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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
8 February 2007 (08.02.2007)

PCT

(10) International Publication Number
WO 2007/015270 A2

(51) International Patent Classification:
A61K 9/14 (2006.01) *A61K 47/48* (2006.01)
A61K 9/20 (2006.01) *A61K 31/343* (2006.01)

(21) International Application Number:
PCT/IN2006/000274

(22) International Filing Date: 1 August 2006 (01.08.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
696/KOL/2005 2 August 2005 (02.08.2005) IN

(71) Applicant *(for all designated States except US)*: **LUPIN LIMITED** [IN/IN]; 159, Cst Road, Kalina, Santacruz (east),, Mumbai-400 098 ,, Maharashtra (IN).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **VELHAL, Avinash, K.** [IN/IN]; Lupin Ltd. (Research Park), 46A/47A, Nande Village,, Taluka Mulshi, Pune 411 042, Maharashtra (IN). **RAGHAVAN, Vineeth** [IN/IN]; Lupin Ltd. (Research Park), 46A/47A, Nande Village,, Taluka Mulshi, Pune 411 042, Maharashtra (IN). **JAYANTHI, Suryakumar** [IN/IN]; Lupin Ltd. (Research Park), 46A/47A, Nande Village,, Taluka Mulshi, Pune 411 042, Maharashtra (IN). **SEN, Himadri** [IN/IN]; Lupin Ltd. (Research Park), 46A/47A, Nande Village,, Taluka Mulshi, Pune 411 042, Maharashtra (IN).

(74) Agents: **MAJUMDAR, Subhash** et al.; S. Majumdar & Co., Harish Mukherjee Road, Kolkata 700 025 (IN).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, 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, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) **Title:** NOVEL CONTROLLED RELEASE COMPOSITIONS OF SELECTIVE SEROTONIN REUPTAKE INHIBITORS

(57) **Abstract:** A controlled release pharmaceutical composition of a selective serotonin reuptake inhibitor. The composition essentially comprises of a core comprising the active ingredient, one or more controlled release polymer(s) and one or more pharmaceutically acceptable excipients. The composition optionally will have a coating comprising one or more controlled release polymers. The composition is prepared by mixing the active ingredient with one or more controlled release polymers and one or more pharmaceutically acceptable excipients. Thereafter the mixture is granulated, dried, lubricated and compressed into tablets. The composition is used in the manufacture of a medicament, for treating and/or preventing the disorders. The active is released between about 2-8 hours with about 10-25% of active is released in vitro in 2 hours in 0.1N HCl, 750 ml dissolution medium using USP Dissolution tester, paddle method at 150 rpm. About 20-55%, 50-75% and 70-95% of active is released in vitro in 4,6 and 8 hours respectively in pH 7.5 Tris buffer, 1000 ml dissolution medium using USP Dissolution tester, paddle method at 150 rpm.

WO 2007/015270 A2

NOVEL CONTROLLED RELEASE COMPOSITIONS OF SELECTIVE SEROTONIN REUPTAKE INHIBITORS

Field of the Invention

The present invention relates to a novel controlled release composition comprising a selective serotonin reuptake inhibitor or a pharmaceutically acceptable salt thereof.

Background of the Invention

Paroxetine, disclosed in U.S. Pat. No. 4,007,196 is a selective serotonin reuptake inhibitor (SSRI) and is currently marketed worldwide for the treatment and/or prophylaxis of depression. Paroxetine is used in the form of the crystalline hemihydrate as disclosed in U.S. Pat. No. 4,721,723.

By controlled release, it is meant that the release of the active substance from the dosage form is modified to occur at a slower rate than that from the immediate release product, such as a conventional swallow tablet or capsule.

