

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
13 December 2007 (13.12.2007)

PCT

(10) International Publication Number
WO 2007/143290 A2

(51) International Patent Classification:

A61K 9/28 (2006.01)

(21) International Application Number:

PCT/US2007/067397

(22) International Filing Date: 25 April 2007 (25.04.2007)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

60/811,547

7 June 2006 (07.06.2006) US

(71) Applicant (for all designated States except US): NEUROSCI, INC. [US/US]; 1458 Clear Brook Drive, Dayton, OH 45440 (US).

(72) Inventor; and

(75) Inventor/Applicant (for US only): VISHNUPAD, Krishna [US/US]; 1458 Clear Brook Drive, Dayton, OH 45440 (US).

(74) Agent: SERIO, John, C.; Brown Rudnick Berlack Israels LLP, One Financial Center, Boston, MA 02111 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, 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, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, 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, MT, 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).

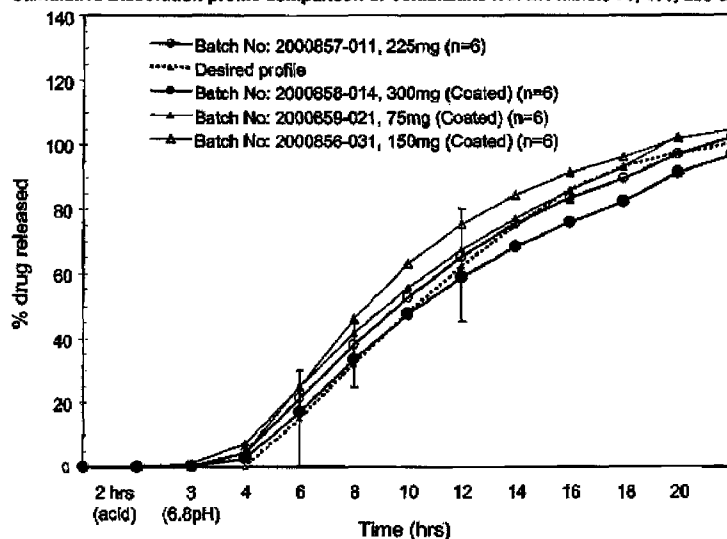
Published:

— 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: DELAYED-RELEASE COMPOSITIONS OF EXTENDED RELEASE FORMS OF VENLAFAXINE

Cumulative Dissolution profile comparison of Venlafaxine HCl ER tablets 75, 150, 225 & 300mg



(57) Abstract: The present disclosure relates to a delayed controlled release composition of at least one form of venlafaxine. According to the disclosure a delayed controlled release composition of venlafaxine hydrochloride is provided by a blend of polymers in the core formulation. The core formulation having extended release polymers is coated with a non-permeable polymer blend formed of a water in-soluble polymer and an enteric coating polymer, which does not release the active drug in either acid or base for up to about 4 hours. Upon disintegration of the non-permeable coating the active drug is released in a sustained manner due to the polymers within the core formulation. The delayed release prevents the substantial release of venlafaxine into the stomach.

DELAYED-RELEASE COMPOSITIONS OF EXTENDED RELEASE FORMS OF VENLAFAXINE

CROSS REFERENCE RELATED APPLICATION

This application claims priority to U.S. Provisional Application No. 60/811,547, filed on June 7, 2006, the contents of which are incorporated in its entirety by reference.

FIELD OF THE INVENTION

The present invention relates to delayed controlled release compositions for oral administration of at least one form of venlafaxine, to processes for their preparation and to their medical use. In particular, the delayed modified release composition relates to a delayed controlled release composition of at least one form of venlafaxine.

BACKGROUND OF THE INVENTION

A delayed controlled release regimen for pharmaceuticals are desirably maintained within their therapeutic window so that by which an acceptable therapeutic concentration of drug at the site(s) of action is attained after a selected period of ingestion advantageous to the active pharmaceutical and is then maintained constant for the duration of the treatment. Providing that proper dose size and frequency of administration are correct, therapeutic "steady-state" plasma concentrations of a drug can be achieved promptly and maintained by the multiple administrations of conventional oral dosage forms. Unfortunately, there are a number of potential limitations associated with conventional instant release oral dosage forms. Unfortunately, patient compliance is one of the greatest limitations. These limitations have led to the need to consider presenting therapeutically active pharmaceuticals in extended-release or delayed extended release preparations.

For many reasons, oral ingestion is the traditionally preferred route of drug administration, providing a convenient method of effectively achieving both local and systemic effects. An ideal oral drug delivery system should steadily deliver a measurable and reproducible amount of drug to the target site over a prolonged period and maintained levels of drug within an acceptable therapeutic window. Extended-release (ER) delivery systems should provide a uniform concentration/amount of the drug at the absorption site and thus, after absorption, allow maintenance of plasma concentrations within a therapeutic range over an extended period of time, which can minimize side effects and also reduces the frequency of administration. It is desirable that ER dosage forms release drug slowly, so that plasma concentrations are maintained at a therapeutic level for a prolonged period of time. As a result, ER products provide numerous benefits compared with immediate-release compositions, including greater effectiveness in the treatment of chronic conditions, reduced side effects, greater convenience, and higher levels of patient compliance due to a simplified dosing schedule. However, it is desirable in some pharmaceuticals to combine an extended release delivery system with a delay in an initial release

Many drug delivery systems have been developed with the aim of eliminating the cyclical changes in plasma drug concentration seen after the administration of a conventional delivery system. A variety of terms have been used to describe these systems: delayed release, repeat action, prolonged release, sustained release, extended release, controlled release and modified release. Pharmaceutical standards consider the terms controlled release, prolonged release, sustained release and extended-release as being interchangeable.

Controlled-release formulations have been described in the prior art and many methods have been used to provide controlled-release pharmaceutical dosage forms in order to maintain

therapeutic serum levels of medicaments and to minimize the effects of missed doses of drugs caused by a lack of patient compliance. Anti-depressants and psychotropic drugs are excellent candidates for controlled-release formulations as discontinuation of these drugs, most often as a result of a lack of patient compliance due to a complicated or multiple daily dosing schedule, can often result in the lack of efficacy in these medication and problems with severe discontinuation symptoms.

One such antidepressant compound that benefits from an extended release formulation is Venlafaxine, which is chemically designated as (R/S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol or ($\pm$)-1-[α [α -(dimethylamino)methyl]p-methoxybenzyl]cyclohexanol, is a bicyclic compound with antidepressant properties affecting neurotransmitters within the brain. These neurotransmitters, can for example be serotonin, dopamine, and norepinephrine. Neurotransmitters are manufactured and released by nerve cells. The neurotransmitters migrate to neighboring nerve cells and cause the cells to become more or less active. It is believed that an imbalance in these neurotransmitters is the cause of depression and also may play a role in anxiety. Venlafaxine is believed to work by inhibiting the release or affecting the action of these neurotransmitters.

Venlafaxine is chemically unrelated to other antidepressants, but is sometimes categorized as a serotonin-norepinephrine reuptake inhibitor (SNRI). At low dosages, venlafaxine blocks serotonin reuptake, similarly to a selective serotonin reuptake inhibitor (SSRI). At medium dosages, venlafaxine blocks the reuptake of norepinephrine as well as serotonin. At high dosages, venlafaxine blocks the reuptake of norepinephrine, serotonin and is also a weak blocker of the reuptake of dopamine. Unfortunately, current formulations of venlafaxine do not allow higher doses associated with this dual mechanism of action.

