OPIC
Office de la propriété intellectuelle du Canada

CIPO
Canadian Intellectual Property Office

(12) (19) (CA) **Brevet-Patent**

(11) (21) (C) **2,124,012**
(86) 1992/11/23
(87) 1993/05/27
(45) 2000/02/01

(72) Philippon, Francis, FR
(72) Boutin, Marie-Sylvie, FR
(72) Coussin, Gérard, FR
(72) Bruna, Etienne, FR
(73) Laboratoires Prographarm, FR

(51) Int.Cl.[6] A61K 31/55, A61K 9/54
(30) 1991/11/22 (07/797,496) US

(54) **FORMULATION DE DILTIAZEM A LIBERATION PROLONGEE**
(54) **SUSTAINED RELEASE DILTIAZEM FORMULATION**

(57) Formulation à base de diltiazem à libération prolongée pour administration orale comprenant un microgranule exempt d'acide organique pouvant avoir un effet irritant, ledit microgranule comprenant : a) une particule sphérique inactive centrale; b) une pluralité de couches primaires et secondaires en alternance entourant la particule sphérique pour former un noyau, et, c) un revêtement extérieur comprenant des premières couches membranaires intérieures appliquées audit noyau, et une seule membrane extérieure formant une couche relativement épaisse et homogène entourant lesdites premières couches membranaires intérieures; le nombre des couches de la première membrane intérieure et l'épaisseur de la membrane extérieure simple étant choisis de façon à ce que la libération du diltiazem s'effectue à partir du microgranule à une vitesse permettant une absorption contrôlée de ce dernier pendant une période de vingt quatre heures après l'administration orale.

(57) Prolonged release diltiazem-based formulation for oral administration comprising an organic acid-free microgranule capable of having an irritating effect. Said microgranule comprises: a) a central inactive spherical particle; b) a plurality of alternating primary and secondary layers surrounding the spherical particle, thereby forming a core, and c) an outer coating comprising initial membranous inner layers applied to said core, and a single outer membrane forming a relatively thick and even layer surrounding said initial membranous inner layers; the number of layers of the first inner membrane and the thickness of the single outer membrane being chosen to that diltiazem is released from the microgranule at a speed ensuring the latter's controlled absorption during a period of twenty four hours following oral administration.

ABSTRACT

Prolonged release diltiazem-based formulation for oral administration comprising an organic acid-free microgranule capable of having an irritating effect. Said microgranule comprises: a) a central inactive spherical particle; b) a plurality of alternating primary and secondary layers surrounding the spherical particle, thereby forming a core, and c) an outer coating comprising initial membranous inner layers applied to said core, and a single outer membrane forming a relatively thick and even layer surrounding said initial membranous inner layers; the number of layers of the first inner membrane and the thickness of the single outer membrane being chosen to that diltiazem is released from the microgranule at a speed ensuring the latter's controlled absorption during a period of twenty four hours following oral administration.

SUSTAINED RELEASE DILTIAZEM FORMULATION

Diltiazem-cis-(+)-3-(acetyloxy)-5-[2-(dimethylamino)-ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5H)-one hydrochloride is a benzothiazine derivative.

It is a calcium ion influx inhibitor, i.e. a slow channel blocker or calcium antagonist. It has a molecular weight of 450.98 and is a white to off-white crystalline powder, which is soluble in water, methanol and chloroform.

Diltiazem hydrochloride has been shown to be useful in alleviating symptoms of chronic heart diseases, particularly angina pectoris and myocardial ischemia, while displaying a low incidence of side effects.

It is conventionally administered orally.

Diltiazem is extensively metabolized by the liver and excreted by the kidneys and in bile. Although the precise mechanism of its anti-anginal action is still being delineated, diltiazem is believed to act in the following ways. Diltiazem has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished in reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads. In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential.

Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and non-ischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Like other calcium antogonists, diltiazem decreases

sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In humans, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure; in exercise tolerance studies in patients with ischemic heart disease, it reduces the double product (heart rate x blood pressure) at the level of the heart for any given work load.

Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous administration) of about 40%.

Various types of sustained release diltiazem formulations have been described in the literature ("The Use of Diltiazem Hydrochloride in Cardiovascular Disorders", McAuley and Schroeder, Pharmacotherapy, Vol. 2, No. 3, p. 121, May/June 1982) and in the following United States patents : US-A-5,002,776, US-A-4,960,596, US-A-4,917,899, US-A-4,894,240, US-A-4,891,230 and US-A-4,721,619. However, all but one of these patents, i.e. US-A-4,960,596, involve the use of an organic acid which may have an irritating effect.

