EXTENDED RELEASE FORMULATION

Background of the Invention

Extended release drug formulations are conventionally produced as compressed tablets by hydrogel tablet technology. To produce these sustained release tablet drug dosage forms, the active ingredient is conventionally compounded with cellulose ethers such as methyl cellulose, ethyl cellulose or hydroxypropylmethylcellulose with or without other excipients and the resulting mixture is pressed into tablets. When the tablets are orally administered, the cellulose ethers in the tablets swell upon hydration from moisture in the digestive system, thereby limiting exposure of the active ingredient to moisture. As the cellulose ethers are gradually leached away by moisture, water more deeply penetrates the gel matrix and the active ingredient slowly dissolves and diffuses through the gel, making it available for absorption by the body. An example of such a sustained release tablet dosage form of the analgesic/antiinflammatory drug etodolac (Lodine®) appears in US patent 4,966,768. US patent 4,389,393 discloses sustained release therapeutic compressed solid unit dose forms of an active ingredient plus a carrier base comprised of a high molecular weight hydroxypropylmethyl-cellulose, methyl cellulose, sodium carboxymethylcellulose and or other cellulose ether.

Where the production of tablets is not feasible, it is conventional in the drug industry to prepare encapsulated drug formulations which provide extended or sustained release properties. In this situation, the extended release capsule dosage forms may be formulated by mixing the drug with one or more binding agents to form a uniform mixture which is then moistened with water or a solvent such as ethanol to form an extrudable plastic mass from which small diameter, typically 1 mm, cylinders of drug/matrix are extruded, chopped into appropriate lengths and transformed into spheroids using standard spheronization equipment. The spheroids, after drying, may then be film-coated to retard dissolution. Gelatin capsules are filled with the film-coated spheroids in the quantity needed to obtain the desired therapeutic effect. Spheroids releasing the drug at different rates may be combined in a gelatin capsule to obtain desired release rates and blood levels. US patent 4,138,475 discloses a sustained release pharmaceutical composition consisting of a hard gelatin capsule filled with film-coated spheroids comprised of propanolol in admixture with microcrystalline cellulose wherein the film coating is composed of ethyl cellulose, optionally, with hydroxy-propylmethylcellulose and/or a plasticizer.

Venlafaxine, 1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol, is an important drug in the neuropharmacological arsenal used for treatment of depression. Venlafaxine and the acid addition salts thereof are disclosed in US patent 4,535,186. Venlafaxine hydrochloride is presently administered to adults in compressed tablet form in doses ranging from 75 to 350 mg/day , in divided doses two or three times a day. In therapeutic dosing with venlafaxine hydrochloride tablets, rapid dissolution results in a rapid increase in blood plasma levels of the active compound shortly after administration followed by a decrease in blood plasma levels over several hours as the active compound is eliminated or metabolized, until sub-therapeutic plasma levels are approached after about twelve hours following administration, thus requiring additional dosing with the drug. With the plural daily dosing regimen, the most common side effect is nausea, experienced by about forty five percent of patients under treatment with venlafaxine hydrochloride. Vomiting also occurs in about seventeen percent of the patients.

EP 0797991 A1 discloses encapsulated venlafaxine sustained release formulations wherein hydroxypropylmethylcellulose was used in making practical venlafaxine-containing spheroids. EP O797991 A1 states that it was completely unexpected that an extended release formulation containing venlafaxine hydrochloride could be obtained because the hydrochloride of venlafaxine proved to be extremely water soluble. Further, numerous attempts to produce extended release tablets by hydrogel technology proved to be fruitless because the compressed tablets were either physically unstable (poor compressibility or capping problems) or dissolved too rapidly in dissolution studies. Typically, the tablets prepared as hydrogel sustained release formulations gave 40-50% dissolution at 2 hrs, 60-70% dissolution at 4 hrs and 85-100% dissolution at 8 hrs.

EP O797991 A1 states further that numerous spheroid formulations were prepared using different grades of microcrystalline cellulose and hydroxypropyl methylcellulose, different ratios of venlafaxine hydrochloride and filler, different binders such as polyvinylpyrrolidone, methylcellulose, water, and polyethylene glycol of different molecular weight ranges in order to find a formulation which would provide a suitable granulation mix which could be extruded properly. In the extrusion process, heat buildup occurred which dried out the extrudate so much that it was difficult to convert the extruded cylinders into spheroids. EP O797991 A1 then states further that addition of hydroxypropylmethylcellulose 2208 to the venlafaxine hydrochloride-microcrystalline cellulose mix made production of spheroids practical.

