CONTROLLED RELEASE COMPOSITIONS OF BETAHISTINE

The present invention relates to controlled-release formulation of betahistine or of its pharmaceutically acceptable salts.

Betahistine, or N-methyl-2-pyridineethanamine, is an orally active vasodilator used in the therapy of vertigo as such or in form of hydrochloride, dihydrochloride, methanesulfonate, fumarate or citrate salts. Other betahistine salts are disclosed in IT 1,229,237 and EP 397,025.

Betahistine has been commercially available since many years mainly in the form of prompt-release tablets.

The very high solubility of active ingredient requires specific technologies in order to control the release in an oral formulation.

The conventional dosage 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 usually ranging from 24 to 48 mg.

The preparation of a pharmaceutical form with a suitable release profile of Betahistine would accordingly be advantageous, particularly if it would allow a once-a-day administration, while keeping the concentration of active ingredient steadily within the therapeutic dosage range.

Sustained release compositions of Betahistine have been disclosed for instance in EP 502642, EP 0016890 and in EP 1158963 but there is still the need of improved formulations, particularly with respect to the reliability, convenience and constancy in the industrial productive processes as well as to the stability of the formulation and to the possibility of fine tuning and adjustment of the release characteristics.

The present invention provides stable, improved controlled-release tablets of betahistine comprising:

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a) a non hydrophobic core, comprising betahistine, an organic or inorganic acid and an hydrophilic polymer or mixtures of hydrophilic polymers;

b) a first coating layer (pre-coating) comprising an hydrophilic polymer and a water insoluble excipient;

c) optionally, a second coating layer (final, aesthetic coating) comprising hydrophilic polymers and coloring/opacizers agents.

A first embodiment of the invention accordingly provides controlled release tablets as defined above comprising the core a) and the coating layer b) (pre-coating).

A second embodiment of the invention provides controlled release tablets comprising the core a) and both coating layers b) and c).

In addition to a), b) and c) the formulation will usually also comprise, if required, conventional excipients used commonly in the preparation of oral solid pharmaceutical forms.

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

Examples of suitable hydrophilic polymers included in the core a) and in the coating layers b) and optionally c) comprise acrylic acid polymers or co-polymers, starch polymeric derivatives, polyethylene glycols, alginates, cellulose, and derivatives (ethers, esters and salts).

Hydroxypropylcellulose is particularly preferred.

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

The organic or inorganic acid included in the core have typically pKa values ranging from 0.5 to 8, preferably from 2 to 6. Citric acid is preferred, in any hydration form.

The percentage of acid in the tablet can be up to 15% by weight,

preferably from 2 to 5% by weight, based on the weight of the tablet.

The percentage of hydrophilic polymer into the core ranges from 5 to 60%, preferably from 10 to 40%, based on the final weight of the tablet.

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

a) subjecting betahistine, hydrophilic polymer/s and an acid excipient to wet granulation and subsequent drying;

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

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

d) subjecting tablets from step c) to polymeric coating in order to provide a better protection of the active ingredient and to obtain further modifications of the release characteristics.

The pre-coating layer can effectively control the first Betahistine released amounts, therefore improving the control of the release already provided from the polymers contained in the core and extending the ability to more strongly decrease the released Betahistine amounts. This coating is obtainable by applying a co-dispersion, in suitable evaporating vehicle, of at least one of the above mentioned hydrophilic polymers with a water insoluble excipient (such as talc, titanium dioxide, calcium salts, lacquers, silica, starches, and their derivatives) in quantities ranging from 2 to 150 mg for each tablet, preferably less than 100 mg/tablet.

Next examples can show the pre-coating effect on the in-vitro released amounts.

The release characteristics of the composition can be varied adjusting the ratio of insoluble filler to hydrophilic polymer.

In particular this ratio ranges from 1 part of polymer/1 part of water insoluble excipient to 1 part/40 parts of thereof, more particularly from 1 part

to 10-20 parts of thereof.

Finally, the final coating can be applied without significative in vitro modifying on the Betahistine release.

The in vitro total released amount of the active ingredient can be reached for example in 5 up to 24 hours.

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

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

EXAMPLE 1

Each core contains:

Betahistine 2 HCl	2.00
Anhydrous Citric Acid	6.00
Hydroxypropylmethylcellulose Low viscosity	60.00
Hydroxypropylmethylcellulose High viscosity	60.00
Microcrystalline cellulose	86.00
Talc	15.00
Silica	1.00

A precoating layer (10 mg/tablet) containing:

Hydroxypropylmethylcellulose low viscosity	1.00
Talc	9.00

is applied on the tablet in order to fine tune the release characteristics.

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

time (min)	% released
0	0
30	24
120	55
300	86
360	97

EXAMPLE 2

Each core contains:

Betahistine 2 HCl	2.00
Anhydrous Citric Acid	6.00
Hydroxypropylmethylcellulose Low viscosity	60.00
Hydroxypropylmethylcellulose High viscosity	60.00
Microcrystalline cellulose	86.00
Talc	15.00
Silica	1.00

A precoating layer (10 mg/tablet) containing:

Hydroxypropylmethylcellulose low viscosity	1.00
Talc	9.00

and an optional coating layer (11 mg/tablet)

Pharmacoat 606	5.00
Titanium Dioxide	1.00
Macrogol 6000	2.30
Talc	2.70

are applied on the tablet in order to fine tune the release characteristics.

