PHARMACEUTICAL DILTIAZEM FORMULATION

The present invention relates to a controlled release preparation and to a process for its preparation. In particular it relates to a controlled release preparation containing diltiazem.

Diltiazem is a calcium antagonist which has been shown to be useful in treating chronic heart disease such as angina and hypertension.

It is an object of the present invention to provide a controlled release diltiazem preparation suitable for once daily administration for the treatment of hypertension and angina.

The present invention therefore provides a controlled release composition comprising spheroid cores consisting of diltiazem or a pharmaceutically acceptable salt thereof together with a spheronising agent, and, optionally, a sugar and/or a sugar alcohol and/or a colourant, said cores being coated with a controlled release layer.

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.

A controlled release pharmaceutical composition according to the present invention is one that achieves slow release of a drug over an extended period of time and extends the duration of drug action over that achieved by conventional delivery.

The term "spheroid" 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.

The spheroid cores for use according to the present invention 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.

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 cores.

Optionally the spheroid cores may also contain sugar (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 coated with a material which permits release of the diltiazem at a controlled rate in an aqueous medium. Suitable controlled release coating materials include those well known in the art such as water insoluble waxes and polymers such as polymethacrylates (for example Eudragit polymers, Trade Mark) or preferably water insoluble celluloses particularly ethylcellulose. The coating 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% by wt. ethylcellulose, 5% to 15% by wt. colloidal anhydrous silica, 5% to 15% by wt. dibutyl sebacate and 5% to 15% by wt. polysorbate 80 (Tween 80, Trade Mark).

The controlled release film coating layer can be formed on the surface of the diltiazem containing spheroid cores 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 the 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 composition.

The controlled release composition according to the invention may be prepared by

(a) granulating a mixture comprising diltiazem or a pharmaceutically acceptable salt thereof, water and 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
(e) film coating the spheroid cores

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

The composition according to the present invention may suitably be administered once daily. Conveniently for once daily administration the dosage form contains from 120mg to 300mg of diltiazem or a pharmaceutically acceptable salt thereof, preferably diltiazem hydrochloride.

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.	120
Microcrystalline cellulose E.P. (Avicel PH101)	30.0
Purified water E.P.	q.s.
	150

Controlled release film coat

Material	mg
Diltiazem hydrochloride spheroid core	150
Ethylcellulose N10 U.S.N.F.	7.38
Colloidal anydrous silica E.P.(Aerosil, Registered Trade Mark 130)	0.988
Dibutyl sebacate U.S.N.F.	0.742
Polysorbate 80 E.P. (Tween 80)	0.791
Dichloromethane BS 1994	q.s.
Methanol B.P. 1973	q.s.
	160

Capsule formulation

	mg
Diltiazem controlled release spheroids	160
Magnesium stearate EP	0.480
Gelatin capsule shells size 3	

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 coated spheroids were filed into gelatin capsule shells.

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.

Diltiazem Dissolution

Time (hours)	Diltiazem controlled release spheroids
1	9
2	23
3	37
4	48
5	57
6	63
8	72
10	77
12	81
15	86
20	90

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CLAIMS

1. A controlled release composition comprising spheroid cores consisting of diltiazem or a pharmaceutically acceptable salt thereof together with a spheronising agent, and, optionally, a sugar and/or a sugar alcohol and/or a colourant, said cores being coated with a controlled release material.

2. A composition according to claim 1 wherein the spheroid core comprise between 40% and 98% by weight of diltiazem or a pharmaceutically acceptable salt thereof.

3. A composition according to claim 2 wherein the spheroid cores comprise between 70% and 85% by weight of diltiazem or a pharmaceutically acceptable salt thereof.

4. A composition according to any one of claims 1 to 3 wherein the spheronising agent is present in an amount of from 15% to 40% by weight of the spheroid cores.

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

6. A composition according to anyone of claims 1 to 5 wherein the controlled release coating material comprises a water insoluble polymer.

7. A composition according to claim 6 wherein the coating material comprises ethylcellulose.

8. A composition according to any one of claims 1 to 7 wherein the controlled release coating material further comprises one or more plasticisers, surfactants and tack-modifiers.

9. A composition according to claim 8 wherein the controlled release coating comprises 50% to 95% by weight ethylcellulose, 5% to 15% by weight colloidal anhydrous silica, 5% to 15% by weight dibutyl sebacate and 5% to 15% by weight polysorbate 80.

10. A composition according to any of claims 1 to 9 wherein the controlled release coating material is present in an amount of from 2% to 8% by weight of the composition.

11. A capsule comprising controlled release coated spheroid cores according to any one of claims 1 to 10.

12. A process for preparing a composition according to any one of claims 1 to 10 which comprises

(a) granulating a mixture comprising diltiazem or a pharmaceutically acceptable salt thereof, water and 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
(e) coating the spheroid cores with a controlled release material.

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