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(54) Title: ANTISPASMODIC MODIFIED RELEASE FORMULATIONS

(57) Abstract: The present invention relates to modified release formulations comprising an antispasmodic as the active agent and their areas of use.

ANTISPASMODIC MODIFIED RELEASE FORMULATIONS

Introduction

The present invention relates to modified release formulations comprising an antispasmodic as the active agent and their areas of use.

The Prior Art

Mebeverine is an antispasmodic active agent having the chemical name (*RS*)-4-(ethyl[1-(4-methoxyphenyl)propan-2-yl]amino)butyl 3,4-dimethoxybenzoate.

The active agent is in dragee (100 mg), modified release capsule (200 mg) and liquid (10 mg/ml) dosage forms. These pharmaceutical formulations comprising the active agent are used in the treatment of irritable bowel syndrome, chronic irritable colon, spastic constipation, mucous colitis, spastic colitis and similar diseases and for symptoms of abdominal pain and spasms related to these diseases, persistent diarrhea with or without constipation and bloating in stomach and bowels.

Bioavailability of the active agent is pretty low and this requires intake of more than one dose daily in order to observe therapeutic effect. For instance, dragee form is suggested to be taken four times daily in the treatment of said diseases. Similarly, liquid dosage forms are used three times a day.

However, one of the significant factors for adaptation to the treatment is the dose range to be taken. When daily dose is increased from one to four, adaptation of the patient to the treatment is influenced negatively. Adaptation to the treatment increases as frequency of intake decreases. In addition, mebeverine taken three or four times a day may lead to severe side effects in patients and treatment cost of such a treatment applied this way is pretty high.

On the other hand, in order to improve therapeutic activity in the treatment of bowel diseases, the active agent is preferred to act directly in bowels. Mebeverine, which already has a pretty low bioavailability, is metabolized until reaching to the bowels when taken by the oral route and the required therapeutic activity cannot be provided.

To this end, dosage forms of the active agent that can directly be applied into the bowels such as suppository can be developed. However, these dosage forms cause serious limitations in

terms of patient adaptation. Patients express that they do not feel comfortable during and after use of the dosage form and they do not want to use the dosage form.

When the prior art is taken into consideration, it is seen that there is need for novel dosage forms comprising mebeverine which have high bioavailability and improved patient adaptation.

Formulations comprising the active agent are formulated in form of modified release capsules for use twice a day in the prior art. Decreasing the frequency of administration of the active agent provides advantages such as improving the efficiency, decreasing undesired effects, reducing fluctuations on pharmacokinetic criteria therefore on clinical effect, improving adaptation of patients and increasing treatment costs.

There exist various studies on modified release dosage forms of the active agent. For instance, in a study published by P. M. Dandagi et. al.*, formulations which are formulated in form of modified release microspheres are disclosed. Formulations according to this study are prepared by emulsifying a polymer solution composed of mebeverine and methacrylic group polymers and obtaining modified release microspheres from this emulsion *(*pH-Sensitive Mebeverine Microspheres for Colon Delivery, Indian J Pharm Sci. 2009 Jul-Aug; 71(4): 464–468).*

However, microsphere formulations produced according to the method given in this study pose various difficulties. First of all, the method given in the study is a considerably difficult method to apply in which emulsion conditions (environment, temperature etc.) have to be adjusted in earnest. Following their obtainment, the microspheres are washed with petroleum ether or n-hexane at a temperature in the range of 40 °C and 60 °C and dried at room temperature for at least 3 hours. These process steps carry significant risks in terms of leading to chemical degradation in the formulations. Formulating a formulation using minimum number of chemical processes is preferable in terms of pharmaceutical technology.

On the other hand, particle size has to be adjusted sensitively in the microspheres obtained by this method. In the case that the obtained microspheres do not have homogeneous particle size, desired release properties cannot be provided in the final dosage form and efficiency of the treatment decreases.

