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ATTORNEYS FOR PLAINTIFFS

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

SMITHKLINE BEECHAM CORPORATION, d/b/a GLAXOSMITHKLINE, SMITHKLINE BEECHAM P.L.C., and SB PHARMCO PUERTO RICO INC.,	
Plaintiffs,	Civil Action No. _____
v.	
MYLAN LABORATORIES INC. and MYLAN PHARMACEUTICALS INC.,	
Defendants.	

VERIFIED COMPLAINT AND DEMAND FOR JURY TRIAL

Plaintiffs SmithKline Beecham P.L.C., SmithKline Beecham Corporation d/b/a GlaxoSmithKline, and SB Pharmco Puerto Rico Inc, for their Complaint

against Defendants Mylan Laboratories Inc. and Mylan Pharmaceuticals Inc., hereby allege as follows:

THE PARTIES

1.A Plaintiff SmithKline Beecham P.L.C. is a public limited company organized under the laws of England and Wales with its principal place of business at 980 Great West Road, Brentford, Middlesex, TW89GS, England.

1.B Plaintiff SmithKline Beecham Corporation is a Pennsylvania corporation having its principal place of place of business at One Franklin Plaza, Philadelphia, Pennsylvania 19102.

1.C Plaintiff SB Pharmco Puerto Rico Inc. is a company organized and existing under the laws of Puerto Rico with its principal place of business at State Road No. 172, Km. 9.1/Bo. Certenejas, Cidra, Puerto Rico, 00739. Plaintiff SB Pharmco Puerto Rico Inc. is the holder of New Drug Application ("NDA") No. 02-0936 for Paxil CR®. Plaintiffs SmithKline Beecham P.L.C., SmithKline Beecham Corporation, and SB Pharmco Puerto Rico Inc. are hereinafter collectively referred to as "GlaxoSmithKline" or "GSK".

1.D Upon information and belief, Defendant Mylan Laboratories Inc. ("Mylan Laboratories") is a corporation organized under the laws of

Pennsylvania having a place of business at 1500 Corporate Drive, Canonsburg, Pennsylvania 15317.

1.E Upon information and belief, Defendant Mylan Pharmaceuticals Inc. ("Mylan Pharmaceuticals") is a corporation organized under the laws of West Virginia having a place of business at 781 Chestnut Ridge Road, Morgantown, West Virginia 26504.

1.F Upon information and belief, Mylan Pharmaceuticals is a wholly-owned subsidiary of Mylan Laboratories, and Mylan Pharmaceuticals and Mylan Laboratories have officers or directors in common. Further, on information and belief, the acts of Mylan Pharmaceuticals complained of herein were aided and abetted by and done with the cooperation, participation, and assistance of or at least for the benefit of Mylan Laboratories. Mylan Pharmaceuticals and Mylan Laboratories are hereinafter collectively referred to as "Mylan."

NATURE OF THE ACTION

2. This is a civil action for the infringement of United States Patent No. 7,229,640 ("the '640 patent"). This action relates to an Abbreviated New Drug Application ("ANDA") filed by Mylan Pharmaceuticals with the United States Food and Drug Administration ("FDA") for approval to market a generic version of GSK's Paxil CR® drug product. This action arises under the patent laws of the United States, 35 U.S.C. § 100 *et seq.*

JURISDICTION AND VENUE

3. This Court has jurisdiction over the subject matter of this action pursuant to 28 U.S.C. §§ 1331 and 1338.

4. Upon information and belief, Mylan is registered to do business in New Jersey and Corporation Service Company, 830 Tavern Road, West Trenton, New Jersey 08628, is its registered agent in New Jersey. In addition, Mylan sells various products and does business throughout the United States, including within this judicial district. Upon information and belief, Mylan has submitted to the jurisdiction of the United States District Court for the District of New Jersey. This Court has personal jurisdiction over Mylan by virtue of, *inter alia*, the above-mentioned facts.

5. Venue is proper in this judicial district pursuant to 28 U.S.C. §§ 1391(b), (c), and 1400(b).

THE '640 PATENT

6. On June 12, 2007, the '640 patent, titled "Paroxetine Controlled Release Compositions," was duly and legally issued to SmithKline Beecham P.L.C. A true and correct copy of the '640 patent is attached hereto as Exhibit A.

