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Regulation 3.1(2)

AUSTRALIA
Patents Act 1990

PATENT REQUEST AND NOTICE OF ENTITLEMENT

We EUROCELTIQUE, S.A.

of 122 Boulevard De La Petrusse, LUXEMBOURG

being the Applicant and Nominated Person, request the grant of a patent for an invention entitled PHARMACEUTICAL COMBINATION FORMULATION which is described in the accompanying standard complete specification.

Convention priority is claimed from the following basic application:

Basic Applicant	Application Number	Application Date	Country	Country Code
Euroceltique S.A.	GB 9117361	12 August 1991	Great Britain	GB

Ian Richard BUXTON; Adrian BROWN; Helen CRITCHLEY; Stewart Thomas LESLIE; Sandra Therese Antoinette MALKOWSKA; Derek Alian PRATER and Ronald Brown MILLER are the actual inventors of the invention.

The inventors made the invention for and on behalf of the nominated person in the course of their duties as employees of the nominated person.

The basic application was the first application made in a Convention country in respect of the invention the subject of this request.

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EUROCELTIQUE, S.A.
By their Patent Attorney

GRIFFITH HACK & CO

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PHARMACEUTICAL COMBINATION FORMULATION

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(56) Prior Art Documents
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(57) Claim

1. A unitary oral dosage form suitable for once daily administration for the treatment of hypertension comprising diltiazem or a pharmaceutically acceptable salt thereof in controlled release form and hydrochlorothiazide in immediate release form.

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ORIGINAL

COMPLETE SPECIFICATION

STANDARD PATENT

Invention Title: PHARMACEUTICAL COMBINATION FORMULATION

The following statement is a full description of this invention, including the best method of performing it known to us:

GH&CO REF: 17930-Y AMP:RK

PHARMACEUTICAL COMBINATION FORMULATION

The present invention relates to a solid oral dosage form and to a process for its preparation. In particular it relates to a solid oral dosage form comprising a combination of diltiazem and hydrochlorothiazide for the treatment of hypertension.

Thiazide diuretics and in particular hydrochlorothiazide are widely used in antihypertensive therapy. Diltiazem is a calcium antagonist which has been shown to be useful in treating chronic heart disease such an angina and hypertension. The administration of diltiazem together with hydrochlorothiazide has been reported to produce significant additive effects in mild to moderate hypertension with twice-daily dosing (see Burris et al, JAMA, 263,(11), 1507-12, 1990).

It is an object of the present invention to provide a combined dosage form comprising diltiazem and hydrochlorothiazide suitable for once daily administration for the treatment of hypertension.

The present invention therefore provides a solid oral dosage form comprising diltiazem or a pharmaceutically acceptable salt thereof in controlled release form and hydrochlorothiazide in immediate release form.

Suitable pharmaceutically acceptable salts of diltiazem for use according to the present invention include pharmaceutically acceptable acid addition salts. The hydrochloride salt is particularly preferred.

The dosage forms according to the invention utilize diltiazem or its pharmaceutically acceptable salts in controlled release form. Known controlled release systems which may be used according to the invention include diffusion, erosion or osmosis controlled delivery systems. Dissolution may be through a rate-controlling

barrier or from a matrix system. Controlled release matrices containing swellable polymers which are capable of modifying the diffusion of the active ingredient across the barrier have also been described.

Erosion-controlled release systems deliver the active ingredient by slow dissolution or break up of the matrix. Suitable adjuvants such as hydrophilic gel-forming adjuvants or hydrophobic adjuvants may be added. In a hydrophilic matrix the release of the active ingredient will be controlled by the gel layer formed on contact with water or digestive fluids. Where hydrophobic adjuvants are employed, it is their erosion which controls the release rate.

In osmotic systems delivery of the active ingredient is controlled by the permeability of the membrane and the osmotic pressure generated by core matrix.

Alternatively release of the active ingredient may also be pH or time controlled.

Suitable materials for inclusion in a controlled release matrix include, for example

(a) Hydrophilic or hydrophobic polymers, such as gums, cellulose esters, cellulose ethers, protein derived materials, nylon, acrylic resins, polylactic acid, polyvinylchloride, starches, polyvinylpyrrolidones, cellulose acetate phthalate. Of these polymers, cellulose ethers especially substituted cellulose ethers such as alkylcelluloses and acrylic resins (for example methacrylates such as methacrylic acid copolymers) are preferred. The controlled release matrix may conveniently contain between 1% and 80% (by weight) of the hydrophilic or hydrophobic polymer.