U.S. Pat. Nos. US 4,839,177 relates to a system for the controlled release of active substances, consisting of: (a) a deposit core comprising effective amount of the active substances and having defined geometric form, (b) a support-platform applied to said deposit core wherein the said deposit core contains, mixed with the active substance, at least one member selected from the group consisting of (a) 5-80% by weight of the total weight of the deposit core of a polymeric material having a high degree of swelling on contact with water or aqueous liquids and 90-10% by weight of the total weight of the deposit core of a gellable polymeric material, and (b) a single polymeric material having both swelling and gelling properties and other adjuvants able to provide the mixture with suitable characteristics for compression and for intake of water, and wherein said support platform consists of polymeric material insoluble in aqueous liquids and partially coating said deposit core.

U.S. Pat. No. 5,422,123 discloses a system for controlled release comprising of a deposit-core comprising an effective amount of the active substance and having defined geometric form, and a support-platform applied to said deposit-core, wherein said deposit-core contains at least the active substance, and at least one member selected from

the group consisting of (1) a polymeric material which swells on contact with water or aqueous liquids and a gellable polymeric material wherein the ratio of the said swellable polymeric material to said gellable polymeric material is in the range 1:9 to 9:1, and (2) a single polymeric material having both swelling and gelling properties, and wherein the support-platform is an elastic support, applied to said deposit-core so that it partially covers the surface of the deposit-core and follows changes due to hydration of the deposit-core and is slowly soluble and/or slowly gellable in aqueous fluids. The support-platform may comprise polymers such as hydroxypropylmethylcellulose, plasticizers such as a glyceride, binders such as polyvinylpyrrolidone, hydrophilic agents such as lactose and silica, and/or hydrophobic agents such as magnesium stearate and glycerides. The polymer(s) typically make up 30 to 90% by weight of the support-platform, for example about 35 to 40%. Plasticizer may make up at least 2% by weight of the support-platform, for example about 15 to 20%. Binder(s), hydrophilic agent(s) and hydrophobic agent(s) typically total up to about 50% by weight of the support-platform, for example about 40 to 50%.

U.S. Pat. No. 6,482,440 relates to pharmaceutically active materials comprising specific antidepressant compounds contained in microparticles formulated so as to release the antidepressant compounds over an extended period of time.

PCT Appl. No. WO 2005/034954 relates to stable pharmaceutical compositions of paroxetine comprising the drug, microcrystalline cellulose, at least one modified release polymer and one or more additional pharmaceutical inert excipients, wherein the composition is prepared by wet granulation. Compressed tablets are further coated with enteric polymers and further with nonfunctional film coating polymers.

U.S. Pat. Appl. No. 2002/0090394 discloses a controlled and delayed release formulation containing a selective serotonin reuptake inhibitor such as paroxetine. Release of the drug is delayed by pH sensitive coat using hydroxypropylmethylcellulose phthalate, cellulose acetate phthalate, and Eudragit etc. followed by controlled release. This results in reducing the incidence of nausea and vomiting associated with the administration of paroxetine by releasing the drug predominantly in the small intestine.

This patent application describes a novel controlled release formulation of a selective serotonin reuptake inhibitor or a pharmaceutically acceptable salt thereof comprising a controlled release matrix formulation.

Object of the Invention

The present invention provides a novel controlled release composition comprising a SSRI or a pharmaceutically acceptable salt thereof.

Further, the present invention provides the use for treating and/or preventing the disorders by administering an effective and/or a prophylactic amount of novel controlled release composition comprising SSRI or a pharmaceutically acceptable salt thereof, to an individual in need thereof.

Summary of the Invention

The present invention describes novel controlled release compositions of SSRI or a pharmaceutically acceptable salts thereof comprising:

a) a core comprising the active ingredient; one or more controlled release polymer(s) and pharmaceutically acceptable excipients; and optionally
b) a coating comprising one or more controlled release polymer(s).

Further, the present invention discloses the use of novel controlled release composition comprising SSRI or a pharmaceutically acceptable salt thereof for treating and/or preventing the disorders.

Detailed Description of Invention

The present invention provides a novel controlled release composition of SSRI or a pharmaceutically acceptable salts thereof.