7. The '640 patent contains claims directed to drug formulations involving paroxetine, which is a Selective Serotonin Reuptake Inhibitor used to treat many disorders including depression, anxiety, and alcoholism. The '640

patent is listed in the Food and Drug Administration ("FDA") Orange Book as a patent associated with GSK's PAXIL CR® drug product.

8. The '640 patent covers a controlled and delayed release composition of paroxetine that reduces the incidence of nausea and vomiting when administered. The '640 patent also covers a method of treating one or more identified diseases, including depression, by administering a controlled and delayed release formulation of paroxetine. The claims of the '640 patent are valid and enforceable.

8. GSK has all right and title to the '640 patent, including the right to sue for and obtain equitable relief and damages for infringement thereof.

ACTS GIVING RISE TO THIS ACTION

9. GSK is the holder of an approved NDA No. 02-0936 under Section 505(a) of the Federal Food, Drug, and Cosmetic Act ("FFDCA"), 21 U.S.C. § 355(a), for paroxetine hydrochloride controlled release tablets, which are marketed in the United States under the trade name Paxil CR®.

10. Upon information and belief, on or before September 9, 2005, Defendants submitted ANDA No. 77-873 and a supplement thereto to the FDA under § 505(j) of the FFDCA, 21 U.S.C. § 355(j), seeking approval to engage in the commercial manufacture, use, offer for sale and sale of generic versions of paroxetine hydrochloride controlled release tablets, 12.5 mg and 25 mg.

11. Upon information and belief, by filing the Mylan ANDA, Mylan has necessarily represented to the FDA that Mylan's proposed paroxetine hydrochloride controlled release tablets have the same active ingredient as GSK's Paxil CR®, have the same route of administration, dosage form, and strengths as Paxil CR®, are bioequivalent to Paxil CR®, and have the same or substantially the same proposed labeling as Paxil CR®.

12. By letter dated November 8, 2005, Mylan notified GSK that Mylan's ANDA No. 77-873 contains "Paragraph IV Certifications" to several U.S. patents that were identified in the FDA's Orange Book.

13. On or around June 20, 2007, pursuant to 21 U.S.C. § 355(b)(1), the '640 patent was identified in the Orange Book under GSK's NDA No. 02-0936 as a patent "with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use, or sale of the drug" PAXIL CR®.

14. By letter dated June 20, 2007, GSK notified Mylan that the '640 patent was listed in the Orange Book.

15. On June 20, 2007, Mylan sent GSK notice that it is amending ANDA No. 77-873 to include a paragraph IV certification alleging that the '640 patent is not infringed and invalid. Mylan's notice also informed GSK that Mylan

is seeking approval to market its generic paroxetine hydrochloride controlled release drug product before the expiration of the '640 patent.

16. On June 21, 2007, Mylan responded to GSK's letter of June 20, 2007, and informed GSK that "Mylan has received tentative approval from the FDA to market its Paroxetine Hydrochloride Controlled Release Product (12.5 mg and 25 mg). This approval becomes final on June 29, 2007 and Mylan plans to launch its product immediately thereafter."

17. Defendants' submission of ANDA No. 77-873 to the FDA, amendment to include a paragraph IV certification for the '640 patent, and expressed intent to "seek[] approval from FDA to market the proposed drug products prior to expiration of that patent", constitute infringement of the '640 patent under 35 U.S.C. § 271(e)(2)(A).

18. Mylan has not obtained any license or other authority under the '640 patent to make, use, offer to sell, sell or import its paroxetine hydrochloride controlled release drug product anywhere within the United States. As a result, if Mylan commercially makes, uses, offers for sale, sells, or imports any of the proposed generic versions of GSK's Paxil CR® drug product, or induces or contributes to such conduct, it would further infringe the '640 patent under 35 U.S.C. § 271(a), (b), and/or (c).

19. Mylan had notice of the '640 patent before making, offering to sell or selling its paroxetine hydrochloride controlled release drug product within the United States. Accordingly, Mylan's infringement is willful.