(b) Digestible, long chain (C_8-C_{50}, especially C_8-C_{40}), substituted or unsubstituted hydrocarbons, such as fatty acids, hydrogenated vegetable oils such as Cutina (Trade Mark), fatty alcohols, glyceryl esters of fatty acids for example glyceryl monostearate mineral oils and waxes (such as beeswax, glycowax, castor wax or carnauba wax). Hydrocarbons having a melting point of between 25°C and 90°C are preferred. Of these long chain hydrocarbon materials, fatty (aliphatic) alcohols are preferred. The matrix may contain up to 60% (by weight) of at least one digestible, long chain hydrocarbon.

(c) Polyalkylene glycols. The matrix may contain up to 60% (by weight) of at least one polyalkylene glycol.

A suitable matrix comprises one or more cellulose ethers or acrylic resins, one or more C_{12}-C_{36}, preferably C_{14}-C_{22}, aliphatic alcohols and/or one or more hydrogenated vegetable oils.

A particularly suitable matrix comprises one or more alkylcelluloses, one or more C_{12-36} (preferably C_{14-22}) aliphatic alcohols and optionally one or more polyalkylene glycols.

The cellulose ether is preferably a substituted cellulose ether such as alkylcellulose and is preferably a substituted alkylcellulose such as ethylcellulose or a hydroxy (C_1 to C_6) alkyl cellulose, such as hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxypropylmethylcellulose phthalate and especially hydroxyethylcellulose. Preferably the matrix contains between 2% and 60%, especially between 3% and 30% (by wt) of the cellulose ether.

The acrylic resin is preferably a methacrylate such a~ methacrylic acid copolymer USNF Type A (Eudragit L, Trade Mark), Type B (Eudragit S, Trade Mark), Type C (Eudragit L 100-55, Trade Mark), Eudragit NE 30D, Eudragit E, Eudragit RL and Eudragit RS. Preferably the matrix contains between 2% and 60% by weight, particularly between 3% and 50% by weight of the acrylic resin.

The aliphatic alcohol may be, for example, lauryl alcohol, myristyl alcohol or stearyl alcohol but is preferably cetyl alcohol or cetostearyl alcohol. The amount of the aliphatic alcohol or hydrogenated vegetable oil will be determined by the precise rate of diltiazem release required and also on whether the polyalkylene glycol is present or absent. In the absence of polyalkylene glycol, the matrix preferably contains between 8% and 40%, especially between 12% and 36% (by wt) of the aliphatic alcohol. When polyalkylene glycol is present in the oral dosage form, then the combined weight of the aliphatic alcohol and the polyalkylene glycol preferably constitutes between 2% and 40%, especially between 8% and 36% (by wt) of the matrix.

The polyalkylene glycol may be, for example, polypropylene glycol or, which is preferred, polyethylene glycol. The number average molecular weight of the at least one polyalkylene glycol is preferably between 200 and 15000 especially between 400 and 12000.

In addition to the above ingredients, the controlled release matrix may also contain suitable quantities of other materials, e.g. diluents, lubricants, binders, granulating aids, colorants, surfactants, anti-adherents, flavorants and glidants that are conventional in the pharmaceutical art.

The diltiazem containing controlled release matrix of the invention can readily be prepared by dispersing the active ingredient in the controlled release system using conventional pharmaceutical techniques such as wet granulation, dry blending, dry granulation or coprecipitation.

In a preferred embodiment of the present invention the controlled release component comprises a plurality of beads, the beads comprising diltiazem or a pharmaceutically acceptable salt thereof and optionally a bead forming agent.

The term "bead" is conventional in the pharmaceutical art and means a spherical granule having a diameter of between 0.1mm and 2.5mm, especially between 0.5mm and 2mm. Included within this are inert cores composed of excipients which are coated with the active ingredient. Suitable inert excipients include sucrose, starch and microcrystalline celluloses. Preferably however the bead comprises spheroids comprising the active ingredient and optionally a spheronising agent.