The invention of this application represents an improvement in the encapsulated, extended release dosage form of venlafaxine disclosed in EP 0797991 A1. Applicants

have now discovered that equally suitable venlafaxine-containing sustained release spheroids can be made without the use of hydroxypropylmethylcellulose as disclosed in EP 0797991 A1, particularly for spheroids containing lower amounts of venlafaxine than those specifically disclosed in EP 0797991 A1. The absence of hydroxypropylmethylcellulose in the spheroids enables the manufacturing process for making the spheroids to be improved, particularly for commercial scale production.

Brief Description of the Invention

In accordance with this invention, there are provided further extended release (ER), encapsulated formulations containing venlafaxine hydrochloride as the active drug component, which provide in a single dose, a therapeutic blood serum level over a twenty four hour period.

Through administration of the venlafaxine formulation of this invention, there is provided a method for obtaining a flattened drug plasma concentration to time profile, thereby affording a tighter plasma therapeutic range control than can be obtained with multiple daily dosing. In other words, this invention provides a method for eliminating the sharp peaks and troughs (hills and valleys) in blood plasma drug levels induced by multiple daily dosing with conventional immediate release venlafaxine hydrochloride tablets. In essence, the plasma levels of venlafaxine hydrochloride rise, after administration of the extended release formulations of this invention, for between about five to about eight hours (optimally about six hours) and then begin to fall through a protracted, substantially linear decrease from the peak plasma level for the remainder of the twenty four hour period, maintaining at least a threshold therapeutic level of the drug during the entire twenty-four period. In contrast, the conventional immediate release venlafaxine hydrochloride tablets give peak blood plasma levels in 2 to 4 hours. Hence, in accordance with the use aspect of this invention, there is provided a method for moderating the plural blood plasma peaks and valleys attending the pharmacokinetic utilization of multiple daily tablet dosing with venlafaxine hydrochloride which comprises administering to a patient in need of treatment with venlafaxine hydrochloride, a one-a-day, extended release formulation of venlafaxine hydrochloride.

The use of the one-a-day venlafaxine hydrochloride formulations of this invention reduces by adaptation, the level of nausea and incidence of emesis that attend the administration of multiple daily dosing. In clinical trials of venlafaxine hydrochloride ER, the probability of developing nausea in the course of the trials was greatly reduced after the first week. Venlafaxine ER showed a statistically significant improvement over conventional venlafaxine hydrochloride tablets in two eight-week

and one 12 week clinical studies. Thus, in accordance with this use aspect of the invention there is provided a method for reducing the level of nausea and incidence of emesis attending the administration of venlafaxine hydrochloride which comprises dosing a patient in need of treatment with venlafaxine hydrochloride with an extended release formulation of venlafaxine hydrochloride once a day in a therapeutically effective amount.

Detailed Description of the Invention

1-[2-(dimethylamino)-1-(4-methoxyphenyl)ethyl]cyclohexanol hydrochloride, i.e. venlafaxine hydrochloride, is polymorphic. Of the forms isolated and characterized to date, Form I is considered to be the kinetic product of crystallization which can be converted to Form II upon heating in the crystallization solvent. Forms I and II cannot be distinguished by their melting points but do exhibit some differences in their infrared spectra and X-ray diffraction patterns. Any of the polymorphic forms such as Form I or Form II may be used in the formulations of the present invention. Microcrystalline cellulose, which is a component of the spheroid cores of the invention, may be any pharmaceutical grade of Microcrystalline Cellulose, NF, for example, Avicel® PH101.

In one aspect, this invention provides an improved core of the extended release spheroids comprised of venlafaxine hydrochloride and microcrystalline cellulose, which are preferably substantially free of hydroxypropylmethylcellulose. In one embodiment of this aspect, the spheroid core is comprised of from about 30 to about 40 percent by weight of venlafaxine hydrochloride, and preferably from about 35 to 40 percent by weight of venlafaxine hydrochloride. In a further embodiment of this aspect, the spheroid core is comprised of from about 6 to about 29 percent, preferably about 8 to about 25 percent, and more preferably from about 8 to about 18 percent, by weight of venlafaxine hydrochloride.

In another aspect of the invention, the spheroid core has a coating comprising ethyl cellulose and hydroxypropylmethylcellulose. The coating is preferably comprised of 80 to 90 percent of ethyl cellulose and 10 to 20 percent hydroxypropyl-methylcellulose on a weight to weight basis. In the embodiment in which the spheroid core is comprised of from about 30 to about 40 percent by weight of venlafaxine hydrochloride, the coating is preferably of from about 2 to about 12 percent, and more preferably about 6 to about 8 percent, by weight of the total weight of the coated spheroid. In the embodiment in which the spheroid core is comprised of from about 6 to about 29 percent by weight of venlafaxine hydrochloride, the coating is preferably of

from about 2 to about 8 percent, and more preferably about 3 to about 6 percent, by weight of the total weight of the coated spheroid.