20. Mylan's conduct in infringing the '640 patent renders this case exceptional within the meaning of 35 U.S.C. § 285.

21. Mylan intends to make, use, offer to sell, and/or sell its infringing paroxetine hydrochloride controlled release drug product to major and regional prescription wholesalers imminently. If Mylan is not restrained and enjoined, Mylan's generic paroxetine hydrochloride controlled release drug product will eviscerate the market for GSK's Paxil CR® drug product. If this is allowed to occur, the market for this product will never be the same, even if an injunction issues at some future time. Damages would not be adequate to compensate GSK for this loss.

22. As a result, GSK will be irreparably harmed by Defendants' infringing activities unless those activities are enjoined by this Court. GSK does not have an adequate remedy at law.

PRAYER FOR RELIEF

WHEREFORE, GlaxoSmithKline prays for judgment as follows:

A. That Defendants have infringed the '640 patent;

B. That Defendants' infringement of the '640 patent has been, and continues to be, willful;

C. That, pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval of any of Mylan Pharmaceuticals' ANDA identified in this Complaint shall not be earlier than the expiration date of the '640 patent, including any extensions;

D. That Defendants, their officers, agents, servants and employees, and those persons in active concert or participation with any of them, are temporarily restrained and preliminarily and permanently enjoined from commercially manufacturing, using, offering for sale or selling the proposed generic versions of GSK's Paxil CR® drug product identified in this Complaint, and any other product that infringes or induces or contributes to the infringement of the '640 patent, prior to the expiration of the '640 patent, including any extensions;

E. That GSK be awarded monetary relief if Defendants commercially manufacture, use, offer for sale, or sell any proposed generic version of GSK's Paxil CR® drug product, or any other product that infringes or induces or contributes to the infringement of the '640 patent, within the United States prior

to the expiration of that patent, including any extensions, and that any such monetary relief be awarded to GSK with prejudgment interest;

F. That all of Mylan's generic paroxetine hydrochloride controlled release drug product that have been manufactured and distributed be recalled;

G. That this case be declared exceptional within the meaning of 35 U.S.C. § 285 and awarding GSK the attorney fees, costs, and expenses it incurs prosecuting this action; and

H. That GSK be awarded such other and further relief as this Court deems just and proper.

CERTIFICATION PURSUANT TO L.CIV.R. 11.2

Plaintiffs, by their undersigned counsel, hereby certify pursuant to L.Civ.R. 11.2 that the matters in controversy are not the subject of any other action pending in any other court or of any pending arbitration or administrative proceeding other than the ANDA referenced herein.

DEMAND FOR JURY TRIAL

Plaintiff GlaxoSmithKline hereby demands a trial by jury for all the issues so triable.

Dated: June 25, 2007

Respectfully submitted,

s/ Thomas R. Curtin

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VERIFICATION

Sherry M. Knowles, of full age, being duly sworn according to the law, upon her oath deposes and says:

I am Senior Vice President and Global Head of the Corporate Intellectual Property of SmithKline Beecham Corporation, doing business as GlaxoSmithKline, the plaintiff in the above matter. I have reviewed the allegations made in this Verified Complaint and they are true and accurate to the best of my knowledge and belief.

Sworn to and subscribed before me
This 25th day of June, 2007

Notary Public

DIANE L. CAMPELLONE
NOTARY PUBLIC OF NEW JERSEY
My Commission Expires January 9, 2011

Exhibit A

US007229640B2

(12) **United States Patent**
Leonard et al.

(10) **Patent No.: US 7,229,640 B2**
(45) **Date of Patent: Jun. 12, 2007**

(54) **PAROXETINE CONTROLLED RELEASE COMPOSITIONS**

(75) Inventors: **Graham Stanley Leonard**, St. Albans (GB); **David Philip Elder**, Hertford (GB)

(73) Assignee: **SmithKline Beecham p.l.c.**, Brentford (GB)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **10/024,858**

(22) Filed: **Dec. 18, 2001**

(65) **Prior Publication Data**

US 2002/0090394 A1 Jul. 11, 2002

Related U.S. Application Data

(63) Continuation of application No. 09/391,796, filed on Sep. 9, 1999, which is a continuation of application No. 08/817,911, filed as application No. PCT/EP96/03252 on Jul. 19, 1996, now abandoned.