Selective serotonin reuptake inhibitors (SSRI) include sertraline, fluoxetine, fluvoxamine, citalopram, escitalopram and paroxetine.

SSRI used in the present invention is suitably in the form of the free base or a pharmaceutically acceptable salt thereof. Paroxetine is used preferably in the form of the hydrochloride hemihydrate.

SSRI in the form of a controlled release composition can be used to treat and prevent the following disorders: Alcoholism, Anxiety, Depression, Obsessive Compulsive Disorder, Panic Disorder, Chronic Pain, Obesity, Senile Dementia, Migraine, Bulimia, Anorexia, Social Phobia, Pre-Menstrual Syndrome (PMS), Adolescent Depression, Trichotillomania, Dysthymia, Substance Abuse.

These disorders are herein after referred to as "the disorders".

The preparation comprises:

a) a core comprising the active ingredient; one or more controlled release polymer(s) and pharmaceutically acceptable excipients; and optionally

b) a coating comprising one or more controlled release polymer(s).

Controlled release polymers used in the core and coating of this composition include one or more of cellulose derivatives, alginic acids derivatives, polymethacrylates, polysaccharides, alkylene oxides, hydrogenated vegetable oil and the like. Specific examples of cellulose derivatives include hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose (HPMC), methylcellulose, carboxy methylcellulose, ethyl cellulose and hydroxy ethyl cellulose. Alginic acid derivatives as used herein include alginic acid and its physiologically acceptable salts such as those of sodium, potassium, calcium, and the like. Examples of polymethacrylates are various types of methacrylic acid derivatives and copolymers thereof such as various grades available under the trade name of Eudragit®. Examples of polysaccharides include chitosan, gellan, xanthan gum and the like. Examples of alkylene oxide include polyethylene oxide. Controlled release polymers used in the core may range from about 10-50% w/w in the core and from about 1-15% w/w in the coating.

HPMC is cellulose ether, and is widely used as controlled release polymer. It is commercially available as Methocel® in various grades. Examples of HPMC of low viscosity grades include Methocel E-5 LV, Methocel E-15 LV, Methocel E-50 LV, Methocel K-100 LV CR Premium and Methocel F-50 LV. Examples of HPMC of medium viscosity grade include Methocel E4M, Methocel K4MCR, Methocel K15M Premium, Methocel K100 M Premium and Methocel F4M.

Eudragit L-30 D-55 is a 30% aqueous dispersion soluble in intestinal fluids from pH 5.5.

Pharmaceutically acceptable excipients comprise diluents, disintegrants, binders and lubricants.

Diluents referred to in the present invention include one or more selected from mannitol, dextrose, xylitol, sorbitol, sucrose, microcrystalline cellulose, calcium carbonate, calcium phosphate dibasic, calcium phosphate tribasic, calcium sulfate, lactose, starches, vinyl polymers and the like known to a person skilled in the art.

Disintegrants referred to in the present invention include one ore more of microcrystalline cellulose, croscarmellose sodium, crospovidone, carboxymethyl starch sodium, sodium starch glycolate, and the like.

Binders referred to in the present invention include one or more selected from those well known in the art to a person skilled in the art, as exemplified can be celluloses such as hydroxypropyl cellulose, hydroxy ethyl cellulose, ethyl cellulose, hydroxypropyl methyl cellulose, methyl cellulose or mixtures thereof, acrylates, methacrylates, povidone and other materials known to have cohesive and desirable binding properties.

Lubricants referred to in the present invention include one or more selected from those well known in the art, as exemplified can be stearates, hydrogenated vegetable oil, sodium stearyl fumarate, talc, colloidal silicon dioxide, palmitic acid, carnauba wax,

glyceryl monostearate, microcrystalline wax, polyoxyethylene monostearates, fats and stearic acid or mixtures thereof.