Venlafaxine is well absorbed after oral administration and its metabolism has been well documented. Following absorption, venlafaxine undergoes extensive pre-systemic metabolism in the liver, primarily to O-desmethylvenlafaxine (ODV), but also to N-desmethylvenlafaxine (NDV), N,O-didesmethylvenlafaxine (DDV), and N,N,O-tridesmethylvenlafaxine (TDV). In vitro studies indicate that the formation of ODV is catalyzed by CYP2D6; this has been confirmed in a clinical study showing that patients with low CYP2D6 levels ("poor metabolizers") had increased levels of venlafaxine and reduced levels of ODV compared to people with normal levels of CYP2D6 ("extensive metabolizers"). The differences between CYP2D6 poor and extensive metabolizers, however, are not expected to be clinically important because the sum of venlafaxine and ODV is similar in the two groups and venlafaxine and ODV are pharmacologically approximately equiactive and equipotent.

Approximately 87% of a venlafaxine dose is recovered in the urine within 48 hours as unchanged venlafaxine (5%), unconjugated ODV (29%), conjugated ODV (26%), or other minor active metabolites (27%). Renal elimination of venlafaxine and its metabolites is the primary route of excretion. The metabolic pathway of venlafaxine can be summarized as follows: Venlafaxine's elimination half-life of about 4 hours is short, and its active metabolite has a half-life of about 8 hours. This results in venlafaxine needing to be administered twice daily and a lack of patient compliance in keeping to this daily dosing schedule has the potential to produce discontinuation problems. Unfortunately, sudden discontinuation of venlafaxine can result in withdrawal symptoms, which can include, fatigue, dizziness, nausea, headache and dysphoria. It has been found recently that delaying the sustained release of a drug such as venlafaxine may have therapeutic benefits. Accordingly, it is desirable that venlafaxine be formulated in a delayed controlled-release oral formulation.

Venlafaxine, as its hydrochloride salt, is available as a second-generation extended-release tablet and is marketed under the brand name Effexor® XR for once daily use. Such a formulation has eliminated the discontinuation problems seen with instant release Effexor®, the first-generation immediate-release form of venlafaxine, which is usually administered twice daily. Extended-release formulations of venlafaxine have been described in the prior art. U.S. Pat. Nos. 6,274,171, 6,403,120, and 6,419,958, for example, disclose formulations comprising a therapeutically effective amount of venlafaxine hydrochloride in film-coated spheroids. The spheroids comprise a core having venlafaxine hydrochloride, microcrystalline cellulose, and optionally hydroxypropylmethylcellulose.

The cores are coated with a mixture of ethylcellulose and hydroxypropylmethylcellulose and subsequently packaged into hard gelatin capsules. These patents also describe and claim methods and compositions for obtaining therapeutic blood plasma concentrations of venlafaxine over a twenty-four hour period with diminished incidence of nausea and emesis which comprise administering orally to a patient in need thereof, an extended-release formulation providing a peak blood plasma level of venlafaxine of no more than about 150 ng/ml 4-8 hours after administration. U.S. Pat. No. 6,703,044 apparently teaches a formulation wherein a delayed-burst release of venlafaxine is achieved at least three hours after administration resulting in dispersion of the venlafaxine mainly through the colon into the blood stream as a result of colon absorption over a period of at least 24 hours. A compressed core comprising a burst controlling agent as well as a disintegrant characterizes the formulation. The core is coated with a relatively rigid water insoluble, hydrophobic polymer, in which particles of water insoluble but hydrophilic material are embedded. These particles form channels upon contact with aqueous medium, which imbibe liquid and cause the burst-controlling agent to burst the coating thereby enabling

the delayed-burst release of the venlafaxine. The '044 patent apparently also teaches that the formulation provides for a 30% higher bioavailability of the venlafaxine in fasting volunteers when compared to extended-release formulations of venlafaxine presently available on the market.

5 The label for Effexor® XR, on the other hand, states that: "Effexor XR should be administered in a single dose with food either in the morning or evening at approximately the same time each day". It is thought that taking the formulation under fed conditions will reduce nausea and emesis that is a problematic side effect of this current formulation. The only pharmacokinetic study presented in the patent, does not show any bioavailability data in fed
10 volunteers, and hence it is not known whether the formulation taught in the '044 patent will also provide for a higher bioavailability when administered to patients under the conditions recommended by the Effexor® XR label, i.e. under fed conditions. It is desirable that an extended release formulation be available that delays the initial release of a controlled release regimen so that it may be administered to patients under fed or fasting conditions..

15 Venlafaxine is currently among the top five prescribed antidepressant medications within the SSRI/SNRI category of antidepressants. However, only one once-a-day oral dosage form comprising venlafaxine hydrochloride is currently being marketed under the trade name Effexor® XR. Unfortunately, despite claims of a lower incident of nausea and emesis, it has been reported that this once a day formulation has a tendency to cause nausea and emesis by its
20 release within the stomach.

SUMMARY OF THE INVENTION

The present disclosure relates to a modified delayed sustained release formulation of at least one pharmaceutical acceptable form of venlafaxine. According to the disclosure the modified delayed release composition of venlafaxine is provided by a blend of polymers in a core formulation. This core formulation having extended release polymers is coated with a non-permeable polymer blend comprising a water in-soluble polymer and an enteric coating polymer that does not disintegrate substantially in either acid or base mediums for up to about 4 hours. Upon disintegration of the non-permeable coating the active drug is released in a sustained manner due to the extended release polymers within the core formulation.

In one illustrative embodiment the sustained release core tablet is made up of an active pharmaceutical compound, which in a first illustrative embodiment is venlafaxine hydrochloride, and an extended release polymer such as ethyl cellulose, hydroxyl methyl cellulose, mixtures thereof or the like, which retard the release of the active pharmaceutical once the non-permeable polymeric delayed release coating according to the disclosure has disintegrated. It is contemplated within the scope of the disclosure that these extended release polymers can be used alone or in combination with at least one other polymer. It is also contemplated that the core formulation containing these extended release polymers can be used with other therapeutic agents or combinations of therapeutic agents other than venlafaxine.

The delayed release coating according to the disclosure is provided by a innovative polymer blend of a water insoluble polymer and an enteric coating polymer. The polymeric coating blend according to the disclosure is substantially non-permeable to either acid or alkaline conditions for at least up to about 4 hours. Approximately 4 hours after ingestion the non-permeable coating disintegrates and the sustained released core releases the active

pharmaceutical in a controlled extended manner. According to the disclosure this delayed sustained release formulation prevents nausea and emesis by not releasing any substantial amount of drug into the stomach thereby preventing nausea and emesis associated with current formulations.

5 The non-permeable coating membrane is made of a water in-soluble polymer such as but not limited to ethyl cellulose, cellulose acetate, methacrylates, mixtures thereof or the like. The enteric coating polymers include but are not limited to cellulose acetate phalate, hydroxypropyl methyl cellulose phalate, methacrylic acid phalate, mixtures thereof or the like. It is contemplated within the disclosure that other water in-soluble polymers known in the art may be
10 used alone or in mixtures thereof.