The beads preferably contain between 40% and 98%, more preferably between 60% and 85%, especially between 70% and 85% by weight of diltiazem or its pharmaceutically acceptable salts.

In a particularly preferred embodiment of the invention the controlled release component comprises a plurality of spheroids comprising diltiazem or a pharmaceutically acceptable salt thereof and a spheronising agent.

The spheronising agent may suitably be any pharmaceutically acceptable material which may be spheronised together with the active ingredient to form spheroid cores. A preferred spheronising agent is microcrystalline cellulose. The microcrystalline cellulose employed may be, for example, Avicel PH 101 or Avicel PH 102 (Trade Marks, FMC Corporation). Conveniently the spheronising agent, when present, is present in an amount of from 1% to 60%, preferably from 15% to 40% by weight of the spheroid core.

In addition the spheroids may also contain a binder. Suitable binders which may be used are well known in the art and include hydrophilic polymers or hydrocolloids such as cellulose polymers, especially cellulose ethers, acrylic resins and gums. Water soluble hydroxy lower alkyl celluloses such as hydroxypropylcellulose are preferred. The binder is preferably present in an amount of from 1% to 40% by weight of the spheroid core.

Optionally the spheroid core may also contain other pharmaceutically acceptable excipients and diluents which facilitate spheronisation such as sugars (for example sucrose, dextrose, maltose or lactose) or sugar alcohols (for example mannitol, xylitol or sorbitol). Colourants may also be included in the spheroid core.

The spheroid cores are preferably film coated with a material which permits release of the diltiazem at a controlled rate in an aqueous medium. Suitable film coating materials include water insoluble waxes and polymers such as polymethacrylates (for example Eudragit polymers, Trade Mark) or preferably water insoluble celluloses particularly ethylcellulose. This film coat may also include water soluble polymers such as polyvinylpyrrolidone or preferably a water soluble cellulose such as hydroxypropylmethylcellulose and hydroxypropylcellulose. It will be appreciated that the ratio of water insoluble to water soluble material will depend on the release rate required and the solubility of the materials selected. The ratio of water soluble polymer to water insoluble polymer is preferably 1:20 to 1:2. The controlled release coating preferably includes one or more plasticisers conventional in the art such as diethylphthalate but particularly dibutyl sebacate; surfactants such as sorbitan trioleate, sorbitan monolaurate or preferably polysorbate 80 (Tween 80, Trade Mark) and tack-modifiers such as talc or preferably colloidal anhydrous silica.

The amount of plasticiser, when present, will depend on the particular plasticiser selected. In general, the plasticiser is present in an amount of from 1% to 25% by weight of the controlled release film coat. The surfactant, when present, is suitably present in an amount of from 1% to 25% by weight of the controlled release film coat. The tack-modifier, when present, is also suitably present in an amount of from 1% to 25% by weight of the controlled release film coat.

A preferred controlled release film coating comprises 50% to 95% ethylcellulose, 5% to 15% colloidal anhydrous silica, 5% to 15% dibutyl sebacate and 5% to 15% polysorbate 80 (Tween 80, Trade Mark).

The controlled release film coating layer can be formed on the surface of the diltiazem containing spheroid core using conventional coating methods, for example fluidised bed or pan coating. The coating materials may be applied as a solution or suspension. Suitable solvent systems include water, dichloromethane, ethanol, methanol, isopropyl alcohol and acetone or a mixture thereof. The coating solution or suspension preferably contains from 2% to 60%, preferably from 2% to 20% by weight of coating materials.

The amount of controlled release coating material will depend on the desired release rate but is generally in the range of from 1% to 25%, preferably 2% to 8% by weight of the controlled release coated spheroid.

The diltiazem containing spheroids according to the invention may be prepared by

(a) granulating a mixture comprising diltiazem or a pharmaceutically acceptable salt thereof, water and optionally a spheronising agent;
(b) extruding the granulated mixture to give an extrudate;

(c) spheronising the extrudate until spheroid cores are formed;
(d) drying the spheroid cores and optionally
(e) film coating the spheroid cores

The solid oral dosage form according to the invention may be formulated as a bilayer tablet. In a preferred aspect however the solid oral dosage form comprises a core comprising diltiazem or a pharmaceutically acceptable salt thereof in controlled release form and an outer coating layer comprising hydrochlorothiazide for immediate release.

