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(54) Title: CONTROLLED–RELEASE COMPOSITIONS OF BETAHISTINE

(57) Abstract

Oral solid controlled–release formulations of betahistine, obtained subjecting the active ingredient to a melt–granulation process with a fatty compound and then mixing the obtained granulate with a hydrophilic polymer and with conventional excipients.

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CONTROLLED-RELEASE COMPOSITIONS OF BETAHISTINE

The present invention relates to the field of pharmaceutical technology.

More particularly, the invention relates to a novel controlled-release formulation of the active ingredient betahistine or of the pharmaceutically acceptable salts thereof.

Betahistine, or N-methyl-2-pyridineethanamine or 2-[2-(methylamino)ethyl]pyridine or [2-(2-pyridyl)ethyl]methylamine, and the respective salts: hydrochloride, dihydrochloride, methanesulfonate, fumarate and those listed in IT 1,229,237 and EP 0,397,025 patents, is a vasodilator active through the oral route used in the therapy of vertigo.

Betahistine has been commercially available for many years only in the form of prompt-release tablets or drops. No controlled-release pharmaceutical forms of Betahistine or any of the above mentioned salts thereof can be found in literature.

At present the posology of betahistine comprises 2-4 daily administrations, depending on the dosage of the concerned pharmaceutical form, and the total amount of active ingredient pro die is of 32 mg.

The preparation of a pharmaceutical form with a suitable release profile of Betahistine is desired, in that it would reduce the number of daily administrations to only one, while keeping the concentration of active ingredient steadily within the therapeutical dosage range.

It has now been found that controlled-release dosage forms of Betahistine can be prepared effectively

and advantageously using a mixture of one or more hydrophilic or inert polymers capable of adsorbing water, the active ingredient and a lipophilic fatty compound.

Therefore the present provides controlled-release tablets comprising:

a) an active ingredient consisting of betahistine or a pharmaceutically acceptable salt thereof, incorporated in at least one fatty compound;

b) at least one hydrophilic polymer capable of adsorbing water;

c) suitable excipients.

The fatty compound consists of hydrophobic compounds with high molecular weight selected from the group consisting of fatty acids, long-chain fatty acid triglycerids, waxes, vegetable or mineral oils, high molecular alcohols or glycols, the esters and ethers thereof. The use of compounds with melting point ranging from 30 to 140 °C is preferred.

Examples of suitable hydrophilic polymers comprise acrylic acid polymers or co-polymers, polyethylene glycols, alginates, cellulose and derivatives (ethers, esters and salts).

Hydroxypropyl cellulose is particularly preferred.

The formulation can moreover be added with conventional excipients used commonly in the preparation of oral solid pharmaceutical forms.

Examples of these excipients comprise lubricants, diluents, coloring agents and the like.

Each tablet typically contains an amount of active ingredient of 4 - 100 mg, preferably 8 - 64 mg of betahistine dihydrochloride. Particularly preferred are

tablets containing 16 to 48 mg, most preferably 24 to 32 mg, of betahistine dihydrochloride.

The percentage of fatty compound in the tablet ranges from 2 to 40% by weight, preferably from 5 to 15% by weight, based on the weight of the tablet.

The percentage of hydrophilic polymer ranges from 5 to 50%, preferably from 10 to 40%, based on the weight of the tablet.

The invention also relates to multi-layer tablets, preferably double layer tablets, in which at least one layer is a controlled-release one and the other is a prompt-release one.

The tablets according to the invention can be prepared with a process comprising the following steps:

a) subjecting betahistine and the fatty compound to melt-granulation;

b) mixing the granulate from step a) with a hydrophilic compound and with suitable excipients;

c) subjecting to compression the mixture from step b).

The melt-granulation step is carried out heating the mixture above the melting point of the fatty compound in a fluidized bed, in a static oven or in a conventional granulation device.

According to a preferred embodiment of the present invention, the above mentioned process comprises the further step of subjecting the mixture from b) to wet- or dry- granulation before the compression step c).

Tablets can optionally be coated in order to provide a better protection of the active ingredient or to attain further modifications of the release characteristics.