Novel controlled release pharmaceutical compositions comprising core may be prepared by wet granulation method using purified water. The selective serotonin reuptake inhibitor is mixed with one or more controlled release polymer(s) and pharmaceutically acceptable excipients and granulate with purified water. Dry the granules and mix with lubricants and compress into core tablets. These core tablets are optionally coated with a coating composition comprising one or more controlled release polymer(s) and other coating aids like plasticizers and film formers.

Examples of plasticizers include one or more of polyethylene glycol, triethyl citrate, triacetin, diethyl phthalate, dibutyl stearate, dibutyl sebacate, oleic acid, alcohol, mineral oil, castor oil, lanolin, petrolatum, propylene glycol, glycerol and the like.

Examples of film forming polymers include one or more of ethyl cellulose, HPMC, HPC, methylcellulose, hydroxyethyl cellulose; waxes such as polyethylene glycol. The coating may be performed by conventional means using commercially available, ready-to-coat preparations, sold under various brand names such as various grades of Opadry®, Surelease® Dispersions or mixtures thereof and the like.

Opadry® is a film coating system comprising HPMC, polyethylene glycol and titanium dioxide. Surelease® dispersion is a controlled release film coating system comprising ethyl cellulose, ammonium hydroxide, dibutyl sebacate, oleic acid and anhydrous colloidal silica.

The following examples are illustrative of the present invention, and the example should not be considered as limiting the scope of this invention in any way, as these examples and other equivalents thereof will become apparent to those versed in the art, in the light of the present disclosure, and the accompanying claims.

Various types of novel controlled release pharmaceutical composition of SSRI such as paroxetine are described in the following examples:

Examples

Ingredient	%w/w						
	Ex 1	**Ex 2**	**Ex 3**	**Ex 4**	**Ex 5**	**Ex 6**	**Ex 7**
Core Tablet							
Paroxetine HCl Hemihydrate	14.22	14.22	15.24	15.24	15.24	15.24	15.24
Lactose	35.1	35.1	37.58	37.58	37.58	37.58	37.58
Microcrystalline Cellulose	13.33	13.33	14.28	14.28	14.28	14.28	14.28
Methocel K-100 LV CR Pre	33.33	16.66	17.85	17.85	17.85	17.85	17.85
Methocel K-15 M Premium	-	16.66	-	-	-	-	-
Eudragit L-30D-55	-	-	10.71	10.71	10.71	10.71	10.71
Methocel K-100 M Premium	-	-	-	-	-	10.71	-
Sodium Alginate	-	-	-	-	-	-	10.71
Magnesium Stearate	0.7	0.7	0.75	0.75	0.75	0.75	0.75
Hydrogenated Vegetable oil	3.33	3.33	3.57	3.57	3.75	3.75	3.75
Purified Water*	QS	QS	QS	QS	QS	QS	QS
Coating							
Methocel F4M Premium	-	-	-	-	QS	-	-
Methocel E 50 LV Premium	-	-	-	-	QS	-	-
Methocel E-5 LV EP	-	-	-	QS	-	-	-
Opadry	QS	-	QS	-	-	-	-
Surelese dispersion	QS	-	QS	QS	-	-	-
Purified Water*	QS	-	QS	QS	QS	-	-

* Purified water shall be removed during process.

Mix Paroxetine HCl hemihydrate, lactose, microcrystalline cellulose and one or more controlled release polymer(s) as described in the above examples to form a uniform dry mix. Granulate dry mix with required quantity of purified water to get suitable wet

granulate mass. Dry the wet granulate mass in suitable drier and blend with magnesium stearate, hydrogenated vegetable oil in a suitable blender and compress into tablets.

Coating dispersion is prepared by using one or more controlled release polymer(s) described in the above examples; or mixing one or more coating dispersion(s) and optionally, coat tablets to a required build-up using conventional coating techniques.