In a first illustrative embodiment the non-permeable coating formulation according to the disclosure is about 45% by weight ethyl cellulose, 55% by weight enteric coating and a plasticizer. In a further illustrative embodiment the coating formulation according to the invention is a blend of about 48% of ethyl cellulose and cellulose acetate, enteric coating of
15 about 52% and a plasticizer. In yet a further illustrative embodiment the coating formulation according to the invention is a blend of about 46% of ethyl cellulose and cellulose acetate, enteric coating of about 54% and a plasticizer.

According to the disclosure an object of the innovative formulation is that the extended release manner of the active pharmaceutical is substantially provided by the extended release
20 polymers within the core formulation.

According to the disclosure an object of the innovative formulation is that the core formulation is coated with a polymer blend forming a non-permeable coating according to the disclosure that is stable in both acid and alkaline environments for up to about 4 hours. The

combination of the non-permeable coating with the extended release core formulation allows peak plasma levels of the active pharmaceutical up to about 8-12 hours after ingestion and prevents substantial release of the active pharmaceutical within the stomach.

According to the disclosure an object of the innovative formulation is that the extended
5 release manner of the active pharmaceutical is provided within a core that further comprises at least one filler selected from the group consisting of lactose monohydrate, anhydrous lactose, mannitol, sorbitol, microcrystalline cellulose, dibasic calcium, calcium sulfate and mixtures thereof. The at least one filler comprises up to about 85% by weight of the core dry weight. In one illustrative embodiment the filler is lactose monohydrate, and comprises by weight about 5-
10 35% by weight of the core dry weight.

According to the disclosure an object of the innovative formulation is that the extended release manner of the active pharmaceutical is provided within a compressed core that further comprises at least one pharmaceutically acceptable lubricant selected from the group consisting of magnesium stearate, talc, stearic acid, sodium stearyl fumarate, calcium stearate, vegetable oil,
15 silica gel, colloidal silicon dioxide, and mixtures thereof. The at least one lubricant comprises from about 0.02 to about 10%, preferably from about 0.5 to about 5%, more preferably from about 0.5 to about 2% by weight of the core dry weight. The lubricant in one illustrative embodiment is magnesium stearate and comprises about 0.75% of the core dry weight.

It is a further object of the disclosure that the compressed core tablet formulation allows
20 for higher doses of the active pharmaceutical and in the case of venlafaxine allows up to about 300mg within a single tablet.

It is yet a further object of the invention that a tablet containing higher dose of venlafaxine enables greater patient compliance and greater efficacy as it is thought that the dual mechanism of action is only present within higher dosage forms.

According to the disclosure an object of the innovative formulation is that the active
5 pharmaceutical is a pharmaceutically acceptable salt of venlafaxine selected from the group consisting of venlafaxine hydrochloride, venlafaxine besylate, venlafaxine maleate, and venlafaxine fumarate.

According to the disclosure an object of the innovative formulation is that the extended
release manner of the active pharmaceutical is provided within a core having an extended release
10 polymer that further comprises at least one pharmaceutically acceptable binder selected from the group consisting of hydroxypropylmethylcellulose, hydroxypropylcellulose, polyethylene oxide, polyvinylpyrrolidone, copovidone, carbomers, carrageen, polyvinylalcohol and mixtures thereof. It is preferable that the at least one binding agent comprises by weight from about 10 to about 80%, preferably from about 10 to about 40% by weight of the core dry weight. The at
15 least one binding agent in one illustrative embodiment comprises a mixture of at least two binding agents, most preferably hydroxypropylmethylcellulose (13%) and polyvinylpyrrolidone (8%). In a further illustrative embodiment the binding agent is copovidone.

In yet a further illustrative embodiment the active agent is double granulated with a first granulation with a binding agent such as Povidone K-30 and then a further granulation with a
20 binding agent such as Surelease® Clear e-7-19040 (Colorcon, West Point, PA). The double granulation improves compressibility and minimizes hygroscopicity.

According to the disclosure an object of the innovative formulation is that the extended release manner of the active pharmaceutical is provided within a core coated by a non-permeable

membrane coating that is made of a water insoluble polymers such as but not limited to ethyl cellulose, cellulose acetate, methacrylates or the like. The enteric coating polymers include but are not limited to cellulose acetate phalate, hydroxypropyl methyl cellulose phalate, methacrylic acid phalate, mixtures thereof or the like. The non-permeable membrane according to the
5 disclosure has at least one plasticizer that is selected from the group consisting of citrate esters, dibutyl sebacate, dibutyl pthalate, triacetin, castor oil, polyalkyleneglycol, fatty acids, and combinations thereof or the like. In one illustrative embodiment the at least one plasticizer is stearic acid and comprises by weight from about 10 to about 15% of the coating weight.

According to the disclosure an object of the innovative formulation is that the extended
10 release manner of the active pharmaceutical is provided so that the T_{max} of the composition of the disclosure compared to the reference product for venlafaxine is delayed by about 4 hours when the composition is administered under fed or fasting conditions.

According to the disclosure an object of the innovative formulation is that the extended release manner of the active pharmaceutical is provided so that the absorption delayed controlled
15 release pharmaceutical composition for oral administration according to the disclosure is suitable for once daily dosing comprises: a) a core comprising at least one form of venlafaxine selected from the group consisting of venlafaxine, a pharmaceutically acceptable salt of venlafaxine, an active metabolite of venlafaxine, a pharmaceutically acceptable salt of an active metabolite of venlafaxine, and combinations thereof, and pharmaceutically acceptable excipient; at least one
20 extended release polymer and b) a non permeable coating substantially surrounding said core, said non-permeable coating comprising a water-insoluble water-permeable film-forming polymer and an enteric coating polymer that is non-permeable to either acid or alkaline conditions for at least up to 4 hours said non-permeable coating further comprising a plasticizer, wherein said

non-permeable composition provides delayed controlled release of said at least one form of venlafaxine such that the geometric mean ratio of the composition of the invention to the reference product for the AUC_{0-t} and/or the C_{max} for O-desmethylvenlafaxine is greater than 2 after first administration under fed or fasting conditions.

5 According to the disclosure a further object of the innovative formulation is that the extended release manner of the active pharmaceutical is provided so that the absorption delayed controlled release pharmaceutical composition for oral administration according to the disclosure is dose proportional for 150mg, 225mg, 300mg and 450mg doses.

10 **BRIEF DESCRIPTION OF THE DRAWINGS**

These and other advantages, objects and features of the invention will be apparent through the detailed description of the embodiments and the drawings attached hereto. It is also to be understood that both the foregoing general description and the following detailed description are exemplary and not restrictive of the scope of the invention.

15 Fig. 1 is a graphic depiction of cumulative dissolution profile comparison of venlafaxine HCl 75, 150, 225 and 300mg tablets according to the invention; and

Fig. 2 is a graphic depiction of cumulative dissolution profile comparison of venlafaxine HCl 150, tablets according to the invention with the referenced brand product.

20 **DETAILED DESCRIPTION**

Compressibility within drug manufacturing is a problem, which not only affects the processing characteristics and machinability of a drug blend but also affects the final compressed tablet form. When a drug, such as venlafaxine, which is poorly compressible and hygroscopic, is

manufactured special precautions have to be taken to compress such drugs such as maintaining the relative humidity value below about 50% RH during manufacturing and packaging.