The release characteristics of the composition can

be varied adjusting the ratio of fatty compound to hydrophilic polymer.

The in vitro release of the active ingredient can range for example from 6-8 to 24 hours.

The compositions according to the invention can therefore be administered twice or even once a day, depending on the therapeutical requirements to fulfil.

The invention will be further described by means of the following non-limiting examples.

Example 1

Each tablet contains:

- Betahistine dihydrochloride	32.0 mg
- Stearic acid	22.0 mg
- Hydroxypropyl cellulose	120.0 mg
- Polyvinylpyrrolidone	4.0 mg
- Talc	44.0 mg
- Colloidal silica	16.0 mg
- Glyceryl Behenate	12.0 mg

A melt-granulation process is carried out with a high speed granulator, mixing betahistine and stearic acid. The resulting product is mixed with hydroxypropyl cellulose and talc and wet-granulated with a polyvinylpyrrolidone aqueous solution. The resulting granulate is compressed after addition of silica and glyceryl behenate.

The in vitro release profile is reported in the table hereinbelow.

TIME (hours)	**% RELEASED**
1	41.7
2	59.1
3	72.0
4	80.4

5	85.5
6	88.8
7	91.0
8	92.4

Example 2:

Each tablet contains:

- Betahistine dihydrochloride	32.0 mg
- Glyceryl Behenate	22.0 mg
- Hydroxypropyl cellulose	120.0 mg
- Polyvinylpyrrolidone	4.0 mg
- Talc	44.0 mg
- Colloidal silica	16.0 mg
- Glyceryl Behenate	12.0 mg

The preparation procedure is the same as in example 1, using in the melt-granulation the first aliquot of glyceryl behenate (22 mg) in place of stearic acid.

The in vitro release profile is reported in the table hereinbelow.

TIME (hours)	**% RELEASED**
1	48.9
2	66.6
3	78.7
4	87.3
5	93.1
6	96.9
7	99.5
8	101.3

Example 3:

Each tablet contains:

- Betahistine dihydrochloride	32.0 mg
- Cetyl alcohol	22.0 mg
- Hydroxypropyl cellulose	120.0 mg

- Polyvinylpyrrolidone 4.0 mg
- Talc 44.0 mg
- Colloidal silica 16.0 mg
- Glyceryl Behenate 12.0 mg

The preparation procedure is the same as in example 1, using in the melt-granulation cetyl alcohol instead of stearic acid.

The in vitro release profile is reported in the table hereinbelow.

TIME (hours)	**% RELEASED**
1	49.0
2	67.0
3	79.5
4	88.0
5	93.5
6	97.2
7	99.6
8	101.1

Example 4:

Each tablet contains:

- Betahistine dihydrochloride 32.0 mg
- Cetyl alcohol 32.0 mg
- Hydroxypropyl cellulose 120.0 mg
- Polyvinylpyrrolidone 4.0 mg
- Talc 44.0 mg
- Colloidal silica 16.0 mg
- Glyceryl Behenate 12.0 mg

The preparation procedure is the same as in example 3.

The in vitro release profile is reported in the table hereinbelow.

TIME (hours)	% RELEASED
1	44.4
2	61.6
3	74.5
4	84.1
5	91.0
6	95.8
7	99.0
8	101.2

Example 5:

Each tablet contains:

- Betahistine dihydrochloride 32.0 mg
- Hydroxypropyl cellulose 120.0 mg
- Polyvinylpyrrolidone 4.0 mg
- Talc 44.0 mg
- Colloidal silica 16.0 mg
- Glyceryl Behenate 12.0 mg

The preparation procedure involves no melt-granulation step since the fatty compound has been omitted.

The in vitro release profile is reported in the table hereinbelow.

TIME (hours)	% RELEASED
1	55.0
2	75.0
3	88.0
4	96.7
5	101.2

Example 6:

Each tablet contains:

- Betahistine dihydrochloride 32.0 mg
- Cetyl alcohol 22.0 mg

- Talc 10.0 mg

The preparation procedure involves a melt-granulation step of betahistine and cetyl alcohol; the talc acts as a lubricant.