(30) **Foreign Application Priority Data**

Jul. 20, 1995 (GB) 9514842

(51) **Int. Cl.**
A61K 9/20 (2006.01)
A61K 9/22 (2006.01)
A61K 9/24 (2006.01)
A61K 9/28; A61K 9/32

(52) **U.S. Cl.** **424/464**; 424/465; 424/468; 424/472; 424/474; 424/482

(58) **Field of Classification Search** 424/464, 424/465, 468, 472, 474, 482, 451, 457, 475, 424/476, 484, 458, 459
See application file for complete search history.

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Primary Examiner—Humera N. Sheikh
(74) *Attorney, Agent, or Firm*—Wayne J. Dustman; Stephen Venetianer

(57) **ABSTRACT**

A controlled release or delayed release formulation contains a selective serotonin reuptake inhibitor (SSRI) such as paroxtine.

2 Claims, No Drawings

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PAROXETINE CONTROLLED RELEASE COMPOSITIONS

This is a continuation of application Ser. No. 09/391,796, filed Sep. 9, 1999, which is a continuation of application Ser. No. 08/817,911 filed Aug. 26, 1997, now abandoned which is a §371 of PCT/EP96/03252, filed Jul. 19, 1996.

The present invention relates to a novel formulation containing paroxetine or a pharmaceutically acceptable salt thereof, and to its use in the treatment and/or prophylaxis of certain disorders.

U.S. Pat. No. 4,007,196 describes inter alia a compound which is commonly known as paroxetine. This compound is a Selective Serotonin Reuptake Inhibitor (SSRI) and is currently marketed world-wide for the treatment and/or prophylaxis of depression.

The current formulation which is the only marketed formulation of paroxetine hydrochloride is a swallow tablet.

It has now been surprisingly found that controlled release and delayed release formulations containing paroxetine give rise to an unexpected reduction in the side effects associated with swallow tablets.

Accordingly, the present invention provides a controlled release or delayed release formulation containing paroxetine or a pharmaceutically acceptable salt thereof.

A further aspect of the invention provides a controlled release or delayed release formulation containing an SSRI. Examples of SSRIs other than paroxetine include fluoxetine (U.S. Pat. No. 4,314,081), fluvoxamine (U.S. Pat. No. 4,085,225), and sertraline (U.S. Pat. No. 4,536,518).

By controlled release is meant any formulation technique wherein release of the active substance from the dosage from is modified to occur at a slower rater than that from an immediate release product, such as a conventional swallow tablet or capsule.

By delayed release is meant any formulation technique wherein release of the active substance from the dosage form is modified to occur at a later time than that from a conventional immediate release product The subsequent release of active substance from a delayed release formulation may also be controlled as defined above.

Examples of controlled release formulations which are suitable for incorporating paroxetine and other SSRIs are described in:

Sustained Release Medications, Chemical Technology Review No. 177. Ed. J. C. Johnson. Noyes Data Corporation 1980.

Controlled Drug Delivery, Fundamentals and Applications, 2nd Edition. Eds. J. R. Robinson, V. H. L. Lee. Mercel Dekkes Inc. New York 1987.

Examples of delayed release formulations which are suitable for incorporating paroxetine and other SSRIs are described in:

Remington's Pharmaceutical Sciences 16th Edition, Mack Publishing Company 1980, Ed. A. Osol.

Such controlled release formulations are preferably formulated in a manner such that release of active substance such as paroxetine is effected predominantly during the passage through the stomach and the small intestine, and delayed release formulations are preferably formulated such that release of active substance such as paroxetine is avoided in the stomach and is effected predominantly during passage through the small intestine.

Said formulations are preferably formulated such that the release of the active substance is predominantly 1½ to 3 hours post ingestion.

The small intestine is suitably the duodenum, the ileum or the jejunem.

Patients who benefit most from the formulations of the present invention are those who are known to suffer from nausea upon oral administration using swallow tablets.

Preferred formulations are ultimately enteric coated tablets or caplets, wax or polymer coated tablets or caplets or time-release matrices, or combinations thereof.

Particularly preferred formulations are described in U.S. Pat. No. 5,102,666.