It has been surprisingly found that granulating venlafaxine essentially with a binder either in a dry or wet granulation process prior to incorporating in a controlled release matrix increases
5 the compressibility considerably over compositions made using the teachings of prior art. The corresponding increase of hardness values and decrease of friability demonstrated these benefits. More surprising it has been found that the addition of the same concentration of binder to venlafaxine blend including extended release materials and granulating it together, again resulted in poorly compressible granules thereby highlighting the need for essentially granulating
10 venlafaxine with a suitable binder.

According to the present disclosure venlafaxine is pre-granulated with a binder using either a dry or wet process and it is only mixed with the rate controlling polymers. As the polymers may or may not be wetted and remain in dry state, their performance is maximized and hence they can be employed in lower quantities and yet obtain desired dissolution profiles.

15 In another illustrative embodiment according to the disclosure, it has been surprisingly found that a multi step granulation of an active ingredient such as venlafaxine improves compressibility and minimizes hygroscopicity. According to the disclosure, venlafaxine is granulated with a binder such as povidone k-30 and then further granulated with an aqueous ethylcellulose dispersion such as Surelease®, clear E-7-19040 (Colorcon, West Point, PA). It is
20 contemplated within the scope of the disclosure that other binders can be used to achieve this multi-step granulation. It is further contemplated within the scope of the disclosure that one or more additional granulation steps can be undertaken and that other active ingredients can benefit from this multi-step granulation process.

Tablets formulated according to the invention have been found to have a tablet weight reduction and size of at least 20% over marketed formulation allowing for tablets formulations having higher dosage strength. This is an important advantage in improving patient compliance. Moreover due to the reduced weight it is also possible to make dose weight proportionate tablets
5 for the varying strengths of venlafaxine tablets. Those skilled in the art in commercial pharmaceutical production will appreciate the advantages obtained by having dose weight proportionate formulations since such formulations dramatically reduce the operation costs and labor involved in manufacturing separate dose dependent blends.

Compositions of the present invention comprising venlafaxine granules essentially bound
10 with about 0.1% to about 10% binder, preferably about 0.2% to about 5% binder and most preferably about 0.25% to about 4.5% binder and dispersed in a rate-controlling matrix of hydrophilic polymers are explained hereunder in greater detail with respect to individual components and their working ranges.

According to the disclosure the various pharmaceutically acceptable salts of venlafaxine
15 may be used, in one illustrative embodiment the preferred salt form having high water solubility for use herein is venlafaxine hydrochloride, other pharmaceutically salt forms such as venlafaxine fumarate, and venlafaxine succinate are contemplated. It is also contemplated within the scope of the invention that other pharmaceutical compounds having like characteristics can be formulated into extended release dosages by using the compositional techniques of the present
20 invention. It is further contemplated within the scope of the invention that where desired, venlafaxine or a salt thereof may be used in combination with another anti-depressant agent or other pharmaceutical therapeutic class, which may be administered orally in the same dosage

form in accordance with the present invention. It is also contemplated that venlafaxine or a salt thereof may be incorporated in the composition from about 10mg to about 600mg.

The present composition according to the invention is essentially comprised of one or more binders in an amount within the range of from about 0.1% to about 10% binder, preferably about 0.2% to about 5% binder and most preferably about 0.25% to about 4.5% binder by weight of the composition. Binders usually are low viscosity polymers or non-polymeric materials and therefore they do not extend the release of a drug. Although binders improve appearance, hardness & friability of the preparation they are usually not intended to influence the disintegration or dissolution roles of active substance.

Binders which are suitable for use herein include but are not limited to copovidone which is manufactured by free-radical polymerization of 6 parts of vinylpyrrolidone and 4 parts of vinyl acetate in isopropanol. Copovidone is a white or yellowish-white spray-dried powder that has a relatively fine particle size and good flow properties. It has a typical slight odor and a faint taste in aqueous solutions. Because of the ratio of vinylpyrrolidone to vinyl acetate in copovidone, it is almost as universally soluble as polyvinyl pyrrolidone. It dissolves in extremely hydrophilic liquids such as water as well as in more hydrophobic solvents such as butanol. Copovidone has a molecular weight ranging from about 45000 to about 70000 and is available commercially in different grades and trade names such as Kollidon VA 64.

It is contemplated within the scope of the invention that other binders such as polyvinyl pyrrolidone (PVP) with a molecular weight ranging from about 4000 to about 1500000 and preferably about 30,000-1500000 can be used as a binder. Polyvinylpyrrolidone is available in different grades based on K-value and molecular weights such as polyvinyl pyrrolidone with K value of 24-26, 29-32 or 85-95. Preferably polyvinyl pyrrolidone with K value 85-95 (Plasdone

K-90/D®, Kollidon 90F®) can be used in the present invention having high molecular weight (1,000,000-1,500,000) and greater binding capacity. More preferably polyvinyl pyrrolidone with a K value of 30 is contemplated in the scope of this disclosure.

It is also contemplated that other binders can be used such as but not limited to an aqueous ethylcellulose dispersion such as Surelease®, clear E-7-19040 (Colorcon, West Point, PA), hydroxypropyl methyl cellulose, hydroxypropyl cellulose, hydroxy ethyl cellulose, polyvinyl alcohol, sodium carboxy methyl cellulose, starches such as corn starch, modified corn starch, sugars, gum acacia and the like.

Venlafaxine hydrochloride granules prepared with copovidone (copolyvidone, Kollidon VA 64) have been found to have good compressibility. Venlafaxine hydrochloride is essentially granulated with suitable binders, the binder concentration ranging from about 0.1% to about 10% binder, preferably about 0.2% to about 5% binder and most preferably about 0.25% to about 4.5% binder. Although concentrations above 4% can give also give binding effect, there is no substantial increase in binding hence higher concentrations are not employed or necessary.

The solvent used with the binder for granulation is preferably water. It is contemplated that other solvents such as isopropyl alcohol or the like can also be employed. Venlafaxine hydrochloride granules so formed are uniformly dispersed in a controlled release matrix comprising of rate controlling polymers.

"Controlled-release" as used herein to describe a method and composition for making an active ingredient available to the biological system of a host. A controlled release preparation according to the present invention is one that achieves slow release of a drug over an extended period of time, thereby extending the duration of drug action over that achieved by conventional delivery. This admixture is typically compressed under pressure to produce a tablet. Drug is

released from this tablet by diffusion and erosion. For drugs of relatively high solubility, the preferred polymeric matrices are those with a relatively high molecular weight. With such systems, release of the drug is achieved by allowing the gastric fluid to diffuse into the matrix where fluid dissolves the matrix-held drug and then diffuses outward while the matrix retains its integrity, or disintegrates at a rate that is considerably slower than the rate at which the drug is dissolved from matrix. Controlled release is thus achieved by the integrity of the matrix and the need for the gastric fluid to diffuse into the matrix to reach the drug.

Preferred polymers for the controlled release system of high solubility drug of the present invention are those which ensure rapid hydration of the polymer matrix to minimize variable and significant burst of drug, yet effectively control the release of drug being liberated from the discrete particles or drug granules. The hydrophilic water-soluble polymers may be used individually or in combination. Examples of polymers suitable for this invention include the polymers well known in the pharmaceutical art for their release retarding properties and may be selected from the group comprising acrylic polymers such as available as Eudragit RS, Eudragit RL, natural gums as xanthan gum, karaya gum, locust bean gum, guar gum, gelatin gum, gum arabic, tragacanth, carrageenan, pectin, carboxymethyl cellulose (CMC) agar, alginic acid, sodium alginate polyvinylpyrrolidone, hydroxypropylcellulose, hydroxypropylmethyl cellulose, methyl cellulose, vinyl acetate copolymers, polyethylene oxide, methacrylic acid copolymers, maleic anhydride/methyl vinyl ether copolymers and derivatives and mixtures thereof.