The in vitro release profile is reported in the table hereinbelow.

TIME (hours)	% RELEASED
1	89.1
2	101.2

Example 7:

Each tablet contains:

- Betahistine dihydrochloride 32.0 mg
- Glyceryl Behenate 22.0 mg
- Talc 10.0 mg

The preparation procedure is the same as in example 6.

The in vitro release profile is reported in the table hereinbelow.

TIME (hours)	% RELEASED
1	79.0
2	92.3
3	98.2
4	100.5

Example 8:

Each tablet contains:

- Betahistine dihydrochloride 32.0 mg
- Low viscosity hydroxypropyl cellulose 30.0 mg
- High viscosity hydroxypropyl cellulose 90.0 mg
- Polyvinylpyrrolidone 4.0 mg
- Talc 32.0 mg

- Colloidal silica 16.0 mg
- Glyceryl Behenate 12.0 mg

The preparation procedure involves wet-granulation followed by mixing with lubricants, then compression.

The in vitro release profile is reported in the table hereinbelow.

TIME (hours)	**% RELEASED**
1	84.3
2	101.5

Example 9:

Each tablet contains:

- Betahistine dihydrochloride 32.0 mg
- Low viscosity hydroxypropyl cellulose 60.0 mg
- High viscosity hydroxypropyl cellulose 60.0 mg
- Polyvinylpyrrolidone 4.0 mg
- Talc 32.0 mg
- Colloidal silica 16.0 mg
- Glyceryl Behenate 12.0 mg

The preparation procedure is the same as in example 8.

The in vitro release profile is reported in the table hereinbelow.

TIME (hours)	**% RELEASED**
1	55.0
2	75.0
3	88.0
4	96.7
5	101.2

Example 10:

Each tablet contains:

- Betahistine dihydrochloride 32.0 mg
- Ethylcellulose 168 mg
- Hydrogenated castor oil 15.0 mg
- Colloidal silica 5.0 mg

The preparation procedure involves dry-granulation and compression.

The in vitro release profile is reported in the table hereinbelow.

TIME (hours)	% RELEASED
1	62.2
2	81.1
3	91.8
4	98.2
5	102.1

Example 11:

Each tablet contains:

- Betahistine dihydrochloride 32.0 mg
- Ethylcellulose 152.0 mg
- Stearic acid 22.0 mg
- Hydrogenated castor oil 15.0 mg
- Colloidal silica 5.0 mg

The preparation procedure is the same as in example 10.

The in vitro release profile is reported in the table hereinbelow.

TIME (hours)	% RELEASED
1	30.2
2	39.8
3	46.9
4	52.7

5	57.7
6	62.0
7	65.8
8	68.3

Example 12:

Each tablet contains:

- Betahistine dihydrochloride	32.0 mg
- Ethylcellulose	152.0 mg
- Stearic acid	22.0 mg
- Mannitol	10.0 mg
- Hydrogenated castor oil	15.0 mg
- Colloidal silica	10.0 mg

The preparation procedure is the same as in example 10.

The in vitro release profile is reported in the table hereinbelow.

TIME (hours)	**% RELEASED**
1	23.9
2	35.1
3	43.3
4	49.6
5	54.4
6	58.1
7	60.8
8	62.9

Example 13:

Each tablet contains:

- Betahistine dihydrochloride	32.0 mg
- Cetyl alcohol	22.0 mg
- Hydroxypropyl cellulose	122.0 mg
- Polyvinylpyrrolidone	4.0 mg
- Talc	44.0 mg

- Colloidal silica	16.0 mg
- Glyceryl Behenate	12.0 mg
- Hydroxypropyl methylcellulose	7.5 mg
- Lactose monohydrate	3.5 mg
- Macrogol 4000	2.5 mg
- Titanium dioxide	1.5 mg

The tablets were obtained by coating the tablets according to Example 3, using the last four components listed.

