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(54) **Title:** EXTENDED RELEASE PHARMACEUTICAL FORMULATION COMPRISING VENLAFAXINE HYDROCHLORIDE

(57) **Abstract:** Disclosed herein an extended release pharmaceutical formulation of venlafaxine comprising venlafaxine or its pharmaceutical acceptable salts in the form of spheroids. Said spheroids having a core consisting of about 40 % to about 55 % by weight of venlafaxine hydrochloride, about 40 % to about 50 % by weight of microcrystalline cellulose, about 0.5 % to about 5% by weight of hydroxypropyl methylcellulose, wherein the core is coated employing a combination of water insoluble and water soluble polymers.

EXTENDED RELEASE PHARMACEUTICAL FORMULATION COMPRISING VENLAFAXINE HYDROCHLORIDE

Field of the Invention

This invention relates to an extended release pharmaceutical formulation comprising venlafaxine or its pharmaceutical acceptable salts in the form of spheroids.

Background of the Invention

Venlafaxine is common name for the compound 1-[2-(dimethylamino)-1-(4-methoxyphenyl) ethyl] cyclohexanol. Chemically, it belongs to a class of hydroxycycloalkanephenethyl amines, useful as antidepressants.

Venlafaxine hydrochloride is presently administered in compressed tablet form in doses ranging from 75 to 350 mg/day. Venlafaxine hydrochloride is also administered orally as extended release formulation in the dosage range of 37.5 mg to 150 mg, for once a day dosage treatment of major depressive disorder, generalized anxiety disorder, social anxiety disorder and panic disorder. It is available as an immediate release tablet and as an extended release capsule under the brand name of Trevilor Retard®.

Venlafaxine hydrochloride, being highly water-soluble, has a potential problem of dose dumping and burst effect from a controlled release matrix. Hence, matrix delivery system is not suitable for consistent and prolonged delivery of the drug at the site of absorption. It is, therefore, essential to develop such dosage forms that ensure consistent delivery and prolonged plasma levels of drug with insignificant contribution to the initial release in case of a failure of the system, thereby avoiding dose dumping.

Coated multi-unit dosage forms are preferred over coated single unit dosage forms because in case of former there is less risk of dose dumping. This phenomenon occurs when there are undesired openings in the coatings, which may be caused during manufacturing or by the patient while handling the dosage form, or by involuntary chewing. Small openings or crack in the coating causes contact of the interior part of

dosage form with body fluids resulting in the release of the drug. The amount of drug released in case of a single unit dose evidently will be much higher than with a multi-unit dosage form such as spheroid.

US Patent No. 6,717,015 assigned to Synthon BV, discloses an extended release tablet of venlafaxine besylate monohydrate, hydroxypropyl methylcellulose and magnesium stearate, as prepared by direct compression method. But such a tablet has questionable release profile to suit the need for once a day dosage form.

US Patent No. 6,696,496 assigned to Synthon BV, discloses a hydrogel tablet consisting of venlafaxine hydrogen maleate, hydroxypropyl methylcellulose (Methocel K 4M EP), microcrystalline cellulose (Avicel PH 102), dibasic calcium phosphate anhydrous (Emcompress) and magnesium stearate, as prepared by direct compression method. Such a formulation results in dose dumping.

US Patent No. 6,274,171 assigned to American Home Products Corporation, describes an extended release once daily pharmaceutical composition consisting of hard gelatin capsules filled with film-coated spheroids. Specifically, an encapsulated dosage form is disclosed that comprises spheroids of therapeutically effective amount of venlafaxine hydrochloride, microcrystalline cellulose and, optionally, hydroxypropyl methylcellulose. The spheroids were further coated with a mixture of ethyl cellulose and hydroxypropyl methylcellulose.

Summary of the Invention

In accordance with a principle aspect of the present invention, there is provided an extended release oral pharmaceutical formulation of venlafaxine or its pharmaceutical acceptable salts in the form of spheroids, wherein said spheroids having a core with superior robustness are prepared by a commercial efficient process.

