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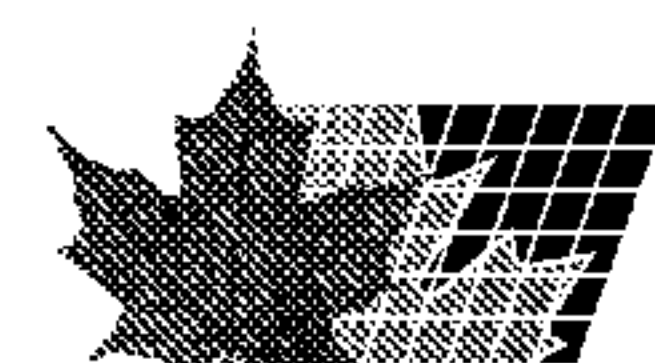
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(54) Titre : COMPOSITIONS A LIBERATION PROLONGEE COMPRENANT DU CHLORHYDRATE DE VENLAFAXINE
UTILISE EN TANT QUE COMPOSE ACTIF
(54) Title: EXTENDED RELEASE COMPOSITIONS COMPRISING AS ACTIVE COMPOUND VENLAFAXINE
HYDROCHLORIDE

(57) **Abrégé/Abstract:**

The present invention relates to an extended release composition comprising as active compound Venlafaxine Hydrochloride, in which Venlafaxine Hydrochloride is coated on a non pareil inert core, which coated core is then coated with polymeric layer which enables the controlled release of the Venlafaxine Hydrochloride.



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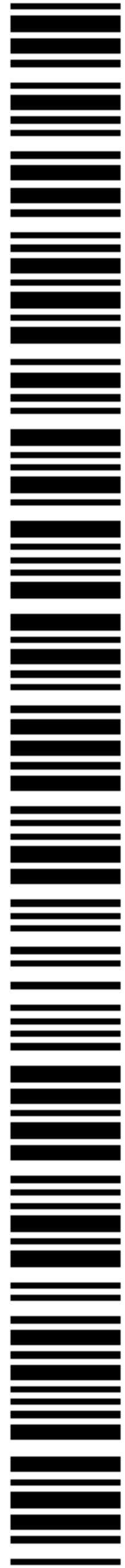
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(54) Title: EXTENDED RELEASE COMPOSITIONS COMPRISING AS ACTIVE COMPOUND VENLAFAXINE HYDROCHLORIDE

(57) Abstract: The present invention relates to an extended release composition comprising as active compound Venlafaxine Hydrochloride, in which Venlafaxine Hydrochloride is coated on a non pareil inert core, which coated core is then coated with polymeric layer which enables the controlled release of the Venlafaxine Hydrochloride.