In a further aspect, the invention provides an extended release formulation comprising a therapeutically effective amount of such coated spheroids containing venlafaxine hydrochloride and microcrystalline cellulose. Further, the invention provides encapsulated, extended release formulations comprising a therapeutically effective amount of such coated spheroids having the following dissolution profile in USP Apparatus 1 (basket) at 100 rpm in purified water at 37°C:

Table A

Time (hours)	Average % Venlafaxine HCl released
2	<30
4	30-55
8	55-80
12	65-90
24	>80.

In a preferred embodiment there is provided a therapeutic spheroid comprising a core comprised of from about 30 to about 40 percent venlafaxine hydrochloride and from about 60 to about 70 percent microcrystalline cellulose and a coating comprised of from about 2 to about 12 percent of the total of a mixture of ethyl cellulose and hydroxypropylmethylcellulose, all on a weight to weight basis, said core preferably being substantially free of hydroxypropylmethylcellulose. In this embodiment, preferably, the core is comprised of from about 35 to about 40 percent venlafaxine hydrochloride and from about 60 to about 65 percent microcrystalline cellulose and the coating is comprised of from about 6 to about 8 percent of the total weight. In this preferred embodiment, the invention also provides an extended release formulation comprising a therapeutically effective amount of such coated spheroids and an encapsulated, extended release formulation comprising a therapeutically effective amount of such coated spheroids having the dissolution profile set out in Table A.

In a further preferred embodiment there is provided a therapeutic spheroid comprising a core comprised of from about 6 to about 29 percent venlafaxine hydrochloride and from about 94 to about 71 percent microcrystalline cellulose and a coating comprised of from about 2 to about 8 percent of the total of a mixture of ethyl cellulose and hydroxypropylmethylcellulose, all on a weight to weight basis, said core preferably being substantially free of hydroxypropylmethylcellulose. In this embodiment, preferably, the core is comprised of from about 8 to about 25 percent, and

more preferably, from about 8 to about 18 percent, venlafaxine hydrochloride and from about 82 to about 75 percent, and more preferably about 82 to about 92 percent, microcrystalline cellulose, and the coating is preferably from about 6 to about 8 percent, and more preferably about 3 to about 6 percent, by weight of the coated spheroid total. In this preferred embodiment, the invention also provides an extended release formulation comprising a therapeutically effective amount of such coated spheroids. and an encapsulated, extended release formulation comprising a therapeutically effective amount of such coated spheroids having the dissolution profile set out in Table A.

In a further aspect, this invention provides a method of preparing the above-described spheroid cores, said method comprising extruding a mixture of venlafaxine hydrochloride and microcrystalline cellulose and then spheronising the resulting mixture. In a further step, such spheroid cores are coated with a mixture of ethyl cellulose and hydroxypropylmethylcellulose to provide the coated, extended release spheroids of the invention, preferably having the desired release rate characteristics. In a further step, the coated spheroids are sieved and selected spheroids are used to fill capsules to provide the extended release capsules of the invention.

The film coating is comprised of 80 to 90 percent of ethyl cellulose, NF and 10 to 20 percent hydroxypropyl methylcellulose, USP on a weight/weight basis. Preferably, the ethyl cellulose has a ethoxy content of 44.0–51% and a viscosity of 50 cps for a 5% aqueous solution, and preferably, the hydroxypropylmethylcellulose is USP 2910 having a viscosity of 6 cps at 2% aqueous solution with a methoxy content of 28–30% and a hydroxypropoxy content of 7–12%. The preferred ethyl cellulose used herein is Aqualon HG 2834. Other equivalents of the hydroxypropylmethyl-cellulose 2910 USP and ethyl cellulose, NF, having the same chemical and physical characteristics as the proprietary products named above may be substituted in the formulation without changing the inventive concept. (EP 0797991 A1 provided that hydroxypropylmethylcellulose 2208 USP, K3, Dow, which has a viscosity of 3 cps for 2% aqueous solutions, a methoxy content of 19–24% and a hydroxypropoxy content of 4–13%, was preferred for use in the spheroid core in order to make extrusion of the spheroids practical.)