In accordance with an aspect of the present invention, there is provided an extended release oral pharmaceutical formulation of venlafaxine hydrochloride in the form of spheroids comprising venlafaxine hydrochloride, diluent, binder, water soluble

polymer and water insoluble polymer and other pharmaceutically acceptable adjuvants, wherein the selection of components of said formulation is done in a manner such that their interplay ensures desired release of venlafaxine hydrochloride to suit the once a day dosing.

In accordance with another aspect of the present invention, there is provided an extended release pharmaceutical formulation comprising a spheroidal core consisting of from about 40 % to about 55 % by weight of venlafaxine hydrochloride, from about 40 % to about 50 % by weight of microcrystalline cellulose, from about 0.5 % to about 5% by weight of hydroxypropyl methylcellulose and a extended release coating on the said core, wherein the extended release coating consists of from about 1 % to about 20 % by weight. Weight percentages are based on the weight of the uncoated spheroidal core. The extended release coating comprises of about 60 % to about 85% by weight of water insoluble polymer and about 15% to about 40 % by weight of water-soluble polymers.

In accordance with yet another aspect of the present invention, there is provided an extended release oral pharmaceutical formulation of venlafaxine hydrochloride, wherein said formulation comprising a spheroidal core consisting of from about 40 % to about 55 % by weight of venlafaxine hydrochloride, from about 40 % to about 50 % by weight of microcrystalline cellulose, from about 0.5 % to about 5% by weight of hydroxypropyl methylcellulose and optionally about 1 % to about 3 % by weight of lactose.

In accordance with still another aspect of the present invention, there is provided an extended release oral pharmaceutical formulation of venlafaxine or its pharmaceutical acceptable salts, wherein the extended release polymer coating is used in an amount from about 1 % to about 20 % by weight based on the weight of the uncoated spheroidal core. Preferably, extended release polymer coating is used in an amount from about 3 to about 15 % by weight based on the weight of uncoated spheroidal core.

Optionally the spheroids may have subcoating of hydroxypropyl methylcellulose before final extended release coating to strengthen the uncoated spheroidal core to endure the wear and tear of the subsequent coating process.

In accordance with yet another aspect of the present invention there is provided an extended release oral pharmaceutical formulation of venlafaxine or its pharmaceutical acceptable salts in the form of spheroids encapsulated into a capsule.

Brief Description of the Drawings:

The accompanying drawings, which are included to provide a further understanding of the invention and constitute a part of this specification

Figure 1 is a graphical depiction of bioavailabilty of Venlafaxine from commercially available formulation **Trevilor Retard®.** [Reference formulation A denoted in graph by symbol (•)] and formulation of example 5 [Test formulation B denoted in graph by symbol (□).

Figure 2 is a graphical depiction of bioavailabilty of O-Desmethyl Venlafaxine from commercially available formulation **Trevilor Retard®.** [Reference formulation A denoted in graph by symbol (•)] and formulation of example 5 [Test formulation B denoted in graph by symbol (□).

Detailed Description of the Invention

While this specification concludes with claims particularly pointing out and distinctly claiming that, which is regarded as the invention, it is anticipated that the invention can be more readily understood through reading the following detailed description of the invention and study of the included examples.

Dissolution profile and bioavailability of the venlafaxine hydrochloride from the formulation of invention is comparable with Trevilor Retard®. Trevilor Retard® is the branded version of German FDA approved extended release pharmaceutical

formulation of venlafaxine hydrochloride.

The inventors surprisingly achieved desired extended release of the drug from an extended release pharmaceutical formulation of venlafaxine after considerably reducing the concentration of the expensive microcrystalline cellulose in said formulation thereby reducing the cost of the formulation by 15-20% and that too without compromising with the quality of the product.

According to the present invention, the pharmaceutical formulation comprises of spheroids filled into capsules. The spheroids of the invention comprises active pharmaceutical agent i.e. venlafaxine hydrochloride, diluent, binder, optional conventional adjuvants, and extended release coating comprising water insoluble and water soluble polymers. Optionally the spheroids may have subcoating of hydroxypropyl methylcellulose before the final extended release coating.

According to the present invention, the pharmaceutical formulation in the form of spheroids filled into capsules contains venlafaxine hydrochloride as the active pharmaceutical agent, which is responsible for eliciting the therapeutic response. The venlafaxine hydrochloride may be present in an amount from about 40 % to about 55 % by weight based on the weight of the uncoated spheroidal core. Preferably, from about 45 % to about 50 % by weight based on the weight of the uncoated spheroidal core. The amount of venlafaxine hydrochloride dispensed in a capsule ranges from 37.5 mg to 150 mg based on the weight of the venlafaxine base.