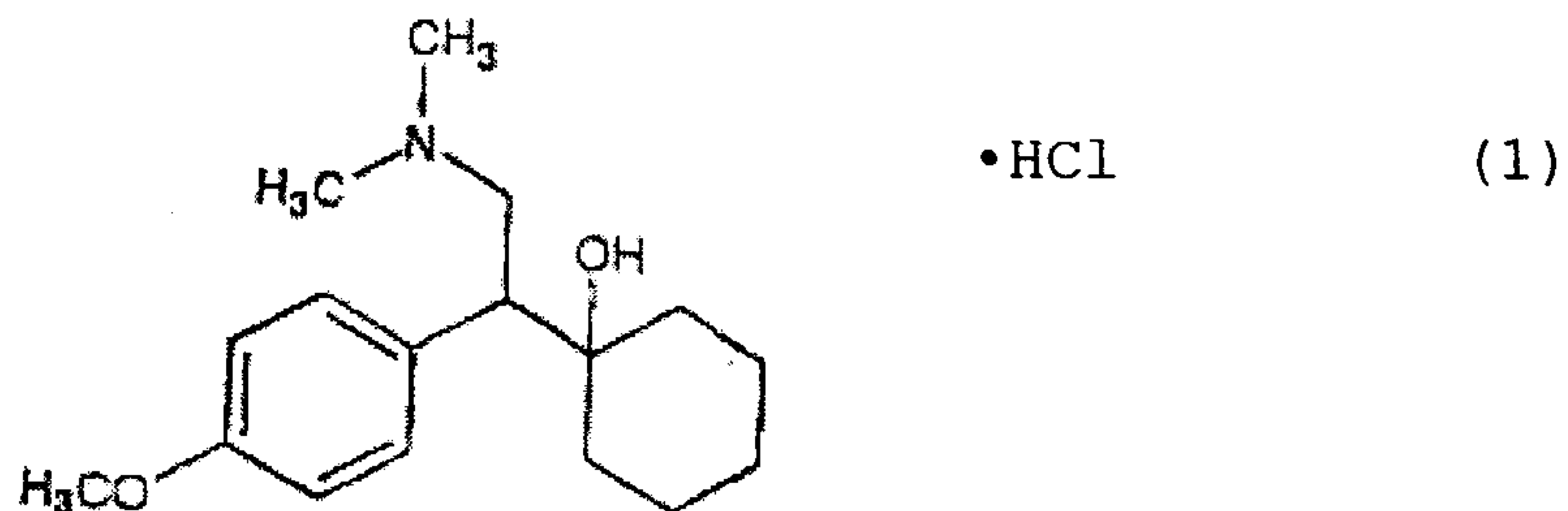
WO 03/041692 A1

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Extended Release Compositions Comprising As Active Compound**Venlafaxine Hydrochloride**

[0001] The present invention relates to extended release compositions comprising as active compound venlafaxine hydrochloride.

[0002] Venlafaxine hydrochloride is an antidepressant having formula (1)



being designated (R/S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl)-ethyl] cyclohexanol hydrochloride or ($\pm$)-1-[a](dimethylamino)-methyl] p-methoxybenzyl cyclohexanol hydrochloride, having the empirical formula of $C_{17}H_{27}NO_2$ hydrochloride and molecular weight of 313.87.

[0003] Venlafaxine hydrochloride is a white to off-white crystalline solid with a solubility of 572 mg/ml in water (adjustment to ionic strength of 0.2 M with sodium chloride). Its octanol:water (0.2 M sodium chloride) partition coefficient

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0.43. EFFEXOR^{*} XR, **the** Brand product, is formulated as an extended release capsule for once-a-day oral administration.

[0004] The drug release has so far been controlled by diffusion through the coating membrane on the spheroids and is not pH-dependent. Known capsules containing venlafaxine hydrochloride comprise amounts equivalent to 37.5 mg, 75 mg, or 150 mg of venlafaxine. The inactive ingredients are mainly cellulose, ethylcellulose, gelatin, hydroxypropylmethylcellulose, iron oxide, and titanium dioxide.

[0005] Controlled or extended release dosage forms of medicament are conventionally produced as hydrogel matrix-based tablets. With this technology, the controlled release dosage forms are simply prepared by mixing the active material with the appropriate rate of controlling polymers and then that mixture is compressed into the desired controlled release tablets. The rate-controlling polymers are normally termed as hydrogels. Examples of such polymers are cellulose ethers such as ethyl cellulose or hydroxypropylcellulose. Patents describing preparation methods of such dosage forms are described, for example, in US Patent Specifications 4,966,768 and 4,389,393.

[0006] In some cases, for example with very water soluble active materials and with relatively high doses, it is not feasible to produce tablets which enable appropriate control

*Trade-mark

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on the drug's release. This is the case, for example with venlafaxine hydrochloride.

[0007] In such a case, a suitable approach is encapsulating the drug and producing extended release capsule dosage forms. When preparation of such dosage forms is considered, the preferred way is to mix the active ingredient with at least one binding agent to form a uniform mixture which is later moistened with water or with an appropriate organic solvent to form an extrudable plastic mass, from which small particles, cylindrical in shape (1 mm diameter), of drug/matrix are extruded, chopped into appropriate lengths and converted to spheroids using spheronization equipment. These spheroids are further dried and then film-coated with an appropriate polymer to form a film with the desired release patterns. The most widely used excipient in the extruding process is microcrystalline cellulose in its different grades; usually, water is used for the wetting process.

