrix comprising two different grades of OXC differing in particle size and further specify ranges for effective particle size and native drug particle size as well as for ratio thereof.

Examiner argues Sehgal discloses a rapidly dispersible dosage form containing oxcarbazepine and dissolving in <2 minutes. Examiner acknowledges Sehgal fails to suggest a 3DP dosage form exhibiting a dispersion time of 15 sec or less and relies upon Yoo as disclosing rapidly dispersible dosage forms exhibiting a dispersion time of 15 sec or less. Examiner relies upon Blau as disclosing formulations containing 35-60% of oxcarbazepine.

Neither Sehgal, Yoo nor Blau discloses use of two different grades of drug particles having different native particle sizes. None of the references discloses need to balance effective particle size and native drug particle size during 3DP.

Sehgal and Blau illustrate wide range of results when different drug particle sizes and granulation approaches are used with tabletting. All achieve much slow disintegration times.

Sehgal (D1) only discloses a compressed dosage form and focuses on use of wetting agent to overcome the need for small particle size oxcarbazepine. ([0003], [0011], [0020]). Sehgal strongly suggests use of larger particles of oxcarbazepine (median particle size: 20-50 microns) in order to obtain "best results". Examples 1-4 ([0040]-[0048]) employ oxcarbazepine with median particle size of about 26 microns. Sehgal only suggests granulated particles and only achieves a "disintegration time in water ≤2 minutes."

Yoo's (D2) 3DP non-compressed matrices have a dispersion time of 15 sec or less; however, Yoo does not recognize the importance of balancing particle size of native drug versus that of drug-containing particles. Yoo does not contemplate granulation of small drug particles into larger drug-containing particles in order overcome problems caused by small drug particles during 3DP process. Yoo only achieves ≤15 sec disintegration time using ungranulated drug particles.

Blau (D3) discloses formulations containing granulated OXC having at least two different particle size populations. The granulated particles are used in compressed tablets and have a disintegration time of ≤30 min. ([0025])

Proper combination of Sehgal, Yoo and Blau suggests that granulation of drug causes a slower rather than faster disintegration time. There is no suggestion or enablement *a priori* that one can achieve dispersion in <15 sec in a 3DP matrix containing granulated particles comprising OXC particles of two different sizes. There is no certainty that a satisfactory dosage form, e.g. with suitable hardness and/or surface features, could even be produced by 3DP.

The instant specification discloses the "effective particle size" of OXC in the bulk powder must be increased without increasing the "actual particle size" of the drug ([0013]) for the purpose of facilitating three-dimensional printing of acceptable dosage forms while keeping the actual drug particle size small to facilitate drug absorption. ([0023], [0024], [004]).

Claimed invention provides preferred ranges for effective particle size and native drug particle size and for ratio thereof and requires combination of two different grades of OXC differing in particle size.

Respectfully submitted,