According to one embodiment of the present invention, the spheroids contain microcrystalline cellulose as the preferred filler. Filler may be present in an amount from about 40 % to about 50 % by weight based on the total weight of the uncoated spheroidal core. Microcrystalline cellulose is commercially available from FMC Corporation, Germany, under the brand name Avicel® PH 101. Microcrystalline cellulose may be used in combination with lactose optionally. Lactose may be used in an amount, which is less than 6% by weight based on the weight of the uncoated spheroidal core.

An optional subcoating of water-soluble cellulose ethers such as hydroxypropyl cellulose or hydroxypropyl methylcellulose can be given on the spheroids to provide more granule strength to spheroids and thereby facilitating the coating of spheroids in fluid bed coater. Subcoating is applied to a level of from about 1% to 5% by weight of the uncoated spheroidal core. Subcoating mainly consists of low viscosity water-soluble polymers.

According to the present invention, the spheroids filled into capsules also contain a binder in the form of hydroxypropyl methylcellulose or hydroxy propyl cellulose, preferably hydroxypropyl methylcellulose of low viscosity grades (3-8 CPS). The binder is used preferably in an amount from about 0.5 % to about 5% by weight.

It is within the scope of the invention to include antistatic agents like colloidal silicon dioxide and talc, colorants like yellow iron oxide and plasticizers like polyethylene glycol in the formulation of the invention. Concentration of usage of the above-mentioned pharmaceutical adjuvants is known to the skilled artisan.

The extended release polymer coating according to the present invention comprising water-soluble and water insoluble polymer to achieve the extended release of venlafaxine hydrochloride from spheroids.

The extended release polymer coating is used in an amount from about 1 to about 20 % by weight based on the weight of the uncoated spheroidal core. Preferably, extended release polymer coating is used in an amount from about 3 to about 15 % by weight of the uncoated spheroidal core.

Suitable water insoluble polymers include but are not limited to cellulose ether, such as low viscosity ethyl cellulose, a cellulose ester, such as cellulose acetate, polyvinyl alcohol, copolymers of acrylate and methacrylates with quarternary ammonium group, such as, Eudragit® RL30 D and Eudragit® RS 30 D (available from Rohm Pharma). Eudragit® RL30 D is chemically known as poly (ethyl acrylate, methyl methacrylate,

trimethylammonioethyl methacrylate chloride) 1:2:0.2. Similarly Eudragit® RS 30 D is chemically known as poly (ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) 1:2:0.1.

The preferred water insoluble polymer is low viscosity (10-50cps) ethylcellulose (available from Dow Chemical and Hercules under the trade name Ethocel® and Aqualon® respectively). Viscosity determination of ethylcellulose is performed at 25^0 C using 5% w/v ethyl cellulose solution in 80:20 mixtures of toluene and ethanol. The viscosity of ethyl cellulose solution increases with the increase in concentration of ethyl cellulose. Different viscosity grades of ethyl cellulose are available under the trade name Ethocel®.

Suitable water-soluble polymers of the present invention include but are not limited to polyvinylpyrrolidone, Poly (ethylene oxide), hydroxymethyl cellulose and low viscosity (5-15cps) hydroxypropyl cellulose. The preferred water-soluble polymer is low viscosity (5-15cps) hydroxypropyl cellulose. Hydroxypropyl cellulose is commercially available from Hercules incorporated Aqualon division, USA under the brand name Klucel® EF. The viscosity of 2 % aqueous solution of Klucel is 7 cps at 25^0 as determined by Brookfield viscometer.

In extended release coating, water insoluble polymer is preferably used in an amount from about 60 to 85 % by weight of the extended release coating and water-soluble polymer is preferably used in an amount of from about 15 to about 40 % by weight of the extended release coating.

According to the present invention, use of low quantity of expensive microcrystalline cellulose as the filler in the formulation results in the cost reduction of the product by 15-20% when compared with the prior arts.