[0008] Polymers widely used for coating are ethyl cellulose or EUDRAGIT^{*} (ammonio methacrylate copolymer, type A or B). Water-soluble ingredients are normally mixed with the ethyl cellulose or with other hydrophobic polymers, such as pore forming agents, to assist the control on the drug's release through the hydrophobic coating layer. The water-soluble

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ingredients, such as hydroxypropylcellulose or polyethylene glycol, may serve as plasticizers as well.

[0009] Venlafaxine hydrochloride has so far been formulated into a controlled release dosage form with the ability to provide in a single dose a therapeutic blood serum level of the drug over a twenty four hour period. By this method, tighter plasma therapeutic range control can be obtained and multiple dosing is avoided in this manner. The sharp peaks and troughs in blood plasma drug levels are avoided as well.

[0010] With the conventional release dosage forms of venlafaxine hydrochloride (tablets), peak blood plasma levels appeared after 2-4 hrs, in contrast to the extended release dosage forms, when plasma levels of venlafaxine hydrochloride rose after administration for between five to eight hrs (average - 6) and then begin to fall through a protracted, substantially linear decrease from the peak plasma level for the remainder of the period, maintaining therapeutic level of the drug during the entire twenty four hours period.

[0011] In WO 99/22724 (AHP, Sherman), a detailed description of preparing an encapsulated dosage form (coated spheroids) of venlafaxine hydrochloride is provided. By the method described therein, a spheroid core is prepared by extruding and spheronizing a mixture of the drug with

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microcrystalline cellulose, and then coating it with an ethyl cellulose hydroxypropylcellulose mixture.

[0012] This dosage form provides an extended release product with the following *in vitro* dissolution specifications:

Time (hrs)	Average % venlafaxine HCL release
2	<30
4	30-55
8	55-80
12	65-90
24	>80

5

[0013] These dissolution characteristics are pH- and RPM-independent.

[0014] In the present invention, an alternative once daily bioequivalent formulation to the innovator's one (EFFEXOR XR, described in WO 99/22724) has been developed.

- 10 [0014.1] 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.
- 15 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.

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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

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[0014.2] 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.

[0014.3] 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.

[0014.4] 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.

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Table 3Plasma 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

[0014.5] 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

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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.

[0014.6] 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 50 µL 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.

[0015] As already mentioned, with high dose water-soluble product, such as venlafaxine hydrochloride (150mg), the usual preferred way of encapsulating it is by preparing and coating appropriate beads, using the extrusion spheronization process.

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[0016] In the present invention, the microencapsulation has been changed, i.e., is being performed by layering the drug over an inert nonpareil core, and then coating it with an appropriate polymeric mixture.

[0017] The present invention thus consists in an extended release composition comprising as active compound venlafaxine hydrochloride, in which venlafaxine hydrochloride is coated on a nonpareil inert core, which coated core is then coated with a polymeric layer which enables the controlled release of the venlafaxine hydrochloride.

[0017.1] According to another aspect of the invention, there is provided a pH-independent extended release dosage form, comprising: venlafaxine hydrochloride in an amount of 30-60% based on the total weight of the dosage form; said venlafaxine hydrochloride being coated on a nonpareil inert core, said nonpareil inert core comprising 30-60% based on the total weight of the dosage form; the venlafaxine hydrochloride being optionally connected to a binder in a binder amount of 0.5-10% based on the total weight of the dosage form; a hydrophilic polymeric or glycerol monostearate (GMS) layer coating said venlafaxine hydrochloride and comprising 0.5-10% based on the total weight of the dosage form; and a controlled release layer coated over said hydrophilic polymeric or GMS layer, said controlled release layer comprising a hydrophobic polymer optionally mixed with a plasticizer, said hydrophobic polymer comprising 2-15% based on the total weight of the dosage form, and said optional plasticizer, when present, comprising 0.1-2% based on the total weight of the dosage form; and said controlled release layer permitting controlled release of the venlafaxine hydrochloride over an approximately 24 hour period.