This invention further provides a process for the manufacture of spheroid cores containing venlafaxine hydrochloride, which process comprises forming the spheroid cores from a composition that comprises venlafaxine hydrochloride and microcrystalline cellulose, the composition being substantially free of hydroxypropyl-methylcellulose. Such process also includes a further step comprising forming spheroids by coating the spheroid cores with a mixture of ethyl cellulose and hydroxypropylmethylcellulose. An additional comprises sieving the spheroids and

using selected spheroids to fill capsules. Preferably, the foregoing process steps are ones in which the spheroid cores are formed by extruding a mixture of venlafaxine hydrochloride and microcrystalline cellulose and spheronizing the resulting mixture.

The following examples illustrate the practice of the invention without limiting its scope.

VENLAFAXINE HYDROCHLORIDE EXTENDED RELEASE CAPSULES WITH HPMC

Example 1

A mixture of 44.8 parts (88.4 % free base) of venlafaxine hydrochloride, 74.6 parts of the microcrystalline cellulose, NF, and 0.60 parts of hydroxypropylmethyl cellulose 2208, USP, are blended with the addition of 41.0 parts water. The plastic mass of material is extruded, spheronized and dried to provide uncoated drug containing spheroids.

Stir 38.25 parts of ethyl cellulose, NF, HG2834 and 6.75 parts of hydroxypropyl methylcellulose 2910, USP in a 1:1 v/v mixture of methylene chloride and anhydrous methanol until solution of the film coating material is complete.

To a fluidized bed of the uncoated spheroids is applied 0.667 parts of coating solution per part of uncoated spheroids to obtain extended release, film coated spheroids having a coating level of 3%.

The spheroids are sieved to retain the coated spheroids of a particle size between 0.85 mm to 1.76 mm diameter. These selected film coated spheroids are filled into hard gelatin capsules conventionally.

Example 2

Same as for Example 1 except that 1.11 parts of the film coating solution per part of uncoated spheroids is applied to obtain a coating level of 5%.

Example 3

Same as for Example 1 except that 1.33 parts of the film coating solution is applied to 1 part of uncoated spheroids to obtain a coating level of 6%.

Example 4

Same as for Example 1 except that 1.55 parts of the film coating solution is applied to 1 part of uncoated spheroids to obtain a coating level of 7%.

The art-skilled person will appreciate that the invention can be practiced utilizing several types of conventional extruders. However, extruders having screw-type gravity feed and cylindrical gear discharge units (for example, Hutt Pellitizer model no. GCS-200/80) or gravity feed and a radial screen discharge unit (for example, Nica Extruder model no. E140) are preferred over those having a gravity feed and a cylindrical discharge unit (for example, Alexanderwerk model no. C1/100/1605).

VENLAFAXINE HYDROCHLORIDE EXTENDED RELEASE CAPSULES WITHOUT HPMC

Example 5

Spheroids of the invention were produced having 8.25% (w/w) venlafaxine hydrochloride and the remainder (91.75%, w/w) being microcrystalline cellulose, with a coating of from 3 to 5 % (w/w), preferably 4%, of the total weight. The spheroids with 8.25% venlafaxine hydrochloride and 4% coating were filled into No. 2 white opaque shells with a target fill weight of 236 mg.

Example 6

Further spheroids of the invention were produced having 16.5% (w/w) venlafaxine hydrochloride and the remainder (83.5%,w/w) being microcrystalline cellulose, with a coating of from 4 to 6 % (w/w), preferably 5%, of the total weight. The spheroids 16.5% venlafaxine hydrochloride and 5% coating were filled into No. 2 white opaque shells with a target fill weight of 122 mg.

The stability of capsules containing the 16.5% (w/w) strength of venlafaxine hydrochloride (in a 18.75 mg dosage capsule) without HPMC in the spheroid core is equivalent to that of such capsules of higher strengths of venlafaxine hydrochloride with HPMC in the spheroid core for up to six months. In both cases, at the end of six months, the venlafaxine strength remained at 98 percent or above of the original strength and there was less than one percent of detectable impurities. Further, with respect to capsules containing the 16.5% (w/w) strength of venlafaxine hydrochloride

without HPMC in the spheroid core, efficacy was demonstrated, on a dose-related basis, in a human clinical trial.

The test for acceptability of the coating level is determined by analysis of the dissolution rate of the finished coated spheroids prior the encapsulation. The dissolution procedure followed uses USP Apparatus 1 (basket) at 100 rpm in purified water at 37°C.