Spheroidal cores are preferably produced by extrusion spheronization process. Alternatively, drug layering on neutral spherical seeds can also produce cores of desirable size. Coating of the spheroidal cores can be carried out in conventional

coating pan. Preferably, coating of cores is carried out in a fluid bed processor fitted with Wurster apparatus.

According to the process for making the spheroidal cores, the venlafaxine hydrochloride, filler and other pharmaceutical excipients are passed through suitable size mesh and are then mixed together in a suitable mixer. The blend so obtained was granulated using an aqueous/non aqueous solution of binder. The wet mass is passed through extruder to form elongated semolina like masses. These masses are next immediately subjected to spheronization to round off into spheroidal cores. Spheroidal cores so formed are dried to achieve desired moisture content and are finally screened through suitable size sieve.

The extended release coating is performed by dissolving ethyl cellulose and hydroxypropylcellulose in a suitable solvent like isopropyl alcohol and spraying the resultant dispersion onto the spheroidal cores, using a coating pan or a fluidized bed apparatus to get the coated spheroidal cores.

The following non-limiting examples illustrate specific embodiments of the present invention. They are, however, not intended to be limiting the scope of the present invention in any way.

EXAMPLE 1 to 5

Table 1

Composition for the extended release pharmaceutical formualtion of venlafaxine hydrochloride:

Ingredients		**Example No./amount in examples given in mg/cap**				
No.	**(A) Spheroidal Core**	1	2	3	4	5
1	Venlafaxine hydrochloride equivalent to venlafaxine	169.7 (150)	169.7 (150)	169.7 (150)	169.7 (150)	169.7 (150)
2	Microcrystalline cellulose	162.0	162.3	162.3	162.0	162.3
3	Hydroxypropyl methylcellulose	---	9.5	9.5	---	3.0
3	Hydroxypropylcellulose	3.0	----	---	4.00	---
4	Lactose	5.9	----	---	4.95	---
5	Colloidal silicon dioxide	---	1.5	1.5	---	---
6	Purified water*	q.s.	q.s	q.s	q.s	q.s
	Total	340.6	343.0	343.0	340.6	335.0
	(B) Sub – Coating (optional)					
6	Hydroxypropyl methylcellulose	6.0	---	---	---	---
7	Hydroxypropylcellulose	---	6.0	---	----	4.40
8.	Talc	1.5	1.2	---	---	1.75
9	Red iron oxide	0.05	1.0	---	---	---
10	Titanium dioxide	--	--			0.35
11	Polyethylene glycol (PEG 400)	0.5	----	---	---	0.52
12	Purified water*	q.s.	q.s.	---	---	q.s.
13	Isopropyl alcohol	--	---			q.s.
	Total	348.7	351.2	---	---	342.02
	(C) Extended release coating					
13	Ethyl cellulose (N-50)	16.10	16.10	16.20	18.8	24.32
14	Hydroxypropylcellulose	1.8	1.8	1.8	3.3	4.29

15	Yellow iron oxide	0.10	0.10	0.1	0.1	0.10
16	Isopropyl alcohol*	q.s.	q.s.	q.s.	q.s.	q.s.
17	Purified water*	q.s.	q.s.	q.s.	q.s.	q.s.
	Total	366.7	369.2	361.1	362.8	370.73

* Not present in the final formulation.

Manufacturing Procedure

a) Venlafaxine hydrochloride, microcrystalline cellulose and lactose (colloidal silicon dioxide) were passed through suitable size mesh and blended together.

b) The blend as obtained in step (a) was granulated with aqueous solution of binder like hydroxypropyl methylcellulose or hydroxypropylcellulose and passed through extruder.

c) Extrudates were transferred to spheronizer to obtain spheroids.

d) The spheroids were dried and passed through suitable size mesh to get uniform size of spheroids.

e) As the case may be spheroids obtained in stage (d) were subcoated with coating solution, prepared using the above-mentioned subcoating composition. In examples 3 and 4, subcoating was avoided.

f) The spheroids obtained in stage (e) were finally coated with coating solution, prepared using the above-mentioned extended release coating composition. The coated spheroids were filled in suitable size capsules.