Conveniently the hydrochlorothiazide outer coating layer includes a water soluble hydrophilic polymer such as a cellulose ether (for example hydroxypropylcellulose or hydroxypropylmethyl cellulose), polyvinylpyrrolidone or xanthan gum. The ratio of polymer to hydrochlorothiazide is preferably from 10:1 to 1:10. Other coating excipients such as plasticisers, surfactants, tack modifiers, opacifiers and colourants may also be present. The hydrochlorothiazide and excipients are preferably present in the ratio of from 10:1 to 1:10.

The hydrochlorothiazide-containing outer coating layer can be formed on the diltiazem containing controlled release spheroid using conventional coating techniques such as fluidised bed coating or pan coating. Suitable solvents for the coating solution include water, ethanol, methanol, isopropanol or dichloromthane. It will be appreciated that the amount of coating material in the coating solution will depend on the ratio of drug to polymer and the viscosity of the solution. Conveniently the coating solution contains from 1% to 60% by weight of coating materials.

The weight ratio of diltiazem to hydrochlorothiazide in the dosage forms according to the invention typically ranges from about 30:1 to 4:1, preferably 20:1 to 6:1. The dosage form according to the present invention may suitably be administered once or twice

daily. Conveniently for once daily administration the dosage form contains 120mg to 480mg of diltiazem or a pharmaceutically acceptable salt thereof, preferably diltiazem hydrochloride, and 6.25mg to 25mg hydrochlorothiazide. A preferred dosage form according to the invention for once daily administration contains 150mg diltiazem hydrochloride and 12.5mg hydrochlorothiazide.

For twice daily administration the dosage form conveniently contains 60mg to 240mg of diltiazem or a pharmaceutically acceptable salt thereof, preferably diltiazem hydrochloride and 3.125mg to 12.5mg hydrochlorothiazide. A preferred dosage form for twice daily administration contains 75mg diltiazem hydrochloride and 6.25mg hydrochlorothiazide.

Compositions according to the invention may be filled into capsules or sachets or compressed into tablets using conventional pharmaceutical techniques.

When the dosage form of the invention is administered orally the hydrochlorothiazide incorporated in the outer coating layer is rapidly released. The release and dissolution rate of the diltiazem in the core is controlled. When administered the dosage form provides rapid diuresis due to the fast release of the hydrochlorothiazide but also maintains an antihypertensive effect over a prolonged period of time because of the controlled release of diltiazem from the core.

In order that the invention may be well understood the following examples are given by way of illustration only.

Example 1

Capsule having the following formulation were prepared

Diltiazem spheroid cores

Material	mg
Diltiazem hydrochloride U.S.P.	150
Microcrystalline cellulose E.P. (Avicel PH101)	37.5
Purified water E.P.	q.s.
	187.5

Controlled release film coat

Material	mg
Diltiazem hydrochloride spheroid core	187.5
Ethylcellulose N10 U.S.N.F.	9.225
Colloidal anydrous silica E.P. (Aerosil 130)	1.235
Dibutyl sebacate U.S.N.F.	0.928
Polysorbate 80 E.P. (Tween 80)	0.989
Dichloromethane BS 1994	q.s.
Methanol B.P. 1973	q.s.
	200

Hydrochlorothiazide film coat

Material	mg
Diltiazem hydrochloride controlled release film coated spheroids	200
Hydrochlorothiazide E.P.	12.5
Hydroxypropylmethylcellulose 5 cps E.P. (Methocel E5)	2.5
Purified water E.P.	q.s.
	215

The diltiazem and microcrystalline cellulose were blended using a high shear mixer. The mixture was wet granulated, and extruded to give an extrudate which was spheronised and dried in a fluid bed drier. The spheroids were sieved to give a particle size of 0.85 to 1.7mm.

The controlled release film coating ingredient were dispersed in the dichloromethane/methanol solvent system and applied to the diltiazem spheroid cores in a fluid bed coater. The resulting film coated spheroids were sieved. The diltiazem containing controlled release spheroids were then film coated with the dispersion of hydrochlorothiazide and hydroxypropylmethylcellulose in a fluid bed coater.