The object of the invention is, above all, to provide a sustained release diltiazem based formulation which no longer presents the drawbacks of the prior art formulations, namely for twice daily administration, which does not have the irritating effect of these formulations and which has a satisfactory dissolution rate or pattern.

It also must

- be easy to manufacture at a good manufacturing price
- be suitable for twice daily administration, or

B

for once daily administration,

- present relative bioavailability equivalent to that of known diltiazem oral formulations.

The sustained release diltiazem formulation for oral administration according to the invention comprises a microgranule or pellet first comprising a sugar or sugar/starch sphere, a plurality of alternating first and second layers surrounding the sphere to produce a core, the first alternating layer comprising a water soluble, pharmaceutically acceptable, polymeric material and the second alternating layer comprising diltiazem or a pharmaceutically acceptable salt thereof to form a core on which two membrane layers are applied of which the first or innermost membrane layer from the core is consisting of a layer of a first water insoluble, pharmaceutically acceptable polymeric material such as ethylcellulose with added talc or other lubricant, and of which the second or outermost membrane layer from the core constitutes a relatively thick single layer coating of a water insoluble pharmaceutically acceptable polymeric material, such as those known under the trademark EUDRAGIT S 100, to which is added a plasticizer such as diethylphthalate, talc or another lubricant.

The number of layers of the inner membrane and the outer membrane is such that the release of the diltiazem from the core occurs at a rate allowing controlled absorption thereof over an eight, twelve or twenty hours period following oral administration, that rate being measured in vitro as a dissolution rate of the pellet which, when measured in an aqueous medium utilizing a paddle apparatus according to United States Pharmacopeia XXII, substantially corresponds to the following dissolution pattern: from 15 to 40% of the total diltiazem is released after 4 hours of measurement; from 40 to 70% of the total diltiazem is released after 8 hours of measurement; from 50 to 85% of the total diltiazem is released

after 12 hours of measurement and from 70 to 100% of the total diltiazem is released after 24 hours of measurement.

The invention will be better understood by reference to the following detailed description when considered in connection with the accompanying drawing wherein the single figure is a graph of the dissolution rate of sustained release diltiazem hydrochloride expressed as percent (%) of active substance released versus time t (in hours) and graphed as the average of the individual values + Sx (difference type) obtained by dissolving the 120 mg capsule sample in 900 ml of water in a paddle apparatus at 100 rpm according to United States Pharmacopeia XXII.

The sustained release diltiazem formulation according to the present invention comprises microgranules or non-pareil seeds or spheres having an average diameter in the range of 0.4 to 0.7 mm and comprising neutral excipients such as sugar or sugar/starch. The microgranules produced in accordance with the invention preferably contain about 20 to 37% by weight of neutral core.

Applied to the core are a plurality of alternating layers of diltiazem or a pharmaceutically acceptable salt thereof, such as the hydrochloride, and of a water soluble pharmaceutically acceptable polymeric material such as polyvinylpyrrolidone (PVP), such as those known under the name PVP K 30, said diltiazem or its salt being applied by projecting active substance under powder form.

Other suitable water soluble polymers are consisting of polyethyleneglycol or polyvinyl alcohol or mixtures of PVP and any of the foregoing products.

This multi-layer arrangement is accomplished in a conventional coating pan utilizing conventional methods such as spraying of the ingredients to form the plurality of successive layers of active ingredient and polymer.

It should be emphasized that no other product, such as an organic acid or talc is used in association with the

diltiazem hydrochloride or PVP or other polymer.

A solution of PVP is prepared in water or in a solubilizing organic solvent (such as ethyl alcohol, acetone, isopropanol, water or a mixtures thereof) and the central core is wetted with the PVP solution.

A desired quantity of the diltiazem is projected or dusted upon the wetted core which then is subjected to a short drying step. The alternating application of PVP and diltiazem layers is repeated until the quantity of diltiazem corresponding to the desired dose is obtained.

The concentration of the polymeric material in the solution is determined by the visocity of the final solution. The ratio of inert core to diltiazem is between 1:1 and 1:10. The active core is obtained through a process which involves a certain number of cycles. Each cycle does not lead to an additional layer on the surface of the core, but rather to an enlargement of the core.