[0018] The composition preferably comprises 30-60% of venlafaxine hydrochloride per weight of the total dosage form.

[0019] In a preferred embodiment of the present invention, the venlafaxine hydrochloride is suitably connected to a binder; said binder may be, e.g., polyvinylpyrrolidone (povidone), hydroxypropylcellulose, hydroxypropylmethylcellulose, etc. The composition preferably comprises 0.5%-10% of the binder per weight of the total dosage form.

[0020] Advantageously the nonpareil inert core is an inert sugar core, a microcrystalline cellulose, or the like. The composition preferably comprises 30 - 60% of the core per weight of the total dosage form.

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[0021] Alternatively, the drug might be sprayed as it is and the water is then used as binding enhancement agent.

[0022] Advantageously, the coated core is coated with an isolating/protecting/separating layer, which layer is suitably composed of polymers such as polyvinylpyrrolidone, hydroxypropylcellulose, hydroxypropylmethylcellulose, microcrystalline cellulose, carrageenan, GMS, etc. The composition preferably comprises 0.5-10% of the isolating layer per weight of the total dosage form.

[0023] The core or the isolating layer is coated then with an additional polymeric layer which enables the controlled release of venlafaxine hydrochloride. Said additional polymeric layer is composed, e.g., of a hydrophobic polymer mixed with an appropriate hydrophobic or hydrophilic plasticizer. Said polymeric layer is suitably sprayed over the coated nonpareil layer or over the isolating layer.

[0024] Appropriate coating polymers are, e.g. EUDRAGIT, cellulose derivatives such as hydroxypropylmethylcellulose, ethyl cellulose, cellulose acetate, etc. Their suitable plasticizers are, e.g., castor oil, dibutyl sebacate, glyceryl monostearate, diethyl phthalate, glyceryl triheptanoate, triethylcitrate, etc.

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[0025] The coating polymeric layer may also be a wax-based coating.

[0026] The composition preferably comprises 2-15% of the hydrophobic polymer per weight of the total dosage form, and preferably 0.1-2% per weight of the hydrophobic plasticizer per weight of the total dosage form.

5 [0026.1] According to another aspect of the invention, there is provided a pH-independent extended release composition, comprising: a nonpareil inert core; a venlafaxine hydrochloride layer coating said inert core, said venlafaxine hydrochloride comprising 30-60% based on the total weight of the composition; an isolating layer coating said venlafaxine hydrochloride layer, said isolating layer comprising a
10 polymer selected from the group consisting of polyvinylpyrrolidone, hydroxypropylcellulose, hydroxypropylmethylcellulose, carrageenan, and glycerol monostearate (GMS); and a controlled release layer coating said isolating layer, said controlled release layer comprising a polymer selected from the group consisting of ammonio methacrylate copolymer, hydroxypropylmethylcellulose, ethyl cellulose, and
15 cellulose acetate, said controlled release polymer layer comprising 2-15% based on the total weight of the composition, wherein said isolating provides at least one function of isolating, protecting and separating the venlafaxine hydrochloride layer from the controlled release layer, and said layers permit pH-independent release of the venlafaxine hydrochloride over an extended time period after oral administration.

20 [0026.2] According to another aspect of the invention, there is provided a pH-independent extended release dosage form having specified dissolution characteristics, comprising: venlafaxine hydrochloride in an amount of 30-60% based on the total weight of the dosage form; said venlafaxine hydrochloride being coated on a nonpareil inert core, said nonpareil inert core comprising 30-60% based on the
25 total weight of the dosage form; the venlafaxine hydrochloride being optionally connected to a binder in a binder amount of 0.5-10% based on the total weight of the dosage form, wherein said binder, when present, is selected from the group consisting of polyvinylpyrrolidone, hydroxypropylcellulose and hydroxypropylmethylcellulose; an isolating layer coating said venlafaxine