Preferred polymers with appropriate hydration characteristics include hydroxypropylmethylcellulose 2208 USP (hydroxypropylmethylcellulose with a methoxyl content of 19-24% and a hydroxypropyl content of 7-12%), viscosity grades ranging from about 4000 to about 100,000cps and hydroxypropylmethylcellulose 2910 USP

(hydroxypropylmethylcellulose with a methoxyl content of 28-30% and a hydroxypropyl content of 7-12%), viscosity grades ranging from about 3 to about 150 cps. Another preferred polymer is sodium carboxy methylcellulose having viscosity of about 2000-50000 cps.

The amount of polymer relative to the drug may vary depending on the release rate
5 desired, nature of the polymers and their physicochemical characteristics. The amount of the polymer in the dosage form generally varies from about 10% to about 50% by weight of the composition. Preferably, the amount of polymers varies from about 15% to about 45% by weight of the dosage form. The polymer concentration can be reduced as they are utilized optimally due to their incorporation in dry form.

10 Additional excipients that are although not essential for the present invention, are required for the tableting process as known to those skilled in art, and may be suitably included.

The composition of the invention therefore typically includes pharmaceutically acceptable excipients. As is well known to those skilled in the art, pharmaceutical excipients are routinely incorporated into solid dosage forms. This is done to ease the manufacturing process
15 as well as to improve the performance of the dosage form. Common excipients include diluents, lubricants, granulating aids, colorants, flavorants, surfactants, pH adjusters, anti-adherents and gildants etc. Such excipients are routinely used in the dosage forms of this invention.

The present invention may additionally include one or more fillers or excipients in an amount within the range of from about 0 to about 90% by weight and preferably from about 1 to
20 about 80% by weight such as lactose, sugar, corn starch, modified corn starch, mannitol, sorbitol, inorganic salts such as calcium carbonate and/or cellulose derivatives such as wood cellulose and microcrystalline cellulose.

As the composition is in the form of a tablet, it may include one or more tableting lubricants in an amount within the range of from about 0.2 to about 8% and preferably from about 0.5 to about 2% by weight of the composition, such as magnesium stearate, stearic acid, palmitic acid, calcium stearate, talc, polyethylene glycol, colloidal silicon dioxide, sodium stearyl fumarate, carnauba wax and the like and mixtures thereof. Other conventional pharmaceutical ingredients, which may optionally be present, include preservatives, stabilizers, and FD &C colors etc.

The composition made according to the present invention may be formulated as tablets within a capsule or a tablet. Most preferably, the composition is a tablet. The tablet may optionally be coated with a thin layer of a film forming polymer or a pharmaceutical excipient. In one illustrative embodiment according to the disclosure, the controlled release core formulation according to the invention is coated using a non-permeable film coating comprising a water insoluble polymer and an enteric coating polymer. The non-permeable film coating is non-permeable to either acid or alkaline conditions for at least up to 4 hours. Without being bound to any particular theory, it is thought that the film coating influence the release properties of the tablet core. According to the disclosure upon disintegration of the non-permeable membrane the sustained release core releases the active pharmaceutical. In one illustrative embodiment the active pharmaceutical is venlafaxine hydrochloride.

The delayed controlled release formulation according to the disclosure can be prepared in accordance with the following method of the invention. A mixture essentially of venlafaxine hydrochloride and a suitable binder such as copovidone is granulated with a suitable solvent such as water to produce substantially uniform granules. The granules are then dried and passed through a 1.5 to 2 mm aperture screen to break down agglomerates. The resulting dry drug

granules are blended with one or more hydrophilic polymers. The resulting mix may then be coated within a non-permeable coating or optionally be mixed with diluents or fillers and finally may be lubricated with lubricant before pressing into tablets and then coated with a non-permeable coating.

5 In a further illustrative embodiment venlafaxine hydrochloride is granulated with providone K-30 dissolved in purified water and then further granulated with Surelease, clear E-7-19040. The resulting drug granules are blended with one or more hydrophilic polymers. The resulting mix may then be coated within a non-permeable coating or optionally be mixed with diluents or fillers and finally may be lubricated with lubricant before pressing into tablets and
10 then coated with a non-permeable coating.

The dosage form of present invention is a solid dosage form, preferably a tablet, which may vary in shape such as oval, triangle, almond, peanut, parallelogram, pentagonal, hexagonal, trapezoidal. The preferred shapes are oval and parallelogram forms.

A controlled release preparation according to the present invention is one that achieves
15 slow release of a drug over an extended period of time, thereby extending the duration of drug action over that achieved by conventional delivery. Preferably, such a preparation maintains a drug concentration in the blood within the therapeutic range for up to 12 hours or more.

Examples

The following examples are presented in order to further illustrate the disclosure. These
20 examples should not be construed in any manner to limit the invention.

Example I

The following example provides a summary of the experimental work culminating in the formulation of the present invention.

Venlafaxine hydrochloride was sifted through a sieve no. #10. The sifted material was granulated with providone K-30 dissolved in purified water and further coated using Surelease®, clear E-7-19040 in a fluid bed processor. The coated granules were sifted through a sieve No. #16. The sifted granules were blended with the following excipients: Methocel K 100 M premium, Methocel K 4 M premium, Pharmatose DCL 15 and magnesium stearate. The resulting blend was compressed into core tablets as follows:

75mg strength: 11mm normal concave punches, plain on both sides; and 150mg strength: 13.5 x 8.2mm oval punches, plain on both sides.

A coating solution was prepared by adding ethylcellulose to acetone under stirring. Hypromellose phthalate was added and the solution was continued to be stirred. Purified water was added and the solution was continued to be stirred. Diethyl phthalate was added and the solution was continued to be stirred until a uniform coating solution was formed. The core tablets were coated with the uniform coating solution. The approximate amounts of the various ingredients are summarized in table 1 below.

Table 1

Coating of Active		(150mg) (225mg) & (300mg)	(75mg)
Sr. No.	Ingredients	Mg/tab	Mg/tab
1.	Venlafaxine HCl	169.5	
2.	Povidone K 30	4.30	
3.	Surelease, clear E-7-19040	25.7	
Matrix tablets:			
4.	Venlafaxine HCl granules	202.72	101.36
5.	Methocel K 100 M premium	127.28	194.64
6.	Methocel K 4 M premium	34.00	50.00
7.	Pharmatose DCL 15	34.00	50.00
8.	Magnesium stearate	4.00	4.00
	Core tablet weight	400mg (150mg eq.) 600mg (225mg eq.) 800mg (300mg eq.)	400mg (75mg eq.)
Coating			

9.	Core tablets		
10.	Ethycellulose (Ethocel 10 cP std. premium)	20.80	10.40
11.	Hypromellose phthalate	23.66	11.83
12.	Acetone	q.s	q.s
13.	Purified water	q.s	q.s
14.	Diethyl phthalate	7.54	3.77
	Coated tablet weight	452mg (150mg eq.) 678mg (225mg eq.) 904mg (300mg eq.)	452mg (75mg eq.)