Thus, a particular aspect of the invention provides a polymeric controlled release composition comprising a reaction complex formed by the interaction of (1) a calcium polycarbophil component which is a water-swellable, but water insoluble, fibrous cross-linked carboxy-functional polymer, said polymer containing (a) a plurality of repeating units of which at least about 80%o contain at least one carboxyl functionality, and (b) about 0.05 to about 1.5% cross-linking agent substantially free from polyalkenyl polyether, said percentages being based upon the weights of unpolymerised repeating unit and cross-linking agent, respectively, with (2) water, in the presence of an active agent selected from the group consisting of SSRIs such as paroxetine. The amount of calcium polycarbophil present is from about 0.1 to about 99% by weight, for example about 10%. The amount of active agent present is from about 0.0001 to about 65% by weight, for example between about 5 and 20%. The amount of water present is from about 5 to about 200% by weight, for example between about 5 and 10%. The interaction is carried out at a pH of between about 3 and about 10, for example about 6 to 7. The calcium polycarbophil is originally present in the form of a calcium salt containing from about 5 to about 25% calcium.

Further particularly preferred formulations are described in U.S. Pat. No. 5,422,123.

Thus, a further particular aspect of the invention provides a system for the controlled release of an active substance which is an SSRI such as paroxetine, comprising (a) a deposit-core comprising an effective amount of the active substance and having defined geometric form, and (b) 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%.

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

Paroxetine hydrochloride hemihydrate may be prepared according to the procedures generally outlined in U.S. Pat. No. 4,721,723.

Paroxetine in the form of a controlled release or delayed release formulation 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 present invention provides a method of treating and/or preventing the disorders by administering an effective and/or a prophylactic amount of a controlled release or delayed release formulation containing paroxetine or a pharmaceutically acceptable salt thereof, to a sufferer in need thereof.

The present invention further provides the use of a controlled release or delayed release formulation containing paroxetine or a pharmaceutically acceptable salt thereof in the manufacture of a medicament, for treating and/or preventing the disorders.

The present invention also provides a pharmaceutical composition for use in the treatment and/or prevention of the disorders which comprises a controlled release or delayed release formulation containing paroxetine or a pharmaceutically acceptable salt thereof.

The following examples illustrate the present invention.

Example 1 (Hydrophilic Matrix)	% w/w
Intragranular	
Paroxetine Hydrochloride	11.45
Methocel E5	1.25
Lactose	12.3
Extragranular	
Methocel K100LV	30.0
Lactose	44.0
Magnesium Stearate	1.0
TOTAL	100.0

Example 2 (Hydrophilic Matrix)	% w/w
Intragranular	
Paroxetine Hydrochloride	11.45
Methocel E5	1.25
Lactose	12.3

-continued

Extragranular	
Methocel K100LV	27.5
Methocel K4M	7.5
Lactose	39.0
Magnesium Stearate	1.0
TOTAL	100.0

Example 3 (pH Sensitive Coat on Immediate Release Core)	% w/w
Tablet Core	
Paroxetine Hydrochloride	11.45
Lactose	64.05
Microcrystalline Cellulose	20.0
Sodium Starch Glycollate	4.0
Magnesium Stearate	0.5
TOTAL	100.0

Tablet Coating (apply approximately 6–10% of tablet core weight)	% w/w
Hydroxypropylmethylcellulose Phthalate	90.0
Triacetin	10.0

Example 4 (pH Sensitive Coat on Immediate Release Core)	% w/w
Tablet Core as in Example 3	
Tablet Coating (apply approximately 6–10% of tablet core weight)	
Cellulose Acetate Phthaulate	90.0
Diethyl Phthalate	10.0

Example 5 (Controlled Release Coating on Immediate Release Core)	% w/w
Tablet Core as in Example 3	
Tablet Coating (apply approximately 5–12% of tablet core weight)	
Eudragit RS 100	86.0
Dibutyl Phthalate	10.0
Talc	4.0
FD&C Yellow No.6	0.01

Example 6 (pH Sensitive Coat on Controlled Release Core.)
Tablet Core as in Example 3
Tablet Coating as in Example 3

Example 7 (Encapsulated Controlled Release Coated Beads)	% w/w (approx)
Pellet	
Non Pareil Seed	30
Paroxetine Hydrochloride	40
Gelatin	8
Lactose	20
Talc	2
	% w/w
Coating	
Glycerylmonostearate	36.6
Glyceryldistearate	53.4
White Wax	10.0

-continued

Example 8 (Controlled release bilayer tablet)