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hydrochloride and comprising 0.5-10% based on the total weight of the dosage form, said isolating layer selected from the group consisting of polyvinylpyrrolidone, hydroxypropylcellulose, hydroxypropylmethylcellulose, carrageenan and GMS; and a controlled release layer coated over said isolating layer, said controlled release layer comprising a polymer mixed with a plasticizer, said controlled release polymer comprising 2-15% based on the total weight of the dosage form, said controlled release polymer selected from the group consisting of ammonio methacrylate copolymer, hydroxypropylmethylcellulose, ethyl cellulose, and cellulose acetate, and said plasticizer comprising 0.1-2% based on the total weight of the dosage form; the parameters being selected so as to control release of the venlafaxine hydrochloride over an approximately 24 hour period in a manner that the following pH and rpm independent *in vitro* dissolution specifications are obtained:

Time (hrs)	Average % venlafaxine HCL release
2	<30
4	30-55
8	55-80
12	65-90
24	>80

[0026.3] According to another aspect of the invention, there is provided a pH-independent extended release dosage form of venlafaxine hydrochloride having dissolution characteristics that are equivalent to those of the venlafaxine hydrochloride dosage form sold under the proprietary name EFFEXOR XR, said dosage form comprising: (i) a nonpareil inert core comprising 30-60% based on the total weight of the dosage form; (ii) an active layer coating the nonpareil inert core, said active layer comprising venlafaxine hydrochloride in an amount of 30-60% based on the total weight of the dosage form; (iii) a hydrophilic polymeric or glycerol monostearate (GMS) layer coating the active layer, said hydrophilic or GMS layer comprising polyvinylpyrrolidone in an amount of 0.5-10% based on the total weight of the dosage form; and (iv) a controlled release layer coating the hydrophilic polymeric

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or GMS layer, said controlled release layer comprising ethyl cellulose an amount of 2-15% based on the total weight of the dosage form, and a dibutyl sebacate plasticizer in an amount of 0.1-2% based on the total weight of the dosage form; wherein said controlled release layer controls the release of the venlafaxine hydrochloride over an approximately 24 hour period.

[0026.4] According to another aspect of the invention, there is provided a method for preparing the pH-independent extended release composition as described herein, comprising: providing the nonpareil inert core; coating the nonpareil inert core with a layer of the venlafaxine hydrochloride; coating the venlafaxine hydrochloride layer with an isolating layer; and coating the isolating layer with a controlled release layer.

[0026.5] According to another aspect of the invention, there is provided a use of venlafaxine hydrochloride for treating a patient in need thereof, wherein the venlafaxine hydrochloride is formulated as a pH-independent extended release composition as described herein.

[0026.6] According to another aspect of the invention, there is provided a use of venlafaxine hydrochloride in the manufacture of a medicament for treating a patient in need thereof, wherein the venlafaxine hydrochloride is formulated as a pH-independent extended release composition as described herein.

[0027] The above processes are conventional processes that may be performed in a fluidized bed coater with a bottom spraying mechanism.

[0028] In the composition according to the present invention, preferably not more than 40% of the drug is released after two hours, not more than 60% released after 4 hours, and not more than 80% after 8 hours.

[0029] The compositions obtained are suitably, e.g., filled into hard gelatin capsules or compressed into tablets.

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[0030] This formulation has an identical *in vitro* dissolution profile as EFFEXOR XR (see Sherman, WO99/22724). They are not sensitive to any changes in dissolution conditions. It is bioequivalent to EFFEXOR XR 150 mg caps.

[0031] The coating process being used to produce the composition
5 according to the present invention is more efficient than the method being used in the Sherman patent. Moreover, it

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enables the preparation of the drug in a single type of equipment, e.g. a fluidized bed coater.

[0032] The present invention will now be illustrated with reference to the following examples, without being limited by them.