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

time (min)	% released
0	0
30	23
120	55
300	86
360	97

EXAMPLE 3

Each core contains:

	mg/tablet
Betahistine 2 HCl	64.00
Anhydrous Citric Acid	12.00
Hydroxypropylcellulose Low viscosity	120.00
Hydroxypropylcellulose High viscosity	120.00
Microcrystalline cellulose	172.00
Talc	30.00
Silica	2.00
A precoating layer (45 mg) contains	
Hydroxypropylcellulose High viscosity	4.5
Talc	40.5

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

time (min)	% released
0	0
60	23
240	60
600	92
720	95

EXAMPLE 4

Each core contains:

	mg/tablet
Betahistine 2 HCl	64.00
Anhydrous Citric Acid	12.00
Hydroxypropylcellulose Low viscosity	120.00
Hydroxypropylcellulose High viscosity	120.00
Microcrystalline cellulose	172.00
Talc	30.00
Silica	2.00

Without precoating layers

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

time (min)	% released
0	0
60	33
240	75
600	99
720	100

EXAMPLE 5

Each core contains:

	mg/tablet
Betahistine 2 HCl	64.00
Anhydrous Citric Acid	12.00
Hydroxypropylmethylcellulose Low viscosity	120.00
Hydroxypropylmethylcellulose High viscosity	120.00
Microcrystalline cellulose	172.00
Talc	30.00
Precipitate silica	2.00

A precoating layer (45 mg) contains:

Hydroxypropylcellulose High viscosity	4.5
Talc	40.5

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

time (min)	% released
0	0
60	27
240	62
600	97
720	100

EXAMPLE 6

Each core contains:

	mg/tablet
Betahistine 2 HCl	64.00
Anhydrous Citric Acid	12.00
Alginate	240.00
Microcrystalline cellulose	172.00
Talc	30.00
Silica	2.00

A precoating layer (55 mg) contains:

Talc	5.00
Alginate	50.00

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

time (min)	% released
0	0
60	44
240	62
600	97
720	101

EXAMPLE 7

Each core contains:

	mg/tablet
Betahistine 2 HCl	64.00
Anhydrous Citric Acid	12.00
Hydroxypropylcellulose Low viscosity	120.00
Hydroxypropylcellulose High viscosity	120.00
Microcrystalline cellulose	172.00
Talc	30.00
Silica	2.00
A precoating layer (55 mg) contains:	
Hydroxypropylcellulose High viscosity	5.0
Talc	50.0

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

time (min)	% released
0	0
60	21
240	67
600	89
720	100

EXAMPLE 8 - Stability of the composition of Example 2

The composition of example 2 has been subjected to accelerated stability tests. The results, reported in the following Table, show that no degradation occurs at the end of the test (3 months) in the reported conditions

TEMPERATURE CONDITIONS	MONTHS	Main degradation Product
	0	Not det.
40°C + 75% UR	1	Not det.
	3	Not det.
25% + 60% UR	3	Not det.
30°C + 60% UR	3	Not det.

CLAIMS

1. Controlled-release tablets of betahistine comprising:
   a) a core comprising betahistine, an organic or inorganic acid and an hydrophilic polymer or mixtures of hydrophilic polymers;
   b) a first coating layer (pre-coating) modulating and effectively improving the betahistine release, comprising an hydrophilic polymer and a water insoluble excipient;
   c) optionally, a second coating layer comprising hydrophilic polymers and colouring agents.

2. Controlled release tablets according to claim 1 comprising the core a) and the coating layer b) (pre-coating).

3. Controlled release tablets according to claim 1 comprising the core a) and the coating layers b) (pre-coating) and c).

4. Tablets according to any one of claims from 1 to 3 containing an amount of active ingredient of 4 - 100 mg.

5. Tablets according to claim 4 containing 8 - 64 mg of betahistine dihydrochloride.

6. Tablets according to any one of claims from 1 to 5 wherein the hydrophilic polymers are selected from acrylic acid polymers or co-polymers, starch polymeric derivatives, polyethylene glycols, alginates, cellulose, and their derivatives (ethers, esters and salts).

7. Tablets according to claim 6 wherein the hydrophilic polymer is hydroxypropyl cellulose.

8. Tablets according to any one of claims from 1 to 7 wherein the percentage of hydrophilic polymer ranges from 5 to 60%, based on the final weight of the tablet.

9. Tablets according to any one of claims from 1 to 8 wherein the organic

or inorganic acid in the core have pKa values ranging from 0.5 to 8.

10. Tablets according to claim 9 wherein the acid is Citric acid in any hydration form.

11. Tablets according to any one of claims from 9 to 10 wherein the percentage of the acid can be up to 15% by weight, based on the weight of the tablet.

12. Tablets according to any one of claims from 2 to 12 wherein the pre-coating composition ranges from 1 part of polymer/1 part of water insoluble excipient to 1 part/40 parts thereof, more particularly from 1 part to 10-20 parts thereof.

13. Tablets according to any one of claims from 2 to 12 where the first coating composition ranges from 2 mg to 150 mg for each tablet, preferably less than 100 mg/tablet.

14. A process for the preparation of the tablets of claims 1 to 13 comprising the following steps:

a) subjecting betahistine, without any hydrophobic pre-treatment hydrophilic polymer/s and an acid excipient to wet granulation and subsequent drying;

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

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

15. Subjecting tablets from step c) to polymeric coating by applying a co-dispersion, in suitable evaporating vehicle, of at least one of the hydrophilic polymers with a water insoluble excipient

16. A process according to claim 15 wherein in the pre-coating practice the water insoluble excipient is selected from talc, titanium dioxide, calcium salts, lacquers, silica, starches, and their derivatives.