As it can be seen, about formulations comprising mebeverine, there appears a need for new approaches which can provide perfect patient adaptation, can be produced easily and have high bioavailability by means of providing appropriate release properties.

As a result of the studies they conducted in line with this need, the inventor has managed to develop new modified release mebeverine formulations.

Advantages of the formulations of the present invention are that they can be produced more easily than the modified release dosage forms in the prior art and they have more stable release properties.

Detailed Description of the Invention

The present invention relates to modified release pellet formulations of mebeverine.

A characteristic feature of the formulations of the present invention is that the formulations comprise mebeverine as the active agent and they are in modified release pellet form.

The term "mebeverine" used herein refers to mebeverine and/or pharmaceutically acceptable solvates, hydrates, enantiomers, racemates, organic salts, inorganic salts, polymorphs, crystalline and amorphous forms of mebeverine or combinations thereof.

The modified release mebeverine pellet formulations of the present invention comprise the active agent at more than 70%, preferably in the range of 70% and 95%, more preferably in the range of 70% and 90% by weight.

The active agent used in the modified release pellet formulations of the present invention comprising mebeverine is preferably mebeverine hydrochloride.

The formulations of the present invention are formulated so as to dissolve in basic intestine pH for improving therapeutic effect. The modified release formulations of the present invention dissolve in a pH value in the range of 6-7.

The term "modified release pellet form" used throughout the text refers to pellet formulations which dissolve in the range of 30% and 55% at the end of 2 hours; in the range of 50% and 80% at the end of 6 hours; at minimum70%, preferably in the range of 70% and 99% at the end of 12 hours in a pH value in the range of 6-7.

In other words, modified release pellet formulations of the present invention dissolve in the range of 30% and 55% at the end of 2 hours; in the range of 50% and 80% at the end of 6 hours; at minimum70%, preferably in the range of 70% and 99% at the end of 12 hours in basic pH range (pH:6-7).

Highest bioavailability and thus therapeutic effect could be obtained with pellet formulations of the present invention which enable the formulations to release in this profile.

The modified release pellet formulations of the present invention comprising mebeverine comprise at least one pharmaceutically acceptable excipient in addition to the active agent mebeverine.

The excipients that can be used in the modified release pellet formulations of the present invention comprising mebeverine are selected from a group comprising disintegrant, diluent, solvent, lubricant, glidant, binder, coloring agent, pH regulating agent, surfactant, stabilizing agent, sweetener and/or taste regulating agent, flavoring agent, plasticizers, rate controlling agents and filling agents or combinations thereof.

The diluents that can be used in the modified release pellet formulations of the present invention comprising mebeverine are selected from a group comprising calcium carbonate, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate, microcrystalline cellulose, dextrose, fructose, lactitol, lactose, magnesium carbonate, magnesium oxide, maltitol, maltodextrin, maltose, mannitol, simethicone, sorbitol, starch, sodium chloride, sucrose, talc, xylitol or combinations thereof.

The diluent used in the modified release pellet formulations of the present invention comprising mebeverine is preferably sucrose. Particle size of the diluent used in the formulations is a significant parameter when preparing the formulations in pellet form as they provide easy processing.

According to this, average particle size of sucrose used in the modified release pellet formulations of the present invention comprising mebeverine is larger than 250 μm, preferably larger than 350 μm, more preferably in the range of 450 μm and 700 μm.

The binders that can be used in the modified release pellet formulations of the present invention comprising mebeverine are selected from a group comprising starches such as potato starch, corn starch, wheat starch; sugars such as sucrose, glucose, dextrose, lactose,

maltodextrin; natural and synthetic gums; gelatine; cellulose derivatives such as microcrystalline cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methyl cellulose, carboxymethyl cellulose, methyl cellulose, ethyl cellulose; polyvinylpyrrolidone (povidone); polyethylene glycol (PEG); waxes; calcium carbonate; calcium phosphate; alcohols such as dibasic calcium phosphate, sorbitol, xylitol, mannitol and water or a combination thereof.