[0033] The process for preparing the composition according to the present invention is suitably performed as follows (all temperatures are given in degrees centigrade):

a. When venlafaxine hydrochloride is connected to a binder the venlafaxine hydrochloride is connected to the binder by methods known *per se*.

b. Stage 1

Coating the nonpareil core with the venlafaxine hydrochloride (advantageously connected with a binder) is performed at an inlet temperature of 45-55° (preferably at 50°) at an outlet temperature of 35-45° (preferably at 40°).

At the end of the spraying process, the composition is dried for 10 minutes without nozzle with 30 cfm air flow.

c.. Stage 2

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The coated core obtained in Stage 1 is coated with the insulating layer at an inlet temperature of $60^{\circ} \pm 3^{\circ}$ at an outlet temperature of $50^{\circ} \pm 2^{\circ}$.

d. Stage 3 (when an insulating layer is present in Stage 2)

The core is coated with a further preliminary layer; the conditions of said coating are:

Inlet temp: $50^{\circ} \pm 2^{\circ}$

Outlet temp: $40^{\circ} \pm 5^{\circ}$

[0034] Example No. 1 (without binder)

Stage 1: Components - Nonpareils 25/30 150 gr
 Venlafaxine hydrochloride 37.5 gr
 H₂O 150 gr.

Stage 2: Components - 150gr layered pellets from stage 1
 ETHOCEL*45cp 15 gr
 METHOCEL*5cp 1 gr
 Ethanol BP 300 gr

At the end of the spray process the composition is dried for 10 minutes without nozzle with 30 cfm.

[0035] Example No. 2

Stage 1: components - Nonpareils (inert sugar pellets) 150gr
 Povidone K-30 3.3 gr.

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Venlafaxine hydrochloride 165 gr.

Ethanol BP 670 gr.

Stage 2: components - 150gr. layered pellets from stage 1

ETHOCEL 45 cp 15 gr

METHOCEL 5 cp 1 gr

Ethanol BP 300 gr

The coating process was performed in a "4" fluidized bed coater made by Coating Place Inc. USA.

[0036] Example No. 3:

Stage 1: components - Nonpareils 25/30 150 gr

Venlafaxine hydrochloride 37.5 gr

Povidone K-30 0.75 gr

Ethanol BP 160 gr

Stage 2: components - 150gr layered pellets from stage 1

EUDRAGIT RS 30 D 150 gr

Triethyl citrate 9 gr

Glycerol monostearate 2.25 gr

Polysorbate 80 1 gr

Water 140 gr

The coating process was performed in a "4" fluidized bed coater, made by Coating Place Inc. USA.

[0037] Example No. 4:

Stage 1: components - Nonpareils 25/30 150gr.

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Povidone K-30 0.75 gr.

Venlafaxine-HCL 37.5 gr.

Ethanol-BP 160 gr.

Stage 2: components - 150 gr. pellets from stage 1.

EUDRAGIT RS 30 D 150 gr.

EUDRAGIT RL 30 D 15 gr.

Triethyl citrate 9 gr.

Glycerol monostearate 2.25 gr.

Polysorbate 80 1 gr

Water 140 gr.

All processes were performed in a "4" fluidized bed coater,
made by Coating Place Inc. USA.

[0038] Example no. 5:

Stage 1: components - 150 gr. Nonpareils 25/30

Povidone K-90 4.5 gr.

Venlafaxine-HCL 150 gr.

Ethanol BP 670 gr.

Water 110 gr

Stage 2: components - 150 gr. pellets from stage 1

Povidone K-30 3.75 gr.

Ethanol-absolute 60 gr.

Stage 3: components - Pellets from stage 2

ETHOCEL 100 cp 8 gr.

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Dibutyl sebacate 0.8 gr.

Ethanol-absolute 300 gr.

[0039] In the above examples, EUDRAGIT RS 30 D is poly(ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride) 1:2:0.1..EUDRAGIT RL 30 D is poly(ethyl acrylate-co-methyl methacrylate-co-trimethylammonioethyl methacrylate chloride) 1:2:0.2. ETHOCEL is ethyl cellulose and METHOCEL is methyl cellulose.