The dissolution of the resulting product was measured by EP basket apparatus at 100rpm in pH 4.5 EP phosphate buffer. The results obtained are recorded below.

Hydrochlorothiazide Dissolution

10 minutes	100%

Diltiazem Dissolution

Time (hours)	Diltiazem controlled release/ hydrochlorothiazide spheroid (%)
1	8
2	20
3	32
4	41
5	50
6	57
8	66
10	73
12	77
15	83

The diltiazem release rate was unchanged by the application of the hydrochlorothiazide layer.

Example 2

Controlled release diltiazem cores having the following formulations were also prepared.

(i) Material		mg
Diltiazem hydrochloride	Jap.P.	120.0
Lactose	E.P.	--
Hydroxyethylcellulose	E.P.	45.0
Povidone K25	B.P.	10.0
Purified water	E.P.	N.D.
Cetostearyl alcohol	B.P.	30.0
Purified talc	E.P.	6.0
Magnesium stearate	E.P.	6.0
Total Weight (mg)		217.0

	Material		mg
(ii)	Diltiazem hydrochloride	Jap.P.	120.0
	Microcrystalline cellulose	E.P.	44.5
	Colloidal anhydrous silica	E.P.	20.0
	Eudragit NE40D		80.0*
	Cetostearyl alcohol	B.P.	52.5
	Magnesium stearate	E.P.	3.0
	Total Weight (mg)		320.0

* mg solids

The diltiazem containing controlled release cores may be film coated with hydrochlorothiazide according to the procedure described in Example 1.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A unitary oral dosage form suitable for once daily administration for the treatment of hypertension comprising diltiazem or a pharmaceutically acceptable salt thereof in controlled release form and hydrochlorothiazide in immediate release form.

2. A dosage form according to claim 1 wherein the controlled release component comprises a plurality of beads comprising diltiazem or a pharmaceutically acceptable salt thereof.

3. A dosage form according to claim 2 wherein diltiazem or a pharmaceutically acceptable salt thereof is present in an amount of from 40% to 98% by weight of the beads.

4. A dosage form according to any one of claims 2 or 3 wherein the controlled release component comprises a plurality of spheroids comprising diltiazem or a pharmaceutically acceptable salt thereof and a spheronising agent.

5. A dosage form according to claim 4 wherein the spheronising agent comprises microcrystalline cellulose.

6. A dosage form according to claim 4 or 5 wherein the spheronising agent is present in an amount of from 15% to 40% by weight of the spheroid core.

7. A dosage form according to any one of claims 4 to 6 wherein the spheroids are coated with a controlled release film coating material.

8. A dosage form according to claim 7 wherein the film coating material comprises a water insoluble polymer.

9. A dosage form according to any one of claim 8 wherein the film coating material comprises ethylcellulose.

10. A dosage form according to any one of claims 7 to 9 wherein the film coating material further comprises one or more plasticisers, surfactants and tack-modifiers.

11. A dosage form according to claim 10 wherein the film coating material comprises 50% to 95% ethylcellulose, 5% to 15% colloidal anhydrous silica, 5% to 15% dibutyl sebacate and 5% to 15% polysorbate 80.

12. A dosage form according to any one of claims 1 to 11 comprising a core comprising diltiazem or a pharmaceutically acceptable salt thereof in controlled release form and an outer coating layer comprising hydrochlorothiazide in immediate release form.

13. A dosage form according to any one of claims 1 to 12 wherein the weight ratio of diltiazem or its pharmaceutically acceptable salt to hydrochlorothiazide is in the range from 30:1 to 4:1.

14. A dosage form according to claim 13 comprising 150mg diltiazem hydrochloride and 12.5mg hydrochlorothiazide.

15. A capsule comprising a dosage form according to any one of claims 1 to 14.

16. A formulation comprising diltiazem or a pharmaceutically acceptable salt thereof and hydrochlorothiazide substantially as herein described with reference to any one of the examples.

17. A process for preparing a formulation comprising diltiazem or a pharmaceutically acceptable salt thereof and hydrochlorothiazide substantially as herein described with reference to any one of the examples.

DATED this 5th day of August 1992

EUROCELTIQUE S.A.

0259.CLA By their Patent Attorneys

GRIFFITH HACK & CO.