Dissolution studies

The formulation of the invention was subjected to an in-vitro dissolution method to determine the rate at which the drug venlafaxine hydrochloride was released from the spheroids filled into capsules. Dissolution method involved USP type I apparatus at 100 rpm wherein water was used as dissolution medium at temperature of 37^0C temperature. The dissolution profiles of the formulations of invention were compared with the Trevilor Retard and the results were summarized in the table 2 below.

Table 2

Dissolution profiles

Time (Hrs)	Dissolution profiles (Drug released in terms of percentage of venlafaxine hydrochloride)				
	Ex. 1	Ex. 2	Ex.3	Ex 5	Trevilor Retard
4	39	55	45	46	43
8	64	74	68	69	69
12	75	82	78	79	80
24	89	91	91	92	89

The results in table 2 above clearly show that the dissolution profiles of formulations of the invention in the form of coated spheroids filled into capsules (Ex.3 and Ex.5), are comparable to the dissolution profile of the commercially available Trevilor Retard capsules.

Bioequivalence studies

In order to assess bioequivalence of the invented formulation of the invention with respect to Trevilor Retard, a randomized, two treatment, two period, two sequence, single dose, crossover bioavailability study on venlafaxine hydrochloride 150 mg extended release capsule (Ex. 5) with respect to venlafaxine 150 mg extended release capsule, available under the brand name Trevilor Retard 150 mg from Wyeth Pharms Inc., in twelve healthy, adult, male, human subjects was carried out under fasting conditions. The results of study in terms of pharmacokinetic parameters are summarized in table below.

Table 3

Pharmacokinetic results

Pharmacokinetic Parameters	Venlafaxine [parent compound (PC)]		O- desmethylvenlafaxine [Active metabolite (AM)]		Ratio of least square means (%) (TF/ RF)		90% confidence interval (TF/ RF)	
	Ex 5 (TF)*	Trevilor Retard (RF)**	Ex. 5 (TF)*	Trevilor Retard (RF)**	(PC)	(AM)	(PC)	(AM)
Cmax (ng/ml)	124.142	114.085	212.609	215.988	108.8	98.9	96.41 to 122.87	92.11 to 106.19
AUC (0>t) (ng.h/ml)	1795.115	1846.317	5891.824	5945.460	99.3	99.0	89.24 to 110.42	93.18 to 105.08
AUC (0>inf.) (ng.h/ml)	1895.391	1929.608	6018.708	6098.785	100.4	98.6	91.26 to 110.48	93.12 to 104.39

The above results clearly signify that the formulation of invention (Ex.5) has bioavailability comparable with Trevilor Retard.

While this invention has been described in detail with reference to certain preferred embodiments, it should be appreciated that the present invention is not limited to those precise embodiments rather, in view of the present disclosure, which describes the current best mode for practicing the invention, many modifications and variations, would present themselves to those skilled in the art without departing from the scope and spirit of this invention.

We Claim:

1. An extended release pharmaceutical formulation of venlafaxine comprising a spheroidal core consisting of about 40 % to about 55 % by weight of venlafaxine hydrochloride, about 40 % to about 50 % by weight of microcrystalline cellulose, about 0.5 % to about 5% by weight of hydroxypropyl methylcellulose, and a extended release coating on the said core, wherein extended release coating comprises about 1 % to about 20% by weight.

2 The pharmaceutical formulation according to claim 1, wherein the extended release coating comprises from about 3 % to about 15 % by weight based on the weight of the spheroidal core.

3. The pharmaceutical formulation according to claim 1, wherein the extended release coating comprises from about 60 % to about 85 % by weight of the water insoluble polymer and from about 15 % to about 40% of water soluble polymer.

4. The pharmaceutical formulation according to claim 2, wherein the water insoluble polymer is ethyl cellulose.

5 The pharmaceutical formulation according to claim 2, wherein the water-soluble polymer is hydroxypropylcellulose.

6 The pharmaceutical formulation according to claim 1, wherein coated spheroids are encapsulated into a capsule.

7 A process for preparing an extended release pharmaceutical formulation as claimed in claim 1 comprising:

blending venlafaxine hydrochloride with microcrystalline cellulose;

granulating the resultant blend with aqueous or non aqueous solution of the hydroxypropyl methylcellulose;

subjecting the resultant wet mass to extrusion-spheronization processes to get the spheroidal core;

drying the resultant spheroidal core;

coating the spheroidal core with an extended release coating comprised of ethyl cellulose and hydroxypropyl cellulose; and

encapsulating the resultant coated spheroids into capsules.