The plasticizers that can be used in the modified release pellet formulations of the present invention comprising mebeverine are selected from a group comprising dibutyl sebacate, diethyl phthalate, castor oil, propylene glycol, glycerol, polyethylene glycols, liquid sorbitol and/or combinations thereof.

The lubricants that can be in the modified release pellet formulations of the present invention comprising mebeverine are selected from a group comprising calcium stearate, magnesium stearate, polyethylene glycol, sodium benzoate, potassium benzoate, sodium lauryl sulfate, talc, stearic acid, zinc stearate or combinations thereof.

The pellet formulations of the present invention comprising mebeverine are coated with a coating comprising at least one pharmaceutically acceptable rate controlling agent and at least another excipient in order to provide release property.

The rate controlling agents that can be used to coat the modified release pellet formulations of the present invention comprising mebeverine can be selected from a group comprising cellulose derivatives such as ethyl cellulose, cellulose acetate, hydroxypropyl cellulose, hydroxymethyl cellulose, methyl cellulose; alginic acid or pharmaceutically acceptable salts of alginic acid (for example sodium alginate), vinyl acetate copolymers, polysaccharides, polyethylene oxide or combinations thereof.

Development studies conducted in scope of the present invention have indicated that the release property required to present therapeutic activity cannot be provided when said pellet formulations are coated with a coating comprising methacrylic acid and its derivatives. Therefore, methacrylic acid or its derivates (for example metal methacrylate) are not used as rate controlling agents for coating of the formulations of the present invention.

Nevertheless, pellet formulations of the present invention are coated with a coating comprising a cellulose derivative rate controlling agent at least at 2%, preferably in the range of 2% and 6%, more preferably in the range of 2% and 5% by weight in proportion to total

dosage form weight and at least another excipient. The rate controlling agents here can be ethyl cellulose, cellulose acetate, hydroxypropyl cellulose, hydroxymethyl cellulose and/or methyl cellulose.

In another aspect, the present invention further discloses a production method for modified release pellet formulations comprising mebeverine.

The modified release pellet formulations of the present invention comprising mebeverine are prepared by preparing pellet formulations comprising mebeverine and at least another excipient; coating the prepared formulations with a coating comprising ethyl cellulose, cellulose acetate, hydroxypropyl cellulose, hydroxymethyl cellulose and/or methyl cellulose and at least another excipient in order to provide modified release property.

Many different methods could be used for production of pharmaceutical pellet formulations; however, the most frequently used methods are:

1. Methods of coating a core of a specific size with the active agent/agents,
2. Methods of spraying to form particles,
3. Methods of direct production of micro pellets from powder mixtures.

Pellets of the present invention are prepared by the method of spraying a pharmaceutically acceptable solvent or solvent mixture on the mixture composed of active agent and at least one excipient.

In other words, modified release pellet formulations of mebeverine of the present invention are prepared according to the method comprising the steps of;

1. Grinding mebeverine,
2. Mixing at least one binder and at least one solvent,
3. Preparing pellets by mixing the mebeverine ground in the first step with the diluent and spraying the solution obtained in the second step on this mixture,
4. Drying and sieving the pellets,
5. Coating the obtained pellets with a coating solution comprising at least one pharmaceutically acceptable rate controlling agent and another excipient,
6. Sieving the coated pellets again.

The pellet formulations of the present invention can optionally be compressed in tablet form or filled into capsules.

The modified release dosage forms of the present invention comprising mebeverine are presented as filled into a capsule made of preferably hard or soft gelatin.

In other words, the modified release pellet formulations of the present invention comprising mebeverine are prepared in capsule dosage form.