Dissolution profile of these novel controlled release compositions of Paroxetine is compared with Paroxetine controlled release tablets available in the market under the brand name Paxil CR. Dissolution study is conducted using USP dissolution tester and the results are as follows:

Paxil CR Tab.			**Ex 3**		**Ex 4**		**Ex 5**		**Ex 6**	**Ex 7**	**Ex 1**	**Ex 2**
Paddle, 150 rpm		**Dissolution condition**	Paddle, 150 rpm									
Tris	*HCl + Tris*	**Media**	*Tris*	*HCl + Tris*	*Tris*	*HCl + Tris*	*Tris*	*HCl + Tris*	*Tris*	*Tris*	*Tris*	*Tris*
% Drug release		**Time in hrs.**	% Drug release									
20.9	0	**1.0**	3.2	5.5	3.0	6.7	5.0	7.8	11.6	13.4	5.6	14.6
42.7	0	**2.0**	7.9	14	10.4	14.7	14.7	21.7	23.9	27.5	18.3	24.8
59.1	5.1	**3.0**	14.6	22.7	18.9	25.4	27.5	39.3	33.5	44.1	38.2	33.7
72.7	22.8	**4.0**	24	32.8	36.0	32.7	42.1	50.8	45.7	59.5	57.7	42.2
86	45	**5.0**	47.6	47	54.1	50.6	57.7	60.4	52.8	67.3	70.7	53.2
93.8	66.3	**6.0**	71.9	66.7	66.3	63.7	72.6	70.0	65.7	80.7	81.6	61.7
	86.5	**7.0**	80.6	81.4	76.5	75.1	82.3	77.9			92.1	67.3
	97.1	**8.0**	90.3	88.3	86.7	89.0	93.3	88.5			99.3	73.2
		9.0	95	95								77.9

About 10-25% of paroxetine had been released in vitro in 2 hours; about 20-55% in 4 hours; about 50-75% in 6 hours and about 70-95% in 8 hours in 0.1N HCl, 750 ml dissolution medium for 2 hours followed by pH 7.5 Tris buffer, 1000 ml dissolution medium using USP dissolution tester, paddle method at 150 rpm.

5

CLAIMS

1. A controlled release pharmaceutical composition comprising a selective serotonin reuptake inhibitor, wherein the composition comprises of:
   a) a core comprising the active ingredient, one or more controlled release polymer(s) and one or more pharmaceutically acceptable excipients; and optionally
   b) a coating comprising one or more controlled release polymer(s)

2. A controlled release pharmaceutical composition according to claim 1, wherein, selective serotonin reuptake inhibitor is sertraline, fluoxetine, fluvoxamine, citalopram, escitalopram and paroxetine.

3. A controlled release pharmaceutical composition according to claim 1, wherein, the controlled release polymer(s) is selected from the group comprising cellulose derivatives, alginic acid derivatives, polymethacrylates, polysaccharides, alkylene oxides or mixtures thereof.

4. A controlled release pharmaceutical composition according to claim 3, wherein, the cellulose polymers are selected from the group comprising hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose (HPMC), methylcellulose, carboxy methylcellulose, and hydroxy ethyl cellulose, ethyl cellulose or mixtures thereof.

5. A controlled release pharmaceutical composition according to claim 3, wherein, the alginic acid derivatives are selected from the group comprising alginic acid and its physiologically acceptable salts such as those of sodium, potassium, calcium or mixtures thereof.

6. A controlled release pharmaceutical composition according to claim 3, wherein, polymethacrylates are selected from the group comprising various types of methacrylic acid derivatives and copolymers thereof.

7. A controlled release pharmaceutical composition according to claim 3, wherein, the polysaccharide are selected from the group comprising chitosan, gellan and xanthan gum.

8. A controlled release pharmaceutical composition according to claim 3, wherein, the alkylene oxide is polyethylene oxide.

9. A controlled release pharmaceutical composition according to claim 1, wherein the controlled release polymer(s) is/are present from about 10-50% w/w in the core and from about 1-15% w/w in the coating.