8. The process according to claim 5, wherein lactose is optionally added along with said microcrystalline cellulose.

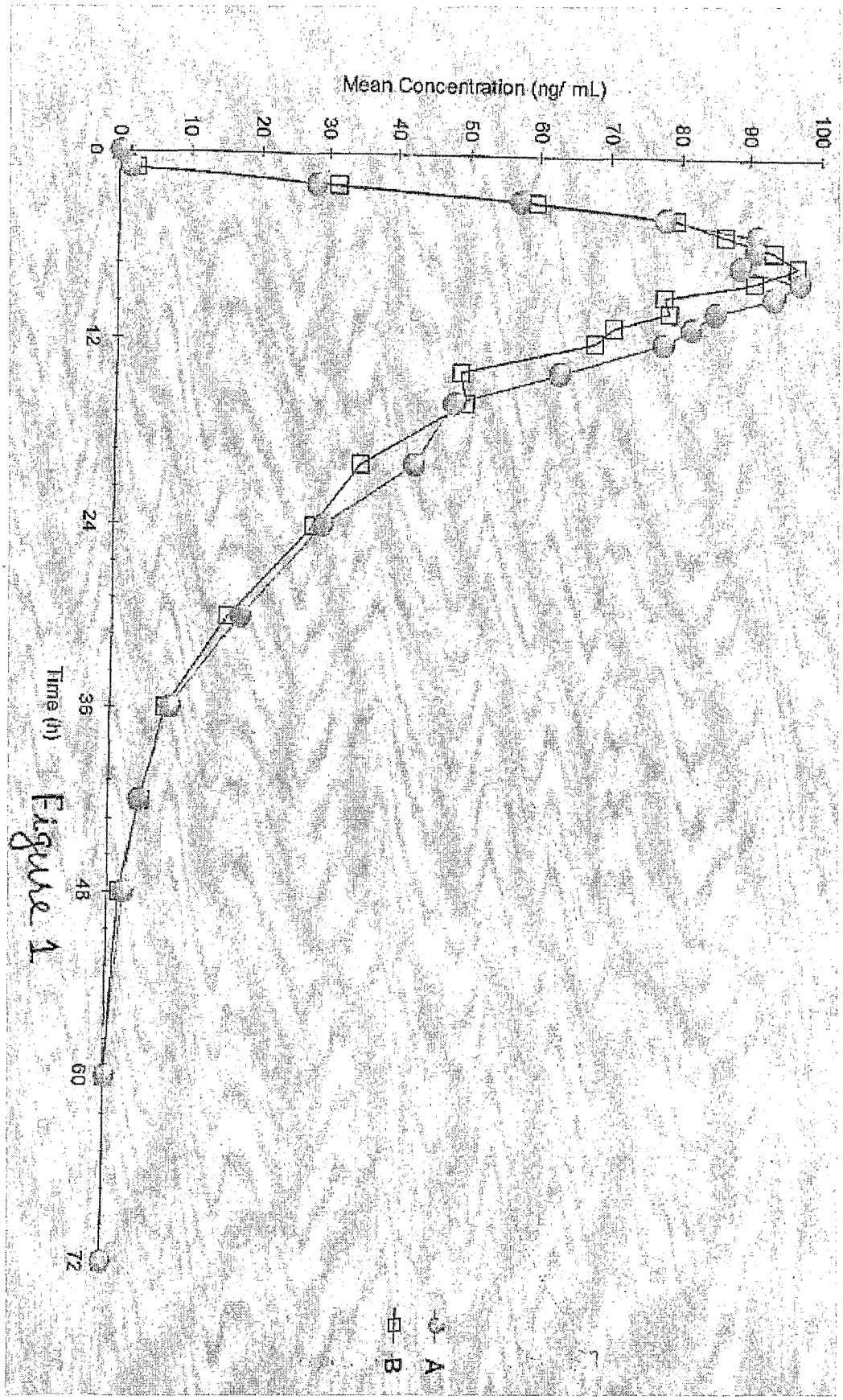

Mean Concentration (ng/ mL)
0
10
20
30
40
50
60
70
80
90
100
0
12
24
36
48
60
72
Time (h)
A
B