Moreover, if one examines the final microgranules, it is not possible to distinguish layers in the active core, whereas actual layers can be distinctively seen in the membrane. Ine one advantageous embodiment, the preferred number of cycles is comprised between 70 and 140.

Thereafter, the product may be air dried in hot air or may be passed through a dessiccation enclosure. The microgranules may be sieved and checked for humidity and grain size.

Numerous types of coatings within the scope of the present invention may be used to make the inner and outer membranes in accordance with the invention. Such different coatings as envisioned by the present invention enable the achievement of products which are at least biologically equivalent to prior art products such as disclosed in U.S. Patent No. 4,721,619.

The inner membrane layer preferably comprises ethylcellulose and a lubricant such as talc. Other accep-

table lubricants are calcium stearate, zinc stearate or magnesium stearate. In some cases, the inner layer may be a polymer such as those known under the trademark EUDRAGIT RS.

The outer membrane coating comprises a water insoluble pharmaceutically acceptable polymeric material which is applied by dissolving the material in a suitable solvent. In addition, the membrane may contain either or both a plasticizer such as diethylphthalate, and a lubricant such as talc or the other lubricants hereabove identified.

According to an advantageous embodiment of the invention, the water insoluble polymeric material of the outer membrane coating is EUDRAGIT S 100. Other suitable plasticizers are polyethyleneglycols, dibutyl phthalate or triacetin (or glycerol triacetate). The outer membrane coating may consist of a single layer or of up to five or more layers.

The polymer marketed under the trademark EUDRAGIT S is slightly permeable to diltiazem and water.

The polymers sold under the trademark EUDRAGIT are polymeric lacquer substances based on acrylic and/or methacrylic acid esters. These products are described in the EUDRAGIT brochures of Firm Röhm Pharma GmbH (1985 and seq.). Other suitable water insoluble polymers are those of the group comprising cellulose acetate phthalate, those marketed under the trademarks EUDRAGIT L, EUDRAGIT RS and AQUACOAT.

In the present invention, the solution of ethylcellulose for the inner membrane layer is prepared utilizing a solvent. These ingredients may be applied by conventional methods, such as by conventional pan coating with a lubricant being poured into the coating pan. The solution may be applied while simultaneously projecting the talc. Drying may be performed in hot air, a short time after which the microgranules are sieved, humidity and grain

size being then checked. Preferably, the number of layers of the inner membrane is comprised between 1 and 20.

The outer membrane coating is preferably applied by a conventional method utilizing a fluidized air-bed equipped with a Würster column in a continuous process. In this equipment, the appropriate outer membrane is sprayed onto the ethylcellulose coated cores. The solution from which is prepared the outer membrane may contain one or more water insoluble polymers dissolved in a suitable solvent such as ethanol, acetone or isopropanol, or in a mixture thereof, in the presence of other additives such as a lubricant, e.g. talc, and a plasticizer such as diethylphthalate. The coating obtained is very homogeneous and regular. The outer membrane coating may comprise from one to five layers or more. Drying may be performed in hot air, after which the microgranules are sieved, before checking humidity and grain size. Thereafter, the product may be put into capsules or tablets.

At no time is shellac used in either membrane. Shellac is unsatisfactory for several reasons, including decreasing the shelf life of the product.

The characteristics of the water insoluble inner and outer membranes of the product obtained this way should enable the diltiazem hydrochloride to be released into an aqueous medium according to the following intervals measured using a paddle apparatus according to the United States Pharmacopeia XXII:

(a) from 15 à 40% of the total diltiazem is released after 4 hours of measurement;

(b) from 40 à 70% of the total diltiazem is released after 8 hours of measurement;

(c) from 50 à 85% of the total diltiazem is released after 12 hours of measurement; and

(d) from 70 à 100% of the total diltiazem is released after 24 hours of measurement;

From the foregoing it can be seen that the

preferred membrane of the present invention contains a combination of two or more water insoluble polymers, one of which is soluble in neutral to weakly alkaline media. One of these polymers, ethylcellulose, is water insoluble and insoluble in neutral to weakly alkaline media. Another of these polymers, namely the one which is marketed under the trademark EUDRAGIT S 100, is water insoluble but soluble in neutral to weakly alkaline media.

In the preferred embodiments, there is approximately 10% of the methacrylic acid copolymer, 0.6% of ethylcellulose N7, 1.25% of plasticizer and 6.5% of talc. These percentages as well as all other percentages set forth herein-above are weight percentages.