Conformance with the dissolution rate given in Table 1 provides the twenty-four hour therapeutic blood levels for the drug component of the extended release capsules of this invention in capsule form. Where a given batch of coated spheroids releases drug too slowly to comply with the desired dissolution rate study, a portion of uncoated spheroids or spheroids with a lower coating level may be added to the batch to provide, after thorough mixing, a loading dose for rapid increase of blood drug levels. A batch of coated spheroids that releases the drug too rapidly can receive additional film-coating to give the desired dissolution profile.

Table 1

Acceptable Coated Spheroid Dissolution Rates

Time (hours)	Average % Venlafaxine HCl released
2	<30
4	30-55
8	55-80
12	65-90
24	>80

Batches of the coated venlafaxine hydrochloride containing spheroids which have a dissolution rate corresponding to that of Table 1 are filled into hard gelatin capsules in an amount needed to provide the unit dosage level desired. The standard unit dosage immediate release (IR) tablet used presently provides amounts of venlafaxine hydrochloride equivalent to 25 mg, 37.5 mg, 50 mg, 75 mg and 100 mg venlafaxine. The capsules of this invention are filled to provide an amount of venlafaxine hydrochloride equivalent to that presently used in tablet form and also up to about 150 mg venlafaxine hydrochloride.

Dissolution of the venlafaxine hydrochloride ER capsules is determined as directed in the U. S. Pharmacopoeia (USP) using apparatus 1 at 100 rpm on 0.9 L of water. A filtered sample of the dissolution medium is taken at the times specified. The absorbance of the clear solution is determined from 240 to 450 nanometers (nm) against

the dissolution medium. A baseline is drawn from 450 nm through 400 nm and extended to 240 nm. The absorbance at the wavelength of maximum absorbance (about 274 nm) is determined with respect to this baseline. Six hard gelatin capsules are filled with the theoretical amount of venlafaxine hydrochloride spheroids and measured for dissolution. Standard samples consist of venlafaxine hydrochloride standard solutions plus a gelatin capsule correction solution.

The percentage of venlafaxine released is determined from the equation

$$\% \text{ Venlafaxine hydrochloride released} = \frac{(As)(Wr)(S)(V1)(0.888)(100)}{(Ar)(V2)(C)}$$

where As is absorbance of sample preparation, Wr is weight of reference standard, mg; S is strength of the reference standard, decimal; V1 is the volume of dissolution medium used to dissolve the dosage form, ml; 0.884 is the percent free base, Ar is the absorbance of the standard preparation, V2 is the volume of reference standard solution, mL; and C is the capsule claim in mg.

Table 2 below is incorporated from EP 0797991 A1 and shows the plasma level of venlafaxine versus time for one 75 mg conventional Immediate Release (IR) tablet administered every 12 hours, two 75 mg extended release (ER) capsules administered simultaneously every 24 hours, and one 150 mg extended release (ER) capsule administered once every 24 hours in human male subjects. The subjects were already receiving venlafaxine hydrochloride according to the dosage protocol, thus the plasma blood level at zero time when dosages were administered is not zero. The ER capsules are those described in EP 0797991 A1 which have HPMC in the spheroids.

Table 2

Plasma venlafaxine level (ng/mL) versus time, conventional tablet (not extended release) versus ER capsule

Time (hours)	75 mg (IR)tablet (q 12 h)	2 x 75 mg (ER)capsules (q 24 hr)	1 x 150 mg (ER)capsules (q 24 h)
0	62.3	55.0	55.8
0.5	76.3		
1	135.6	53.3	53.2
2	212.1	69.8	70.9
4	162.0	138.6	133.3
6	114.6	149.0	143.5
8	86.7	129.3	129.5
10		118.4	114.4
12	51.9	105.1	105.8
12.5	74.7		
13	127.5		
14	161.3	90.5	91.3
16	134.6	78.2	78.5
18	106.2		
20	83.6	62.7	63.3
24	57.6	56.0	57.3

Table 2 shows that the plasma levels of two 75 mg/capsule venlafaxine hydrochloride ER capsules and one 150 mg/capsule venlafaxine hydrochloride ER capsule provide very similar blood levels. The data also show that the plasma level after 24 hours for either extended release regimen is very similar to that provided by two immediate release 75 mg tablets of venlafaxine hydrochloride administered at 12 hour intervals.

Further, the plasma levels of venlafaxine obtained with the extended release formulation do not increase to the peak levels obtained with the conventional immediate release tablets given 12 hours apart. The peak level of venlafaxine from (ER),

somewhat below 150 ng/ml, is reached in about six hours, plus or minus two hours, based upon this specific dose when administered to patients presently under treatment with venlafaxine hydrochloride (IR). The peak plasma level of venlafaxine, somewhat over 200 ng/ml, following administration of (IR) is reached in two hours and falls rapidly thereafter.