Figure 1

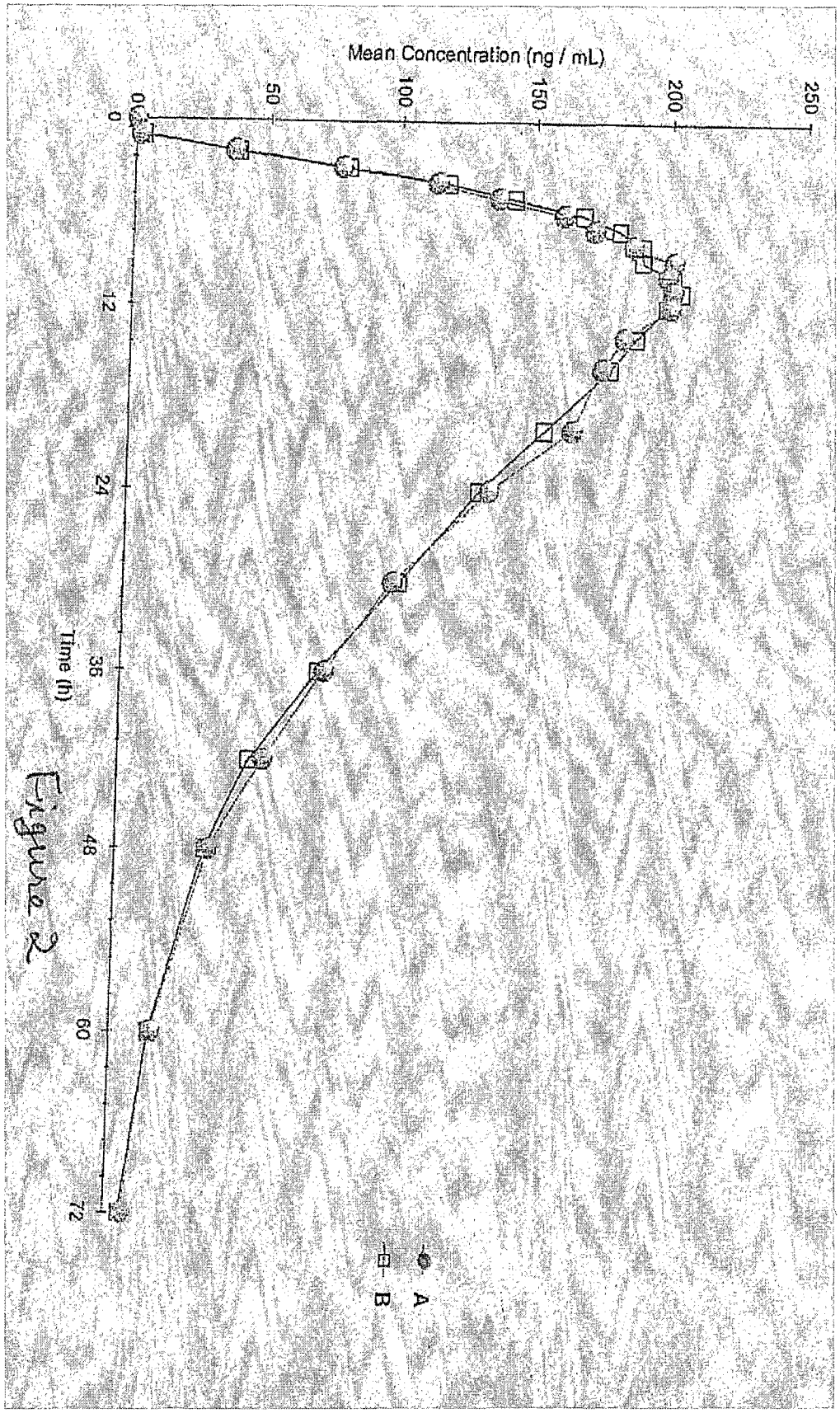

Mean Concentration (ng / mL)
0
50
100
150
200
250
Time (h)
0
12
24
36
48
60
72
A
B

Figure 2