Example II

Table 2 below summarizes the approximate weight of ingredients of the individual tablets and the percentage of the weight of the coating in relation to the total tablet weight.

5 **Table 2**

Formulation	TABLETS		
	150mg	225mg (mg/tablet)	300mg
Venlafaxine HCl granules	202.72	304.308	405.44
Methocel K 100 M	127.04	190.92	254.56
Methocel K 4 M	34.00	51.00	68.00
Pharmatose DCL 15	34.00	51.00	68.00
Reg Stearate	4.0	6.00	8.00
Core tablet weights	401.96	603.00	804.00
Coated Tablet Weight			
Coating	452	678	904
Ethylcellulose	20.80	31.20	41.60
Hypromellose phthalate	23.66	35.49	47.32
Acetone	q.s	q.s	q.s
Purified water	q.s	q.s	q.s
Diethyl phthalate	7.54	11.31	15.08
	52.00	78.00	104.00
Coating weight percentage %	11.5%	11.5%	11.5%

Example III

Table 3 below summarizes the percent weight of ingredients of the individual tablets.

Table 3

Formulation 2	In % of the total tablet weight (coated tablet)	
	150/225/300mg	75mg
Venlafaxine HCl granules	44.85%	22.42%
Methocel K 100 M	28.16%	43.06%
Methocel K 4 M	7.00%	11.06%
Pharmatoze DCL 15	7.00%	11.06%
Reg Stearate	0.88%	0.88%
Ethylcellulose	4.6%	2.3%
Hypromellose phthalate	5.23%	2.62%
Acetone	--	
Purified water	--	
Diethyl phthalate	1.66%	0.83%
	Core tablet 400mg	
	Coated tablet 452mg	
		11.5% coating

Example IV

The delayed controlled release tablets prepared in accordance with the examples above
 5 exhibited the following dissolution profile when tested in an acid medium. These dissolution
 results are summarized in Table 4 as follows:

Table 4

Time (hrs)	Percent Released
0-2	Less than 15%
2-4	Less than 20%
4-6	10-55%
10-12	40-85%
16	Greater than 70%

In accordance with another embodiment of the invention, a therapeutic substance or a
 10 drug can be incorporated into the polymeric core. The therapeutic substance can include any
 substance capable of exerting a therapeutic or prophylactic effect for the patient. For example,

the therapeutic substance can be for inhibiting the activity of vascular smooth muscle cells. The substance can be directed at inhibiting abnormal or inappropriate migration and/or proliferation of smooth muscle cells to inhibit restenosis. The drug may include small molecule drugs, peptides, proteins, oligonucleotides, or double-stranded DNA.

5 Examples of therapeutic substances include aspirin, topiramate and quetiapine fumarate. The substance can also fall under the genus of *antineoplastic*, anti-inflammatory, antiplatelet, anticoagulant, antifibrin, antithrombin, antimitotic, *antibiotic*, antiallergic and antioxidant substances. Examples of antineoplastics and/or antimitotics include paclitaxel, docetaxel, methotrexate, azathioprine, vincristine, vinblastine, fluorouracil, doxorubicin hydrochloride, and
10 mitomycin. Examples of antiplatelets, anticoagulants, antifibrin, and antithrombins include sodium heparin, low molecular weight heparins, heparinoids, hirudin, argatroban, forskolin, vapiprost, prostacyclin and prostacyclin analogues, dextran, D-phe-pro-arg-chloromethylketone (synthetic antithrombin), dipyridamole, glycoprotein IIb/IIIa platelet membrane receptor antagonist antibody, recombinant hirudin, and thrombin. Examples of cytostatic or
15 antiproliferative agents include angiopeptin, angiotensin converting enzyme inhibitors such as captopril, cilazapril or lisinopril, calcium channel blockers (such as nifedipine), colchicine, fibroblast growth factor (FGF) antagonists, fish oil (.omega.-3- fatty acid), histamine antagonists, lovastatin (an inhibitor of HMG-CoA reductase, a cholesterol lowering drug), monoclonal antibodies (such as those specific for Platelet-Derived Growth Factor (PDGF) receptors),
20 nitroprusside, phosphodiesterase inhibitors, prostaglandin inhibitors, suramin, serotonin blockers, steroids, thioprotease inhibitors, triazolopyrimidine (a PDGF antagonist), and nitric oxide. An example of an antiallergic agent is permirolast potassium.

Other therapeutic substances or agents which may be appropriate include alpha-interferon genetically engineered epithelial, endothelial, vascular smooth muscle cells, or other cells; cell cycle inhibitors such as rapamycin and its derivatives and analogs, and flavopiridol; the estrogen receptors such as estrogen, estrogen analogs, tamoxifen, and idoxifene; the retinoid receptors, such as retinal and retinoic acid; the PPAR alpha and gamma receptors such as troglitazone, rosiglitazone and pioglitazone; inhibitors of cell signaling including inhibitors of Ras and the MAP kinase cascade; inhibitors of receptor tyrosine kinases; *steroid* receptors such as clobetasol, dexamethasone, and derivatives or analogs thereof.

Although the illustrative embodiments according to the disclosure, disclose the delayed controlled release formulation having venlafaxine as an active ingredient it will be understood by those skilled in the art that the delayed controlled release formulation may be used for any active pharmaceutical, where it is desirable to delay the release of an extended release formulation.

Preferably, the active pharmaceutical is chosen from one or more of the following categories/groups: abortifacient/interceptive, ace-inhibitor, .alpha.-adrenergic agonist, .beta.-adrenergic agonist, .alpha.-adrenergic blocker, .beta.-adrenergic blocker, adrenocortical *steroid*, adrenocortical suppressant, adrenocorticotrophic hormone, alcohol deterrent, aldose reductase inhibitor, aldosterone antagonist, 5-alpha reductase inhibitor, anabolic, analeptic, analgesic, androgen, angiotensin converting enzyme inhibitor, angiotensin II receptor antagonist, anorexic, antacid, anthelmintic, antiacne, antiallergic, antialopecia agent, antiamebic, antiandrogen, antianginal, antiarrhythmic, antiarteriosclerotic, antiarthritic/antirheumatic, antiasthmatic, antibacterial, antibacterial adjuncts, *antibiotic*, anticancer, anticholelithogenic, anticholesteremic, anticholinergic, anticoagulant, anticonvulsant, antidepressant, antidiabetic, antidiarrheal, antidiuretic, antidote, antidyskinetic, antieczematic, antiemetic, antiepileptic, antiestrogen,