The weight ratio of the water insoluble, pH dependent polymer, such as the one which is marketed under the trademark EUDRAGIT S 100, to diltiazem is in the range of 0.15:1 to 0.24:1.

The ratio of the water insoluble, pH independent polymer, such as ethylcellulose, is in the weight ratio range of 0.009:1 to 0.014:1.

The ratio of lubricant to diltiazem is in the weight ratio range from 0.1:1 to 0.15:1.

The ratio of plasticizer to diltiazem is in the weight ratio range from 0.02:1 to 0.03:1.

MANUFACTURING EXAMPLE I

An amount of 6.0 kg of diltiazem hydrochloride was sieved through a 1.25 mm screen. The powder was applied to starch/sugar microgranules (0.4 mm to 0.7 mm diameter) of which an amount of 3.6 kg is placed in a coating pan using a binding solution of 20% PVP K 30 in alcohol.

The microgranules are coated with a measured volume of binding solution followed by dusting on of a measured amount of powder. The coated microgranules were allowed to dry and this layer formation step is repeated until all of the powder has been applied.

The coated microgranules were then dried overnight

at approximately 25°C.

The microgranules were then subjected to a control test before coating.

The active cores once prepared, are surrounded by a first or inner membrane by applying inside a coating pan 12 layers of a solution consisting of 10% of the product sold under the trademark EUDRAGIT RS in an acetone/isopropanol solution. Talc was dusted on inside the coating pan during this step. The product marketed under the trademark EUDRAGIT RS is an anionic polymer synthetized from acrylic and methacrylic acid ester and comprising a low content of quaternary ammonium groups. The ammonium groups are present as salts and give rise to the permeability of the lacquer films. They provide water insoluble, but permeable, film coatings.

The thus obtained microgranules were then introduced into a fluidized air-bed equipped with a Würster column. Inside this equipment, a polymeric solution mixed with diethylphthalate and talc was sprayed onto the microgranules constituting an outer or second membrane. The polymeric solution consisted of 70% (weight/ weight) of a 7.5% EUDRAGIT S solution in acetone/isopropanol and of 30% (weight/weight) of a 7.5% EUDRAGIT L solution in acetone/isopropanol.

MANUFACTURING EXAMPLE II

Example I was repeated, except that the polymeric solution used in connection with the second membrane is consisting of 25% (weight/ weight) of a 7.5% EUDRAGIT L solution in acetone/isopropanol and of 75% (weight/ weight) of a 7.5% EUDRAGIT S solution in acetone/isopropanol.

MANUFACTURING EXAMPLE III (preferred embodiment)

Example I was repeated, except that the polymeric solution used in connection with the first membrane was ethylcellulose instead of the product marketed under the trademark EUDRAGIT RS and that the polymeric solution used

to apply the outer membrane consisted of the product marketed under the trademark EUDRAGIT S alone.

Data collected with respect to the dissolution

The product of Example III was utilized in clinical testing of humans.

The results obtained, which relate to the industrial product, are as follows:

pH = 6.5 (USP XXII)

Time (h)	Average (6 tests) %	Standard deviation	cv %
1	2.14	0.39	18.42
2	6.06	0.53	8.79
3	11.65	0.69	5.89
4	18.18	0.74	4.06
5	25.15	0.90	3.57
6	32.24	0.95	2.94
7	39.39	0.80	2.02
8	45.66	0.94	2.06

pH = 7.4 (USP XXII)

Time (h)	Average (6 tests) %	Standard deviation	cv %
1	31.00	3.82	12.32
2	87.13	2.22	2.54
3	98.43	1.40	1.43
4	101.88	1.17	1.15

pH = 8.5 (USP XXII)

Time (h)	Average (6 tests) %	Standard deviation	cv %
1	99.66	2.06	2.06
2	98.81	1.16	1.17
3	94.45	0.84	0.89

Water

Time (h)	Average (6 tests) %	Standard deviation	cv %
4	16.68	1.77	10.58
8	43.96	0.96	2.19
12	62.47	0.78	1.25
24	86.46	1.95	2.26

Results of the dissolution test/First manufacturing example

Water

Time (h)	Average (6 tests) %
4	32.83
8	62.66
12	77.81
24	94.92

Results of the dissolution test/Second manufacturing example

Water

Time (h)	Average (6 tests) %
4	37.71
8	66.89
12	80.15
24	95.60

Results of the dissolution test/Third manufacturing example (relating to a laboratory batch)