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CLAIMS:

1. A pH-independent extended release dosage form, comprising:

venlafaxine hydrochloride in an amount of 30-60% based on the total weight of the dosage form;
- 5 said venlafaxine hydrochloride being coated on a nonpareil inert core, said nonpareil inert core comprising 30-60% based on the total weight of the dosage form;

the venlafaxine hydrochloride being optionally connected to a binder in a binder amount of 0.5-10% based on the total weight of the dosage form;
- 10 a hydrophilic polymeric or glycerol monostearate (GMS) layer coating said venlafaxine hydrochloride and comprising 0.5-10% based on the total weight of the dosage form; and

a controlled release layer coated over said hydrophilic polymeric or GMS layer, said controlled release layer comprising a hydrophobic polymer optionally
15 mixed with a plasticizer, said hydrophobic polymer comprising 2-15% based on the total weight of the dosage form, and said optional plasticizer, when present, comprising 0.1-2% based on the total weight of the dosage form; and

said controlled release layer permitting controlled release of the venlafaxine hydrochloride over an approximately 24 hour period.
- 20 2. The dosage form of claim 1, wherein at least one of said controlled release layer, said hydrophilic polymeric or GMS layer, and said optional binder, when present, comprises hydroxypropylmethylcellulose.
3. A pH-independent extended release composition, comprising:

a nonpareil inert core;

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a venlafaxine hydrochloride layer coating said inert core, said venlafaxine hydrochloride comprising 30-60% based on the total weight of the composition;

an isolating layer coating said venlafaxine hydrochloride layer, said
5 isolating layer comprising a polymer selected from the group consisting of polyvinylpyrrolidone, hydroxypropylcellulose, hydroxypropylmethylcellulose, carrageenan, and glycerol monostearate (GMS); and

a controlled release layer coating said isolating layer, said controlled release layer comprising a polymer selected from the group consisting of ammonio
10 methacrylate copolymer, hydroxypropylmethylcellulose, ethyl cellulose, and cellulose acetate, said controlled release layer comprising 2-15% based on the total weight of the composition,

wherein said isolating layer provides at least one function of isolating, protecting and separating the venlafaxine hydrochloride layer from the controlled
15 release layer, and said layers permit pH-independent release of the venlafaxine hydrochloride over an extended time period after oral administration.

4. The composition according to claim 3, wherein the isolating layer comprises a polymer selected from the group consisting of polyvinylpyrrolidone, hydroxypropylcellulose, hydroxypropylmethylcellulose, and carrageenan.

20 5. The composition according to claim 3, wherein the isolating layer is 0.5-10% based on the total weight of the composition.

6. The composition according to claim 3, wherein the venlafaxine hydrochloride layer further comprises a binder.

7. The composition according to claim 6, wherein the binder is selected
25 from the group consisting of polyvinylpyrrolidone, hydroxypropylcellulose, and hydroxypropylmethylcellulose.

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8. The composition according to claim 6, wherein the binder is 0.5-10% based on the total weight of the composition.

9. The composition according to claim 3, wherein the controlled release layer further comprises a plasticizer.

5 10. The composition according to claim 9, wherein the plasticizer is 0.1-2% based on the total weight of the composition.

11. The composition according to claim 9, wherein the plasticizer is selected from the group consisting of castor oil, dibutyl sebacate, glyceryl monostearate, diethyl phthalate, glyceryl triheptanoate, hydroxypropyl cellulose,
10 polyethylene glycol, and triethyl citrate.

12. The composition according to claim 3, wherein the nonpareil inert core is an inert sugar core or a microcrystalline cellulose core.

13. The composition according to claim 12, wherein the core is 30-60% based on the total weight of the composition.

15 14. A use of venlafaxine hydrochloride for treating a patient in need thereof, wherein the venlafaxine hydrochloride is formulated as the pH-independent extended release composition according to claim 3.

15. A use of venlafaxine hydrochloride in the manufacture of a medicament for treating a patient in need thereof, wherein the venlafaxine hydrochloride is formulated as
20 the pH-independent extended release composition according to claim 3.