10. A controlled release pharmaceutical composition according to claim 1, wherein, the core comprises pharmaceutically acceptable excipients selected from the group comprising diluents, disintegrants, lubricants and binders.

11. A controlled release pharmaceutical composition according to claim 10, wherein, the diluents are selected from the group comprising mannitol, dextrose, xylitol, sorbitol, sucrose, microcrystalline cellulose, calcium carbonate, calcium phosphate dibasic, calcium phosphate tribasic, calcium sulfate, lactose, starches, vinyl polymers or mixtures thereof.

12. A controlled release pharmaceutical composition according to claim 10, wherein, the disintegrants are selected from the group comprising microcrystalline cellulose, croscarmellose sodium, crospovidone, carboxymethyl starch sodium, sodium starch glycolate or mixtures thereof.

13. A controlled release pharmaceutical composition according to claim 10, wherein, the binders are selected from the group comprising hydroxypropyl cellulose,

hydroxy ethyl cellulose, ethyl cellulose, hydroxypropyl methyl cellulose, methyl cellulose, acrylates, methacrylates, povidone or mixtures thereof.

14. A controlled release pharmaceutical composition according to claim 10, wherein, the lubricants are selected from the group comprising stearates, hydrogenated vegetable oil, sodium stearyl fumarate, talc, colloidal silicon dioxide, palmitic acid, carnauba wax, glyceryl monostearate, microcrystalline wax, polyoxyethylene monostearates, fats and stearic acidor mixtures thereof.

15. A controlled release pharmaceutical composition according to claim 1, wherein, the coating further comprises coating aids like plasticizers and film formers.

16. A controlled release pharmaceutical composition according to claim 15, wherein, the plasticizers are selected from the group comprising polyethylene glycol, triethyl citrate, triacetin, diethyl phthalate, dibutyl stearate, dibutyl sebacate, oleic acid, alcohol, mineral oil, castor oil, lanolin, petrolatum, propylene glycol, glycerol or mixtures thereof.

17. A controlled release pharmaceutical composition according to claim 15, wherein, the film formers are selected from the group comprising one or more of ethyl cellulose, HPMC, HPC, methylcellulose, hydroxyethyl cellulose and waxes such as polyethylene glycol.

18. The process for preparing a controlled release pharmaceutical composition of SSRI comprising:

a) mixing the active ingredient with one ore more controlled release polymer(s) and one or more pharmaceutically acceptable excipients;
b) granulating the mixture with purified water
c) drying the granules; mixing with lubricants and compressing into tablets and optionally
d) coating the compressed tablets with a coating dispersion comprising one or more controlled release polymer(s).

19. Use of a controlled release pharmaceutical composition of SSRI according to claim 1 in the manufacture of a medicament, for treating and/or preventing the disorders.

20. A controlled release pharmaceutical composition of a selective serotonin reuptake inhibitor comprising

a) a core comprising the active ingredient, one or more controlled release polymer(s) and one or more pharmaceutically acceptable excipients; and optionally

b) a coating comprising one or more controlled release polymer(s),

wherein, about 10-25% of active is released in vitro in 2 hours in 0.1N HCl, 750 ml dissolution medium using USP Dissolution tester, paddle method at 150 rpm.

21. A controlled release pharmaceutical composition according to claim 20, wherein, about 20-55% of active is released in vitro in 4 hours in pH 7.5 Tris buffer, 1000 ml dissolution medium using USP Dissolution tester, paddle method at 150 rpm.

22. A controlled release pharmaceutical composition according to claim 20, wherein, about 50-75% of active is released in vitro in 6 hours in pH 7.5 Tris buffer, 1000 ml dissolution medium using USP Dissolution tester, paddle method at 150 rpm.

23. A controlled release pharmaceutical composition according to claim 20, wherein, and about 70-95% of active is released in vitro in 8 hours in pH 7.5 Tris buffer, 1000 ml dissolution medium using USP Dissolution tester, paddle method at 150 rpm.