Table 3 below is incorporated from EP 0797991 A1 and shows venlafaxine blood plasma levels in male human subjects having a zero initial blood plasma level. Again, a peak blood plasma concentration of venlafaxine is seen at about 6 hours after dosing with venlafaxine hydrochloride extended release capsules in the quantities indicated. The subjects receiving the single 50 mg immediate release tablet showed a peak plasma level occurring at about 4 hours. For comparative purposes, the plasma levels of venlafaxine for subjects receiving the conventional formulated tablet can be multiplied by a factor of three to approximate the plasma levels expected for a single dose of 150 mg. conventional formulation. The ER capsules are those described in EP 0797991 A1 which have HPMC in the spheroids.

Table 3.

Plasma Blood Levels in Human Males Having No Prior Venlafaxine Blood Level

Time (Hours)	1 x 50 mg IR tablet	2 x 75 mg ER capsules	1 x 150 mg ER capsule
0	0	0	0
1	27.87	1.3	0
1.5	44.12	6.0	2.2
2	54.83	20.6	12.8
4	66.38	77.0	81.0
6	49.36	96.5	94.4
8	30.06	93.3	86.9
10	21.84	73.2	72.8
12	15.91	61.3	61.4
14	13.73	52.9	51.9
16	10.67	47.5	41.1
20	5.52	35.2	34.0
24	3.56	29.3	28.5
28	2.53	23.4	22.9
36	1.44	11.9	13.5
48	0.66	5.8	5.2

The blood plasma levels of venlafaxine were measured according to the following procedure. Blood samples from the subjects were collected in heparinized evacuated blood tubes and the tubes were inverted gently several times. As quickly as possible, the tubes were centrifuged at 2500 rpm for 15 minutes. The plasma was pipetted into plastic tubes and stored at -20°C until analysis could be completed.

To 1 mL of each plasma sample in a plastic tube was added 150 µL of a stock internal standard solution (150 µg/ml). Saturated sodium borate (0.2 mL) solution was added to each tube and vortexed. Five mL of ethyl ether was added to each tube which were then capped and shaken for 10 minutes at high speed. The tubes were centrifuged at 3000 rpm for 5 minutes. The aqueous layer was frozen in dry ice and the organic layer transferred to a clean screw cap tube. A 0.3 mL portion of 0.01 N HCl solution was added to each tube and shaken for 10 minutes at high speed. The aqueous layer was frozen and the organic layer removed and discarded. A 50µL portion of the mobile phase (23:77 acetonitrile:0.1M monobasic ammonium phosphate buffer, pH 4.4) was added to each tube, vortexed, and 50 µL samples were injected on a Supelco Supelcoil LC-8-DB, 5 cm x 4.6 mm, 5 µ column in a high pressure liquid chromatography apparatus equipped with a Waters Lambda Max 481 detector or equivalent at 229 nm. Solutions of venlafaxine hydrochloride at various concentrations were used as standards.

Thus, the desired dissolution rate of a sustained release dosage form of venlafaxine hydrochloride, impossible to achieve with hydrogel tablet technology, has been achieved with the further film-coated spheroid compositions of this invention.

What is claimed is:

1. A spheroid core comprising venlafaxine hydrochloride and microcrystalline cellulose, being substantially free of hydroxypropylmethylcellulose.

2. A spheroid core as claimed in claim 1 comprised of from about 30 to about 40 percent by weight of venlafaxine hydrochloride.

3. A spheroid core as claimed in claim 1 comprised of from about 6 to about 29 percent by weight of venlafaxine hydrochloride.

4. A spheroid core as claimed in claim 1 comprised of from about 8 to about 25 percent by weight of venlafaxine hydrochloride.

5. A spheroid core as claimed in claim 1 comprised of from about 8 to about 18 percent by weight of venlafaxine hydrochloride.

6. A spheroid comprising a spheroid core as claimed in any one of claims 1 to 5 which has a coating comprising ethyl cellulose and hydroxypropylmethylcellulose.

7. A spheroid as claimed in claim 6 wherein the coating is comprised of 80 to 90 percent of ethyl cellulose and 10 to 20 percent hydroxypropyl methylcellulose on a weight to weight basis.

8. A spheroid as claimed in claim 2 with a coating of from about 2 to about 12 percent, by weight of the total, of a mixture of ethyl cellulose and hydroxypropylmethylcellulose.