Component	mg/tablet	Function
Active Layer		
Paroxetine Hydrochloride	22.89*	Active
Methocel K4M	15.00	Hydrogel polymer
Lactose monohydrate	62.0	Hydrophilic agent
Polyvinylpyrrolidone	3.0	Binder
Magnesium stearate	1.0	Hydrophobic agent
Syloid 244	1.0	Hydrophilic agent
Support platform		
Compritol 888	15.04	Plasticizer
Lactose monohydrate	29.32	Hydrophilic agent
Polyvinylpyrrolidone	4.0	Binder
Magnesium stearate	1.52	Hydrophobic agent
Methocel E5	29.32	Hydrogel polymer
Iron oxide	0.08	Colourant
Total tablet weight	184.89 mg	

*Equivalent to 20 mg paroxetine as free base.

The powder blend for each layer was wet granulated in a high shear mixer/granulator and dried in a fluid bed drier. The bilayer tablets were compressed on a Manesty triple layer press.

Example 9 (Enteric coated calcium polycarbophil formulation)

Component	mg/tablet	Function
Core		
Paroxetine Hydrochloride	22.89*	Active
Calcium polycarbophil	20.00	Matrix
Lactose anhydrous	146.11	Hydrophilic agent/diluent
Polyvinylpyrrolidone	10.0	Binder
Magnesium stearate	1.0	Hydrophobic agent/lubricant
Water**	0.024	Granulating liquid
Enteric coat		
Eudragit	22.19	Polymer
Talc	1.53	Lubricant
Triethyl citrate	1.00	Plasticizer
Water**	24.6	Diluent
Film coat		
Opadry pink	10.5	Film coat
Water**	94.5	Diluent
Polish coat		
Opadry clear	0.750	
Water**	29.3	Diluent

*Equivalent to 20 mg paroxetine as free base.
**Removed during processing.

The core constituents were wet granulated in a high shear mixer/granulator, and dried in a fluid bed drier. The magnesium stearate was then added and the mixture processed in a low shear mixer. The mix was then compressed on a B type rotary tablet press. Coating was carried out using an Accela cota.

Example 10 (Controlled release bilayer tablet)

Component	mg/tablet	Function
Active Layer		
Paroxetine Hydrochloride	22.89*	Active
Methocel K4M	20.00	Hydrogel polymer
Lactose monohydrate	60.0	Hydrophilic agent

-continued

Example 10 (Controlled release bilayer tablet)

Component	mg/tablet	Function
Polyvinylpyrrolidone	5.0	Binder
Magnesium stearate	1.0	Hydrophobic agent
Syloid 244	1.0	Hydrophilic agent
Support platform		
Compritol 888	14.72	Plasticizer
Lactose monohydrate	30.60	Hydrophilic agent
Polyvinylpyrrolidone	2.80	Binder
Magnesium stearate	0.80	Hydrophobic agent
Methocel E5	30.60	Hydrogel polymer
Syloid 244	0.40	Hydrophilic agent
Iron oxide	0.08	Colourant
Total tablet weight	189.89mg	

*Equivalent to 20 mg paroxetine as free base.

The process was as described in Example 8.

Example 11 (Controlled release bilayer tablet)

Component	mg/tablet	Function
Active Layer		
Paroxetine Hydrochloride	22.89*	Active
Methocel K4M	15.00	Hydrogel polymer
Lactose monohydrate	63.31	Hydrophilic agent
Polyvinylpyrrolidone	2.0	Binder
Magnesium stearate	1.0	Hydrophobic agent
Syloid 244	0.40	Hydrophilic agent
Support platform- as in Example 10.		
Total tablet weight	184.60 mg	

*Equivalent to 20 mg paroxetine as free base.

The process was as described in Example 8.