EXAMPLES:

1. Modified Release Capsule Dosage Form

Component	**% Amount / Capsule**
Pellet Content	
Mebeverine Hydrochloride	77.00
Sucrose	15.00
Binder	1.50
Coating Content	
Ethyl Cellulose	3.50
Plasticizer	0.50
Lubricant	2.50

Production Method:

1. Mebeverine hydrochloride is sieved,
2. The sieved active agent and sucrose are prepared in pellet form with a binder solution composed of the binder and optionally at least one solvent,
3. The obtained pellets are dried and sieved,
4. Dry pellets are coated with a coating solution comprising ethyl cellulose, plasticizer and lubricant,
5. The prepared pellets are filled into capsules and made ready for use.

CLAIMS

1. Modified release pellet formulations comprising mebeverine as the active agent.
2. The modified release pellet formulations according to claim 1, characterized in that the active agent in the formulations is in the form of mebeverine and/or pharmaceutically acceptable solvates, hydrates, enantiomers, racemates, organic salts, inorganic salts, polymorphs, crystalline and amorphous forms of mebeverine or combinations thereof.
3. The modified release pellet formulations according to claims 1-2, characterized in that said formulations comprise more than 70% mebeverine by weight.
4. The modified release pellet formulations according to claims 1-3, characterized in that said formulations comprise 70-95% mebeverine by weight.
5. The modified release pellet formulations according to claims 1-4, characterized in that said formulations comprise 70-90% mebeverine by weight.
6. The modified release pellet formulations according to any preceding claims, characterized in that mebeverine in said formulations is mebeverine hydrochloride.
7. The modified release pellet formulations according to any preceding claims, characterized in that said formulations dissolve in the range of 30% and 55% at the end of the 2nd hour in basic pH range (pH:6-7).
8. The modified release pellet formulations according to claim 7, characterized in that said formulations dissolve in the range of 50% and 80% at the end of the 6th hour in basic pH range (pH:6-7).
9. The modified release pellet formulations according to claims 7-8, characterized in that said formulations dissolve minimum at 70% at the end of the 12th hour in basic pH range (pH:6-7).
10. The modified release pellet formulations according to claim 9, characterized in that said formulations dissolve minimum in the range of 70% and 99% at the end of the 12th hour in basic pH range (pH:6-7).
11. The modified release pellet formulations according to any preceding claims, characterized in that said formulations comprise at least one pharmaceutically acceptable excipient in addition to mebeverine.
12. The modified release pellet formulations according to claim 11, characterized in that the excipients that can be used in the formulations are selected from a group comprising disintegrant, diluent, solvent, lubricant, glidant, binder, coloring agent, pH regulating agent, surfactant, stabilizing agent, sweetener and/or taste regulating agent,

flavoring agent, plasticizers, rate controlling agents and filling agents or combinations thereof.

13. The modified release pellet formulations according to claim 12, characterized in that the diluent that can be used in said formulations is selected from a group comprising calcium carbonate, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate, microcrystalline cellulose, dextrose, fructose, lactitol, lactose, magnesium carbonate, magnesium oxide, maltitol, maltodextrin, maltose, mannitol, simethicone, sorbitol, starch, sodium chloride, sucrose, talc, xylitol or combinations thereof.
14. The modified release pellet formulations according to claim 13, characterized in that the diluent in the formulations is sucrose.
15. The modified release pellet formulations according to claims 13-14, characterized in that the average particle size of the diluent in the formulations is larger than 250 μm.
16. The modified release pellet formulations according to claim 15, characterized in that the average particle size of the diluent in the formulations is larger than 350 μm.
17. The modified release pellet formulations according to claims 15-16, characterized in that the average particle size of the diluent in the formulations is in the range of 450 μm and 700 μm.
18. The modified release pellet formulations according to claim 12, characterized in that the binder that can be used in said formulations is selected from a group comprising starches such as potato starch, corn starch, wheat starch; sugars such as sucrose, glucose, dextrose, lactose, maltodextrin; natural and synthetic gums; gelatine; cellulose derivatives such as microcrystalline cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, hydroxypropyl methyl cellulose, carboxymethyl cellulose, methyl cellulose, ethyl cellulose; polyvinylpyrrolidone (povidone); polyethylene glycol (PEG); waxes; calcium carbonate; calcium phosphate; alcohols such as dibasic calcium phosphate, sorbitol, xylitol, mannitol and water or a combination thereof.
19. The modified release pellet formulations according to claim 12, characterized in that the plasticizer that can be used in said formulations is selected from a group comprising dibutyl sebacate, diethyl phthalate, castor oil, propylene glycol, glycerol, polyethylene glycols, liquid sorbitol and/or combinations thereof.
20. The modified release pellet formulations according to claim 12, characterized in that the lubricants that can be used in said formulations are selected from a group comprising calcium stearate, magnesium stearate, polyethylene glycol, sodium