9. A spheroid as claimed in claim 2 with a coating of from about 6 to about 8 percent, by weight of the total, of a mixture of ethyl cellulose and hydroxypropylmethylcellulose.

10. A spheroid as claimed in any one of claims 3 to 5 with a coating of from about 2 to about 8 percent, by weight of the total, of a mixture of ethyl cellulose and hydroxypropylmethylcellulose.

* C L M S *

11. A spheroid as claimed in any one of claims 3 to 5 with a coating of from about 3 to about 6 percent, by weight of the total, of a mixture of ethyl cellulose and hydroxypropylmethylcellulose.

12. An extended release formulation comprising a therapeutically effective amount of coated spheroids as claimed in any one of claims 6-11.

13. An encapsulated, extended release formulation comprising a therapeutically effective amount of coated spheroids as claimed in any one of claims 6-11having the following dissolution profile in USP Apparatus 1 (basket) at 100 rpm in purified water at 37°C:

Time (hours)	Average % Venlafaxine HCl released
2	<30
4	30-55
8	55-80
12	65-90
24	>80.

14. A therapeutic spheroid comprising a core comprised of from about 30 to about 40 percent venlafaxine hydrochloride and from about 60 to about 70 percent microcrystalline cellulose and a coating comprised of from about 2 to about 12 percent of the total of a mixture of ethyl cellulose and hydroxypropylmethylcellulose, all on a weight to weight basis, said core being substantially free of hydroxypropylmethylcellulose.

15. A therapeutic spheroid as claimed in claim 14, wherein the core is comprised of from about 35 to about 40 percent venlafaxine hydrochloride and from about 60 to about 65 percent microcrystalline cellulose and the coating is comprised of from about 6 to about 8 percent of the total of a mixture of ethyl cellulose and hydroxypropylmethylcellulose, all on a weight to weight basis.

16. An extended release formulation comprising a therapeutically effective amount coated spheroids as claimed in claim 14 or 15.

17. An encapsulated, extended release formulation of comprising a therapeutically effective amount of spheroids as claimed in claim 14 or 15 having the following dissolution profile in USP Apparatus 1 (basket) at 100 rpm in purified water at 37°C:

* C L M S *

Time (hours)	Average % Venlafaxine HCl released
2	<30
4	30-55
8	55-80
12	65-90
24	>80.

18. A therapeutic spheroid comprising a core comprised of from about 6 to about 29 percent venlafaxine hydrochloride and from about 94 to about 71 percent microcrystalline cellulose and a coating comprised of from about 2 to about 8 percent of the total of a mixture of ethyl cellulose and hydroxypropylmethylcellulose, all on a weight to weight basis, said core being substantially free of hydroxypropylmethylcellulose.

19. A therapeutic spheroid as claimed in claim 18, wherein the core comprised of from about 8 to about 25 percent venlafaxine hydrochloride and from about 92 to about 75 percent microcrystalline cellulose and the coating is comprised of from about 3 to about 6 percent of a mixture of ethyl cellulose and hydroxypropylmethylcellulose, all on a weight to weight basis.

20. An extended release formulation comprising a therapeutically effective amount of coated spheroids as claimed in claim 18 or 19.

21. An encapsulated, extended release formulation comprising a therapeutically effective amount of coated spheroids as claimed in claim 18 or 19 having the following dissolution profile in USP Apparatus 1 (basket) at 100 rpm in purified water at 37°C:

Time (hours)	Average % Venlafaxine HCl released
2	<30
4	30-55
8	55-80
12	65-90
24	>80.

22. A spheroid core comprising from about 6 to about 29 percent venlafaxine hydrochloride, from about 94 to about 71 percent microcrystalline cellulose and from about 0.25 to 1 percent hydroxypropylmethylcellulose, on a weight to weight basis.



23. A spheroid core as claimed in claim 22 comprised of from about 8 to about 25 percent venlafaxine hydrochloride, from about 92 to about 76 percent microcrystalline cellulose and from about 0.25 to 1 percent hydroxypropylmethylcellulose, on a weight to weight basis.

24. A spheroid core as claimed in claim 22 or 23 comprised of from about 8 to about 18 percent venlafaxine hydrochloride and from about 92 to about 82 percent microcrystalline cellulose and from about 0.4 to 0.6 percent hydroxypropylmethylcellulose, on a weight to weight basis.

25. A spheroid comprising a core as claimed in any one of claims 22 to 24 which has a coating comprised of a mixture of ethyl cellulose and hydroxypropylmethylcellulose.