antifibrotic, antiflatulent, antifungal, antiglaucoma, antigonadotropin, antigout, antihemorrhagic, antihistaminic, antihypercholesterolemic, antihyperlipidemic, antihyperlipoproteinemic, antihyperphosphatemic, antihypertensive, antihyperthyroid, antihypotensive, antihypothyroid, anti-infective, anti-inflammatory, antileprotic, antileukemic, antilipemic, antimalarial, antimanic, 5 antimethemoglobinemic, antimigraine, antimycotic, antinauseant, **antineoplastic, antineoplastic** adjunct, antineutropenic, antiosteoporotic, antipagetic, antiparkinsonian, antiperistaltic, antipheochromocytoma, antipneumocystis, antiprostatic hypertrophy, antiprotozoal, antipruritic, antipsoriatic, antipsychotic, antipyretic, antirheumatic, antirickettsial, antiseborrheic, antiseptic/disinfectant, antispasmodic, antisiphilitic, antithrombocythemtic, antithrombotic, 10 antitubercular, antitumor, antitussive, antiulcerative, antiurolithic, antivenin, antivertigo, antiviral, anxiolytic, aromatase inhibitors, astringent, benzodiazepine antagonist, beta-blocker, bone resorption inhibitor, bradycardic agent, bradykinin antagonist, bronchodilator, calcium channel blocker, calcium regulator, calcium supplement, cancer chemotherapy, capillary protectant, carbonic anhydrase inhibitor, cardiac depressant, cardiotonic, cathartic, CCK 15 antagonist, central stimulant, cerebral vasodilator, chelating agent, cholecystokinin antagonist, cholelitholytic agent, choleretic, cholinergic, cholinesterase inhibitor, cholinesterase reactivator, CNS stimulant, cognition activator, contraceptive, control of intraocular pressure, converting enzyme inhibitor, coronary vasodilator, cytoprotectant, debriding agent, decongestant, depigmentor, dermatitis herpetiformis suppressant, diagnostic aid, digestive aid, diuretic, 20 dopamine receptor agonist, dopamine receptor antagonist, ectoparasiticide, emetic, enkephalinase inhibitor, enzyme, enzyme cofactor, enzyme inducer, estrogen, estrogen antagonist, expectorant, fibrinogen receptor antagonist, gastric and pancreatic secretion stimulant, gastric proton pump inhibitor, gastric secretion inhibitor, gastroprokinetic,

glucocorticoid, .alpha.-glucosidase inhibitor, gonad-stimulating principle, gout suppressant, growth hormone inhibitor, growth hormone releasing factor, growth stimulant, hematinic, hematopoietic, hemolytic, hemostatic, heparin antagonist, hepatoprotectant, histamine H.sub.1 -receptor antagonist, histamine H.sub.2 -receptor antagonist, HIV proteinase inhibitor, HMG CoA

5 reductase inhibitor, hypnotic, hypocholesteremic, hypolipidemic, hypotensive, immunomodulator, immunosuppressant, intropic agent, insulin sensitizer, ion exchange resin, keratolytic, lactation stimulating hormone, laxative/cathartic, leukotriene antagonist, LH-RH agonist, lipotropic, 5-lipoxygenase inhibitor, lupus erythematosus suppressant, major tranquilizer, matrix metalloproteinase inhibitor, mineralocorticoid, minor tranquilizer, miotic,

10 monoamine oxidase inhibitor, mucolytic, muscle relaxant, mydriatic, narcotic analgesic, narcotic antagonist, nasal decongestant, neuroleptic, neuromuscular blocking agent, neuroprotective, nootropic, nsaid, opioid analgesic, oral contraceptive, ovarian hormone, oxytocic, parasympathomimetic, pediculicide, pepsin inhibitor, peripheral vasodilator, peristaltic stimulant, pigmentation agent, plasma volume expander, potassium channel activator/opener, pressor agent,

15 progestogen, prolactin inhibitor, prostaglandin/prostaglandin analog, protease inhibitor, proton pump inhibitor, pulmonary surfactant, 5.alpha.-reductase inhibitor, replenishers/supplements, respiratory stimulant, retroviral protease inhibitor, reverse transcriptase inhibitor, scabicide, sclerosing agent, sedative/hypnotic, serenic, serotonin noradrenaline reuptake inhibitor, serotonin receptor agonist, serotonin receptor antagonist, serotonin uptake inhibitor, skeletal muscle

20 relaxant, somatostatin analog, spasmolytic, stool softener, succinylcholine synergist, sympathomimetic, thrombolytic, thromboxane A.sub.2 -receptor antagonist, thromboxane A.sub.2 -synthetase inhibitor, thyroid hormone, thyroid inhibitor, thyrotropic hormone, tocolytic, topical protectant, topoisomerase I inhibitor, topoisomerase II inhibitor, tranquilizer, ultraviolet

screen, uricosuric, vasodilator, vasopressor, vasoprotectant, vitamin/vitamin source, vulnerary, Wilson's disease treatment, xanthine oxidase inhibitor.

It will be understood that various modifications may be made to the embodiments and examples disclosed herein. Therefore, the above description and examples should not be
5 construed as limiting, but merely as exemplification of the various embodiments. Those skilled in the art will envision other modifications within the scope and spirit of the claims appended hereto.

What is claimed is:

1. A delayed controlled release composition for oral administration comprising:

a core formulation comprising at least one active pharmaceutical compound and at least one extended release polymer; and

5 a non-permeable coating substantially surrounding said core formulation.

2. The delayed controlled release composition according to claim 1, wherein said active pharmaceutical is selected from the group consisting of a pharmaceutically acceptable salt of venlafaxine, an active metabolite of venlafaxine, a pharmaceutically acceptable salt of an active
10 metabolite of venlafaxine, and combinations thereof.

3. The delayed controlled release composition according to claim 1, wherein said active pharmaceutical is venlafaxine hydrochloride.

15 4. The delayed controlled release composition according to claim 1, wherein said non-permeable coating comprises a water-insoluble polymer and an enteric coating polymer.

5. The delayed controlled release composition according to claim 1, wherein said non-permeable coating is stable in an acid or alkaline medium for up to about 4 hours.

20 6. The delayed controlled release composition according to claim 3, wherein said venlafaxine hydrochloride is contained in a therapeutically effective amount.

7. The delayed controlled release composition according to claim 3, wherein said venlafaxine hydrochloride is between about 10mg to about 450mg.

8. The delayed controlled release composition according to claim 5 wherein said non-permeable coating prevents the substantial release of said venlafaxine in the stomach.

9. The delayed controlled release composition according to claim 8 wherein the prevention of the substantial release of said venlafaxine into the stomach prevents nausea and emesis in a patient.

10

10. A method for preventing nausea and emesis in the dosing of oral pharmaceuticals comprising the steps of :

providing a core formulation comprising at least one active pharmaceutical compound and at least one extended release polymer; and

15 a non-permeable coating substantially surrounding said core formulation said non-permeable coating delaying the release of said active pharmaceutical for up to about 4 hours.

11. The method of preventing nausea and emesis according to claim 10 wherein said non-permeable coating prevents the substantial release of said active pharmaceutical into said stomach.

20

12. The method of preventing nausea and emesis according to claim 10 wherein said active pharmaceutical is selected from the group consisting of a pharmaceutically acceptable salt of

venlafaxine, an active metabolite of venlafaxine, a pharmaceutically acceptable salt of an active metabolite of venlafaxine, and combinations thereof.

13. A delayed controlled release composition for oral administration comprising:

- 5 a compressed core formulation comprising at least one active pharmaceutical compound
and at least one extended release polymer; and
 a non-permeable coating substantially surrounding said compressed core formulation.

14. The delayed controlled release composition according to claim 13, wherein said compressed
10 core formulation allows for higher doses in a single formulation of said active pharmaceutical.

15. A method for manufacturing a delayed controlled release dosage form that has desired compressibility characteristic comprising the steps of :

- providing an active pharmaceutical ingredient,
15 granulating said active pharmaceutical ingredient with a first binder forming a granulated
pharmaceutical active ingredient,
 re-granulating said formed granulated active pharmaceutical ingredient with a second
binder,
 blending in pharmaceutical at least one pharmaceutical excipient forming a
20 pharmaceutical blend,
 compressing said pharmaceutical blend forming a core tablet, and
 coating said core tablet with coating.