benzoate, potassium benzoate, sodium lauryl sulfate, talc, stearic acid, zinc stearate or combinations thereof.

21. The modified release pellet formulations according to any preceding claims, characterized in that said formulations are coated with a coating composed of at least one pharmaceutically acceptable rate controlling agent and at least another excipient.
22. The modified release pellet formulations according to claim 21, characterized in that the rate controlling agents that shall be used in the coating are selected from a group comprising cellulose derivatives such as ethyl cellulose, cellulose acetate, hydroxypropyl cellulose, hydroxymethyl cellulose, methyl cellulose; alginic acid or pharmaceutically acceptable salts of alginic acid (for example sodium alginate), vinyl acetate copolymers, polysaccharides, polyethylene oxide or combinations thereof.
23. The modified release pellet formulations according to claim 22, characterized in that said formulations are coated with a coating comprising a cellulose derivative rate controlling agent at least at 2% by weight in proportion to total dosage form weight.
24. The modified release pellet formulations according to claim 23, characterized in that said formulations are coated with a coating comprising a cellulose derivative rate controlling agent in the range of 2% and 6% by weight in proportion to total dosage form weight.
25. The modified release pellet formulations according to claim 24, characterized in that said formulations are coated with a coating comprising a cellulose derivative rate controlling agent in the range of 2% and 5% by weight in proportion to total dosage form weight.
26. The modified release pellet formulations according to claim 25, characterized in that the cellulose derivative rate controlling agent that shall be used for coating said formulations is selected from a group comprising ethyl cellulose, cellulose acetate, hydroxypropyl cellulose, hydroxymethyl cellulose and/or methyl cellulose.
27. A method for production of modified release pellet formulations according to claim 1, characterized in that said method comprises the steps of preparing pellet formulations comprising mebeverine and at least another excipient; coating the prepared formulations with a coating comprising ethyl cellulose, cellulose acetate, hydroxypropyl cellulose, hydroxymethyl cellulose and/or methyl cellulose and at least another excipient in order to provide the modified release property.
28. The production method according to claim 27, characterized in that the pellet formulations comprising mebeverine and at least another excipient are prepared by

spraying a pharmaceutically acceptable solvent or solvent mixture onto the mixture comprising the active agent and at least one excipient.

29. The production method according to claims 27-28, characterized in that said method comprises the steps of;

I. Grinding mebeverine,

II. Mixing at least one binder and at least one solvent,

III. Preparing pellets by mixing the mebeverine ground in the first step with the diluent and spraying the solution obtained in the second step on this mixture,

IV. Drying and sieving the pellets,

V. Coating the obtained pellets with a coating solution comprising at least one pharmaceutically acceptable rate controlling agent and another excipient,

VI. Sieving the coated pellets again.

INTERNATIONAL SEARCH REPORT

International application No
PCT/TR2013/000204

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/16 A61K9/50 A61K31/24
ADD.

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)
A61K

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 practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 393 747 A2 (PROCTER & GAMBLE [US]) 24 October 1990 (1990-10-24) page 2, line 3 - line 5 page 6, line 9 - line 26 page 6, line 43 - line 51 page 7, line 44 - page 8, line 12 page 9; example 2 -----	1-29

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

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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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INTERNATIONAL SEARCH REPORT

Information on patent family members

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0393747 A2	24-10-1990	AU 5369790 A	25-10-1990
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