26. A spheroid as claimed claim 25 wherein the coating is comprised of 80 to 90 percent of ethyl cellulose and 10 to 20 percent hydroxypropyl methylcellulose on a weight to weight basis.

27. A spheroid comprising a core as claimed claim 25 or 26 wherein the coating is comprised of from about 2 to about 8 percent, by weight of the total, of a mixture of ethyl cellulose and hydroxypropylmethylcellulose.

28. A spheroid comprising a core as claimed in any one of claim 25 to 27 wherein the coating is comprised of from about 3 to about 6 percent, by weight of the total, of a mixture of ethyl cellulose and hydroxypropylmethylcellulose.

29. An extended release formulation comprising a therapeutically effective amount of coated spheroids as claimed in any one of claims 25-28.

30. An encapsulated, extended release formulation comprising a therapeutically effective amount of coated spheroids as claimed in any one of claims 25 to 28 having the following dissolution profile in USP Apparatus 1 (basket) at 100 rpm in purified water at 37°C:

Time (hours)	Average % Venlafaxine HCl released
2	<30
4	30-55
8	55-80
12	65-90
24	>80.

* C L M S *

31. A therapeutic spheroid comprising a core comprised of from about 6 to about 29 percent venlafaxine hydrochloride and from about 94 to about 71 percent microcrystalline cellulose. 0.25 to 1 percent hydroxypropylmethylcellulose and a coating comprised of from about 2 to about 8 percent of the total of a mixture of ethyl cellulose and hydroxypropylmethylcellulose, all on a weight to weight basis.

32. A therapeutic spheroid as claimed in claim 31 wherein the core is comprised of from about 8 to about 25 percent venlafaxine hydrochloride and from about 92 to about 75 percent microcrystalline cellulose and the coating is comprised of from about 3 to about 6 percent of the total of a mixture of ethyl cellulose and hydroxypropylmethylcellulose, all on a weight to weight basis.

33. An extended release formulation comprising a therapeutically effective amount of coated spheroids as claimed in claim 31 or 32.

34. An encapsulated, extended release formulation comprising a therapeutically effective amount of coated spheroids as claimed in claim 31 or 32 having the following dissolution profile in USP Apparatus 1 (basket) at 100 rpm in purified water at 37°C:

Time (hours)	Average % Venlafaxine HCl released
2	<30
4	30-55
8	55-80
12	65-90
24	>80.

35. A method of preparing a spheroid core as claimed in any one of claims 1 to 5 by extruding a mixture of venlafaxine hydrochloride and microcrystalline cellulose and then spheronising the resulting mixture.

36. A method as claimed in claim 35 comprising the further step of coating the spheroid cores with a mixture of ethyl cellulose and hydroxypropylmethylcellulose.

37. A method as claimed in claim 36 comprising the further step of step of sieving the spheroids and using selected spheroids to fill capsules.

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38. A method of preparing a spheroid core as claimed in any one of claims 22 to 24 by extruding a mixture of venlafaxine hydrochloride and microcrystalline cellulose and then spheronising the resulting mixture.

39. A method as claimed in claim 38 comprising the further step of coating the spheroid cores with a mixture of ethyl cellulose and hydroxypropylmethylcellulose.

40. A method as claimed in claim 39 comprising the further step of step of sieving the spheroids and using selected spheroids to fill capsules.

41. A process for the manufacture of spheroid cores containing venlafaxine hydrochloride, which process comprises forming the spheroid cores from a composition that comprises venlafaxine hydrochloride and microcrystalline cellulose, the composition being substantially free of hydroxypropylmethylcellulose.

42. A process as claimed in claim 41 further comprising the step of forming spheroids by coating the spheroid cores with a mixture of ethyl cellulose and hydroxypropylmethylcellulose.

43. A process as claimed in claim 42 further comprising the step of step of sieving the spheroids and using selected spheroids to fill capsules.

44. A process as claimed in any one of claims 41 to 43, in which the spheroid cores are formed by extruding a mixture of venlafaxine hydrochloride and microcrystalline cellulose and spheronizing the resulting mixture.



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(54) Title: EXTENDED RELEASE FORMULATION

(57) Abstract

This invention relates to a 24 hour extended release dosage formulation and unit dosage form thereof of venlafaxine hydrochloride, and antidepressant, which provides better control of blood plasma levels than conventional tablet formulations which must be administered two or more times a day and further provides a lower incidence of nausea and vomiting than the conventional tablets. In its primary aspect, this invention provides an improved core of the extended release spheroids comprised of venlafaxine hydrochloride and microcrystalline cellulose, that is, without the addition of hydroxypropylmethylcellulose.