The in vitro release profile is reported in the table hereinbelow:

TIME (hours)	**% RELEASED**
1	44.5
4	84.7
8	99.8

Example 14:

Each tablet contains:

- Betahistine dihydrochloride	32.0 mg
- Cetyl alcohol	22.0 mg
- Hydroxypropyl cellulose	120.0 mg
- Polyvinylpyrrolidone	4.0 mg
- Talc	44.0 mg
- Colloidal silica	16.0 mg
- Glyceryl Behenate	12.0 mg
- Ethylcellulose	5.0 mg
- Dibutylsebacate	1.0 mg
- Lactose	4.0 mg
- Talc	3.0 mg
- Titanium dioxide	2.0 mg

The tablets were obtained coating the tablets according to Example 3 with use of the last five components listed.

TIME (hours)	% RELEASED
1	38.3
4	76.4
8	98.7

CLAIMS

1. A controlled-release tablet comprising:

a) an active ingredient consisting of betahistine or a pharmaceutically acceptable salt thereof, incorporated in at least one fatty compound;

b) at least one hydrophilic polymer capable of adsorbing water;

c) suitable excipients.

2. A controlled-release tablet as claimed in claim 1, in which said at least one fatty compound is selected from the group consisting of fatty acids, long-chain fatty acid triglycerids, waxes, vegetable or mineral oils, high molecular alcohols or glycols, the esters and ethers thereof.

3. A controlled-release tablet according to claims 1 or 2, in which said at least one fatty compound has melting point ranging from 30 to 140 °C.

4. A controlled-release tablet according to any one of claims 1 – 3, in which said at least one hydrophilic polymer is selected from the group consisting of acrylic acid polymers or co-polymers, polyethylene glycols, alginates, cellulose ethers and esters.

5. A controlled-release tablet as claimed in claim 4, in which said at least one hydrophilic polymer is hydroxypropyl cellulose.

6. A controlled-release tablet according to any one of the above claims, in which the percentage of said at least one fatty compound ranges from 2 to 40% by weight based on the weight of the tablet.

7. A controlled-release tablet according to any one of the above claims, in which the percentage of said at

least one hydrophilic polymer ranges from 5 to 50% by weight based on the weight of the tablet.

8. A controlled-release tablet according to any one of the above claims, containing an amount of active ingredient equivalent to 8 – 64 mg of betahistine dihydrochloride.

9. A controlled-release tablet as claimed in claim 8, containing 16 to 48 mg, preferably 24 to 32 mg, of betahistine dihydrochloride.

10. A process for the preparation of controlled-release tablets according to any one of claims 1 - 9, comprising the steps of:

a) incorporating said active ingredient in said at least one fatty compound by melt-granulation;

b) mixing the granulate from step a) with said at least one hydrophilic compound and with suitable excipients;

c) subjecting to compression the mixture from step b).

11. A process as claimed in claim 10, comprising the further step of subjecting the mixture from step b) to wet-granulation or to dry-granulation before the compression step c).

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/EP 00/01642

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/26 A61K31/4402 A61P1/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 18610 A (LENGERICH BERNHARD H VAN) 7 May 1998 (1998-05-07) abstract page 6, line 2 - line 4 page 11, line 27 -page 14, line 26 page 20, line 28 page 21, line 11 - line 19 page 28, line 22 - line 24; figure 1	1-4,6-9
A	---	10
X	FR 2 432 313 A (FOULHOUX PIERRE) 29 February 1980 (1980-02-29) page 1, line 35 -page 2, line 7 page 2, line 24 - line 30 page 3, line 1 - line 23	1-4

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB 2 280 604 A (RESOURCE MEDICAL LIMITED) 8 February 1995 (1995-02-08) the whole document -----	1-11

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INTERNATIONAL SEARCH REPORT

mation on patent family members

Intern nal Application No
PCT/EP 00/01642

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9818610 A	07-05-1998	AU 4991597 A	22-05-1998
		EP 0935523 A	18-08-1999
		NO 992036 A	28-04-1999
		PL 333095 A	08-11-1999
FR 2432313 A	29-02-1980	NONE	
GB 2280604 A	08-02-1995	IE 940521 A	11-01-1995
		ZA 9404729 A	02-01-1996