16. A method for preparing the pH-independent extended release composition according to claim 3, comprising:

providing the nonpareil inert core;

coating the nonpareil inert core with a layer of the venlafaxine

25 hydrochloride; and

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coating the venlafaxine hydrochloride layer with the isolating layer; and
coating the isolating layer with the controlled release layer.

17. The pH-independent extended release dosage form according to claim 1,
wherein the isolating layer comprises polyvinylpyrrolidone, the controlled release layer is
ethyl cellulose and the controlled release layer further comprises a dibutyl sebacate
plasticizer.

18. A pH-independent extended release dosage form having specified
dissolution characteristics, comprising:

venlafaxine hydrochloride in an amount of 30-60% based on the total
weight of the dosage form;

said venlafaxine hydrochloride being coated on a nonpareil inert core,
said nonpareil inert core comprising 30-60% based on the total weight of the dosage
form;

the venlafaxine hydrochloride being optionally connected to a binder in
a binder amount of 0.5-10% based on the total weight of the dosage form, wherein
said binder, when present, is selected from the group consisting of
polyvinylpyrrolidone, hydroxypropylcellulose and hydroxypropylmethylcellulose;

an isolating layer coating said venlafaxine hydrochloride and comprising
0.5-10% based on the total weight of the dosage form, said isolating layer selected
from the group consisting of polyvinylpyrrolidone, hydroxypropylcellulose,
hydroxypropylmethylcellulose, carrageenan and GMS; and

a controlled release layer coated over said isolating layer, said
controlled release layer comprising a polymer mixed with a plasticizer, said controlled
release polymer comprising 2-15% based on the total weight of the dosage form, said
controlled release polymer selected from the group consisting of ammonio
methacrylate copolymer, hydroxypropylmethylcellulose, ethyl cellulose, and cellulose

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acetate, and said plasticizer comprising 0.1-2% based on the total weight of the dosage form;

the parameters being selected so as to control release of the venlafaxine hydrochloride over an approximately 24 hour period in a manner that the following pH and rpm independent *in vitro* dissolution specifications are obtained:

Time (hrs)	Average % venlafaxine HCL release
2	<30
4	30-55
8	55-80
12	65-90
24	>80

19. The pH-independent extended release dosage form according to claim 18, wherein the isolating layer comprises polyvinylpyrrolidone, the controlled release polymer is ethyl cellulose and the controlled release layer further comprises a dibutyl sebacate plasticizer.

20. A pH-independent extended release dosage form of venlafaxine hydrochloride having dissolution characteristics that are equivalent to those of the venlafaxine hydrochloride dosage form sold under the proprietary name EFFEXOR XR, said dosage form comprising:

(i) a nonpareil inert core comprising 30-60% based on the total weight of the dosage form;

(ii) an active layer coating the nonpareil inert core, said active layer comprising venlafaxine hydrochloride in an amount of 30-60% based on the total weight of the dosage form;

(iii) a hydrophilic polymeric or glycerol monostearate (GMS) layer coating the active layer, said hydrophilic or GMS layer comprising

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polyvinylpyrrolidone in an amount of 0.5-10% based on the total weight of the dosage form; and

- (iv) a controlled release layer coating the hydrophilic polymeric or GMS layer, said controlled release layer comprising ethyl cellulose an amount of 2-15% based on the total weight of the dosage form, and a dibutyl sebacate plasticizer in an amount of 0.1-2% based on the total weight of the dosage form;

wherein said controlled release layer controls the release of the venlafaxine hydrochloride over an approximately 24 hour period.

21. The pH-independent extended release dosage form according claim 20, wherein the venlafaxine hydrochloride in said active layer is connected to a binder in an amount of 0.5-10% based on the total weight of the dosage form.

22. The pH-independent extended release dosage form according to claim 20 or 21, wherein the nonpareil inert core is an inert sugar core or a microcrystalline cellulose core.

23. A use of the pH-independent extended dosage form according to any one of claims 20 to 22 for treating depression in a subject.