16. The method of manufacturing according to claim 15, wherein said pharmaceutical
excipient is an extended release polymer.

17. The method of manufacturing according to claim 15, wherein said coating is a non-
5 permeable coating substantially surrounding said core formulation.

18. The method of manufacturing according to claim 17, wherein said non-permeable
coating delaying the release of said active pharmaceutical ingredient for up to about 4 hours.

10 19. The method of manufacturing according to claim 15, wherein said re-granulation
improves compressibility.

20. The method of manufacturing according to claim 15, wherein said re-granulation
minimizes hygroscopicity.

15 21. The method of manufacturing according to claim 15, wherein said non-permeable
coating prevents release of substantially all pharmaceutical ingredient into a patient's stomach.

22. A delayed controlled release composition for oral administration comprising:
20 a compressed core formulation comprising at least one active pharmaceutical compound
and at least one extended release polymer; and

a non-permeable coating substantially surrounding said compressed core formulation, wherein said delayed controlled release composition provides peak plasma levels of said at least one active pharmaceutical compound after about 6 hours.

Cumulative Dissolution profile comparison of Venlafaxine HCl ER tablets 75, 150, 225 & 300mg

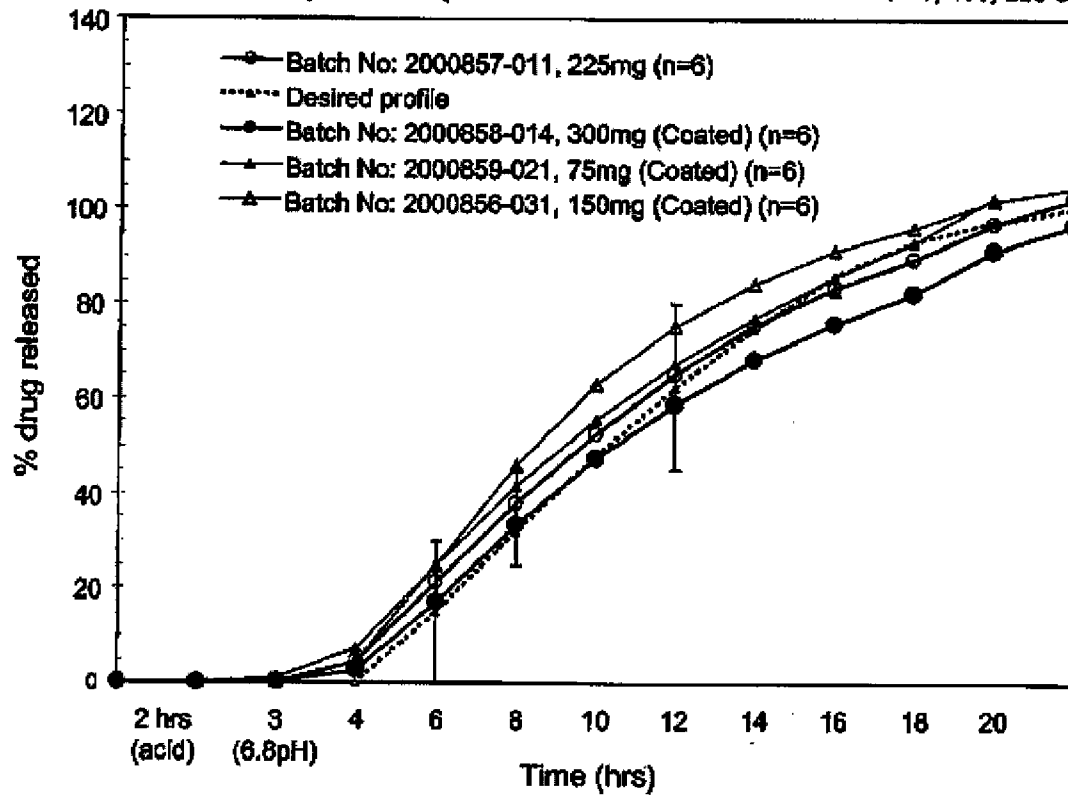


FIG. 1

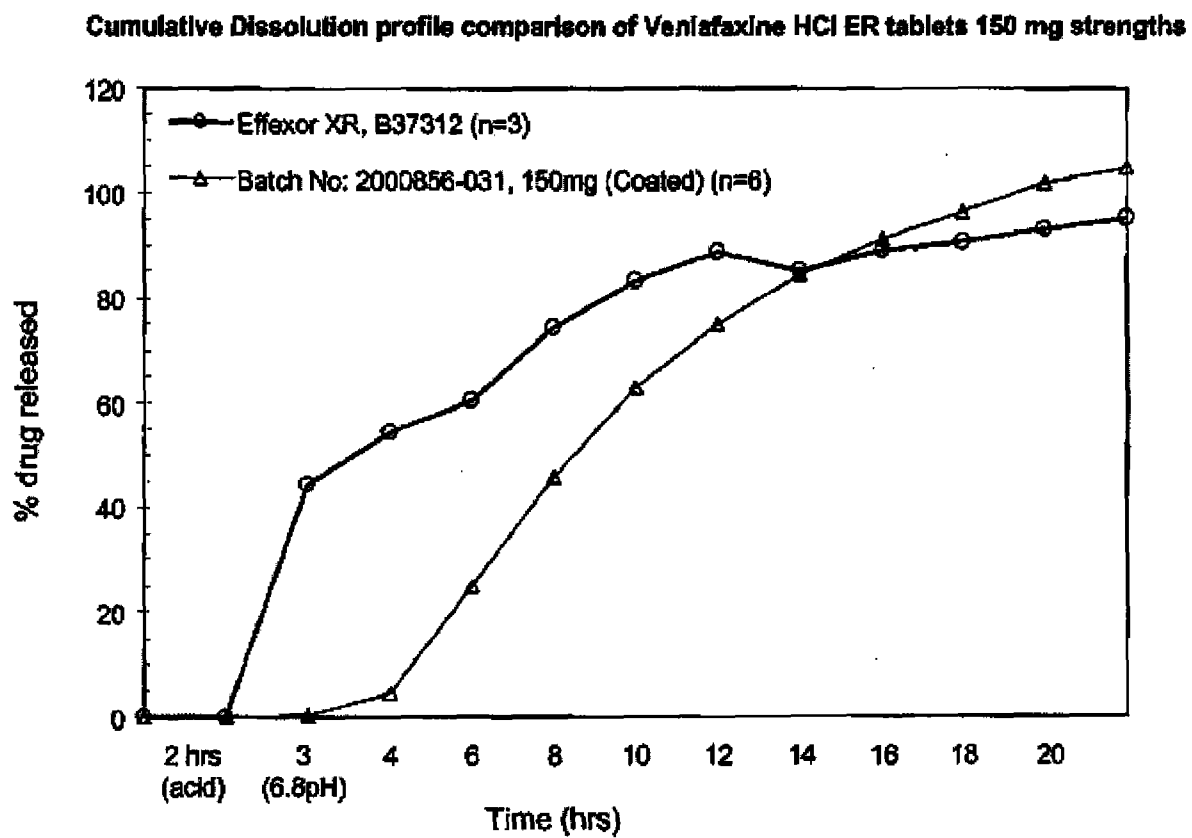


FIG. 2