Example 12 (Enteric coated controlled release bilayer tablet)

Component	mg/tablet	Function
Active Layer		
Paroxetine Hydrochloride	28.61*	Active
Methocel K4M	18.75	Hydrogel polymer
Lactose monohydrate	79.14	Hydrophilic agent
Polyvinylpyrrolidone	2.50	Binder
Magnesium stearate	1.25	Hydrophobic agent
Syloid 244	0.50	Hydrophiic agent
Support platform		
Compritol 888	15.04	Plasticizer
Lactose monohydrate	30.50	Hydrophilic agent
Polyvinylpyrrolidone	4.00	Binder
Magnesium stearate	0.80	Hydrophobic agent
Methocel E5	29.32	Hydrogel polymer
Syloid 244	0.32	Hydrophilic agent
Iron oxide	0.02	Colourant
Enteric coating		
Eudragit	13.27	Polymer
Talc	3.31	Lubricant
Triethyl citrate	1.33	Plasticizer
Water**	36.25	Diluent
Total tablet weight	228.66 mg	

*Equivalent to 25 mg paroxetine as free base.
**Removed during processing.

The process was as described in Example 9.

EXAMPLE 13

GI Tolerance Study

The design of the study is outlined below

Subjects:	Normal healthy volunteers
Design:	Parallel group, placebo controlled, double blind
Treatment:	(a) Placebo, (b) Immediate release paroxetine, (c) Example 8 formulation, (d) Example 8 formulation with enteric coating.
Dosage:	30 mg once daily for 3 days
Number of subjects:	452 evaluable (488 randomised, 485 evaluable)

The study was conducted to compare the incidence, severity and duration of nausea and vomiting, and diarrhoea (theoretically if the controlled release formulations slow down absorption of paroxetine then, as paroxetine is known to be prokinetic to the GI tract there may be an increased incidence).

Adverse experiences (AE) information was assessed each morning at the time of dosing and again 24 hours following the last dose. Investigators and subjects were given diary cards detailing how to classify severity of AEs in order to standardise as much as possible across all 6 centres.

Of the 485 evaluable subjects, 18 (3.7%) withdrew, 17 because of adverse events. Subjects with nausea/vomiting on the day of withdrawal were more common on (b) than either of (c) and (d).

The incidence of nausea/vomiting and diarrhoea is shown in the table below:

	(b)	(c)	(d)	Placebo
Incidence of nausea	59%	49%	39%	13%
Incidence of diarrhoea	15%	21%	20%	7%

The incidence of nausea was increased for both (b) and placebo compared to the expected rates of approximately 25% and 5% respectively for volunteers at these dosages for 3 days duration. The overall incidence of nausea was less on (c) and (d) than on (b). The severity of nausea was also decreased as shown in the next table.

Nausea severity	(b)	(c)	(d)	Placebo
None	50 (41%)	63 (52%)	74 (61%)	104 (87%)
Mild	45 (37%)	40 (33%)	30 (25%)	16 (13%)
Moderate	21 (17%)	17 (14%)	15 (12%)	0 (0%)
Severe	6 (5%)	1 (1%)	3 (2%)	0 (0%)

Severity of diarrhoea is reported in the table below:

Severity of diarrhoea	(b)	(c)	(d)	Placebo
None	104 (85%)	95 (79%)	97 (80%)	112 (93%)
Mild	16 (13%)	16 (13%)	16 (13%)	8 (7%)
Moderate	1 (1%)	8 (7%)	9 (1%)	0 (0%)
Severe	1 (1%)	2 (2%)	0 (0%)	0 (0%)

In conclusion, there appears to be a trend for (c) to reduce the incidence of nausea and the dropout rate due to adverse events in comparison to (b), but analysis of the results was complicated by a statistically significant treatment-by-centre difference. (d) shows a halving in the dropout rate and a fall in incidence of nausea of 20% (a proportional fall of 33%). In addition there is a reduction in severity of nausea of those individuals who report nausea on (c) and (d). There is an increase in incidence of diarrhoea on both of (c) and (d) in relation to (b), but this is confined to an increase in the number of individuals reporting moderate diarrhoea and there is no increase in those with severe diarrhoea.

What is claimed is:

1. A composition, that reduces the incidence of nausea and vomiting associated with the administration of paroxetine, comprising paroxetine, or a pharmaceutically acceptable salt thereof, in a controlled and delayed release swallow pharmaceutical formulation that, upon administration, releases the paroxetine predominantly in the small intestine.

2. A method of treating one or more disease states selected from; 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, Dysthymla and Substance Abuse, which comprises administering an effective amount of a controlled and delayed release swallow pharmaceutical formulation that, upon administration, releases paroxetine or a pharmaceutically acceptable salt thereof, predominantly in the small intestine to an individual in need thereof.

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