Water

Time (h)	Average (6 tests) %	Standard deviation	cv %
4	26.09	1.76	6.76
8	43.96	1.28	2.91
12	57.16	1.08	1.90
24	78.43	0.99	1.26

EXAMPLES OF CAPSULES

The following is an example of a 60 mg diltiazem hydrochloride sustained release capsule:

Diltiazem hydrochloride, USP	60	mg
Sugar spheres, NF	33.3	mg
Povidone, USP	3.9	mg
Methacrylic acid copolymer, NF	11.9	mg
Ethylcellulose, NF	0.7	mg
Diethylphthalate, NF	1.5	mg
Talc, USP	7.5	mg
Isopropyl alcohol, USP	non-residual	
Acetone	non-residual	
Alcohol	non-residual	
TOTAL	118.8	mg

Gelatin capsule #3, colorants red iron oxide, titanium dioxide.

The following example concerns a 90 mg diltiazem hydrochloride sustained release capsule:

Diltiazem hydrochloride, USP	90 mg
Sugar spheres, NF	50 mg
Povidone, USP	5.9 mg
Methacrylic acid copolymer, NF	17.8 mg
Ethylcellulose, NF	1 mg
Diethylphthalate, NF	2.2 mg
Talc, USP	11.2 mg
Isopropyl alcohol, USP	non-residual
Acetone	non-residual
Alcohol	non-residual
TOTAL	178.1 mg

Gelatin capsule #2, colorants red iron oxide, yellow iron oxide, titanium dioxide.

The following example concerns a 120 mg diltiazem hydrochloride sustained release capsule:

Diltiazem hydrochloride, USP	120 mg
Sugar spheres, NF	66.6 mg
Povidone, USP	7.8 mg
Methacrylic acid copolymer, NF	23.8 mg
Ethylcellulose, NF	1.4 mg
Diethylphthalate, NF	3 mg
Talc, USP	15 mg
Isopropyl alcohol, USP	non-residual
Acetone	non-residual
Alcohol	non-residual
TOTAL	237.6 mg

Gelatin capsule #1, colorants red iron oxide, yellow iron oxide, titanium dioxide.

From the above three capsule examples, it readily appears to those skilled in the art that the total amount of active ingredients per capsule will vary from batch to batch, based on the quantity of microgranules required to release the precise number of milligrams of diltiazem

hydrochloride per capsule. The amount of excipients may be varied by ±20%.

The amount of microgranules per capsule may be determined, prior to the filling of the capsules, using the result of the content in diltiazem hydro-chloride of the batch of diltiazem hydrochloride sustained-release microgranules.

C L A I M S

1. Sustained release diltiazem formulation for oral administration comprising a microgranule free of organic acid which may have an irritating effect, the said microgranule comprising:

(a) a central inactive spherical particle;

(b) a plurality of alternating first and second layers surrounding the spherical particle to form a core, the first layer comprising a water soluble, pharmaceutically acceptable polymeric material, and the second layer comprising diltiazem or a pharmaceutically acceptable salt thereof; and

(c) an outer coating comprising

first inner membrane layers applied to said core, said first inner membrane layers, amounting from 1 to 20, comprising a first water insoluble pharmaceutically acceptable polymer, and

a single outer membrane forming a relatively thick and homogeneous layer surrounding said first inner membrane layers and comprising a second water insoluble pharmaceutically acceptable polymeric material different from said first water insoluble pharmaceutically acceptable polymer.

2. Formulation according to claim 1, wherein the water soluble, pharmaceutically acceptable polymeric material is selected from the group comprising polyvinylpyrrolidone, polyethyleneglycol, polyvinyl alcohol and their mixtures.

3. Formulation according to claim 1, wherein the first water insoluble, pharmaceutically acceptable polymeric material is ethylcellulose and wherein the second water insoluble, pharmaceutically acceptable polymeric material is selected from the group comprising a copolymer of acrylic and methacrylic acid esters, cellulose acetate phthalate, and those marketed under the trademarks EUDRAGIT L, EUDRAGIT RS and AQUACOAT.

4. Formulation according to claim 1, including a lubricant in said first membrane layers and in said single outer membrane, said lubricant being selected from the group comprising talc, calcium stearate, zinc stearate or magnesium stearate.

5. Formulation according to claim 1, comprising a plasticizer in said single outer membrane.

6. Formulation according to claim 5, wherein said plasticizer is selected from the group comprising diethyl-phthalate, polyethyleneglycols, dibutyl phthalate and triacetin.

2124012