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(54) Title: PHARMACEUTICAL COMPOSITIONS COMPRISING MEMANTINE

(57) Abstract: The present invention relates to a pharmaceutical tablet composition comprising a non-swelling polymer matrix component having dispersed therein a water-soluble memantine salt, preferably memantine hydrochloride, and a pore-forming agent, to a process of making same and to the use of a polyvinylacetate polymer in a combination with a polyvinylpyrrolidone polymer in making controlled-release composition comprising a water-soluble memantine salt.

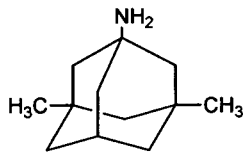
PHARMACEUTICAL COMPOSITIONS COMPRISING MEMANTINE

Background of the Invention

The present invention relates to pharmaceutical compositions that contain memantine, to unit dosage forms made therefrom, and to processes for making the same.

Overview of the prior art

Memantine or 3,5-dimethyl-1-adamantan-amine can be represented by the formula



and is a pharmaceutically active compound used as for treating dementia; e.g. Alzheimer's disease. Memantine has been known for a long time. A process for making it has been published, for example, by Gerzon K, *et. al.*, J. Med. Chem. 6, 760 (1963) /CA 60:4022f/. The pharmaceutical applicability of memantine has been described in U.S. patents 4,122,193 and 5,061,703.

In the current commercial products, e.g., Axura® (Merz) and Namenda (Forest Laboratories), the compound is marketed as a hydrochloride salt. The approved medical products comprise film-coated tablets with immediate release of the drug after oral administration and also a solution for oral administration. While the current commercial products are immediate-release dosage forms, an extended-release dosage form is apparently under development for

future commercial release. The following patent publications may relate to this development activity.

WO2006/0009769 (Forest) discloses modified release formulations comprising memantine hydrochloride and a polymeric "carrier" in the form of a coating and/or matrix. The formulations release at least 70-80% memantine in 4 to 24 hours in a "use environment" such as gastric fluid. A 6h and 12h formulation are preferred and exemplified, which release 70-80 % of the memantine in about 6 or 12 hours, respectively. The polymeric carrier when used as a polymeric matrix can be a hydrophilic or hydrophobic polymer. In a preferred embodiment, the polymeric carrier is a swellable polymeric matrix containing hydroxypropyl methylcellulose (HPMC).

WO2006/138227 (Forest) discloses pharmaceutical beads of memantine having immediate or modified release. The beads may be filled into a capsule or compressed into a tablet. Exemplified modified release beads comprise an inert core, a drug containing layer with binder and glidant, optionally a seal coat layer, a modified release layer, and optionally a topcoat.

While some modified or extended release compositions of memantine hydrochloride have been suggested, it would be beneficial to have an alternate modified or extended release composition available. In particular, such compositions should be simple in manufacture, reliable in pharmaceutical action and stable and safe during handling.

Summary of the Invention

In a first aspect, the present invention relates to a pharmaceutical tablet composition comprising a non-swelling polymer matrix component having dispersed therein a water-soluble memantine salt, preferably memantine hydrochloride, and a pore-forming agent. The preferred

non-swelling polymer matrix component is a polyvinylacetate polymer and the preferred pore-forming agent is polyvinylpyrrolidone. The composition can further contain a filler, particularly a water-insoluble filler, and non-functional excipients.

In particular, the invention relates to the above composition compressed in a form of a tablet, whereby the tablet is a slow-release tablet. Preferably, the tablet is compressed by means of direct compression.

The tablet of the present invention preferably exhibits the following release rate: less than 80 % of memantine is released at 6 hours and 90-100% is released at 12 hours, when measured by an in vitro dissolution test in USP or Ph.Eur. paddle apparatus at 50 rpm, in 900 ml of simulated gastric fluid at 37 $\pm$ 5° C.

Another aspect of the invention relates to a unit dosage form comprising an effective amount of one or more of the above tablets.

A further aspect of the invention relates to a process for making memantine tablets which comprises forming a tablet from the above tablet composition without the aid of a liquid, particularly by a direct compression. Preferably the process comprises blending a water-soluble memantine salt with a non-swellable polymer, a pore-forming agent and, optionally, a filler to form a blend; combining the blend with additional excipients; and compressing the precompression blend into tablets.

Detailed Description of the Invention

The present invention relates to a suitable, stable and technologically simple pharmaceutical composition for slow, suitably controlled delivery of memantine to a human or animal by an oral administration, particularly after the composition is formulated, by a

compression, into a pharmaceutically suitable tablet form. Preferably the tablet delivers memantine throughout the entire digestive tract. No disintegrant is present in the composition, thus the compressed tablet formed from this composition is a nondisintegratable tablet.

In particular, the present invention relates to pharmaceutical compositions of memantine that do not comprise a swellable polymeric matrix. Matrices made from a swellable polymer, particularly the HPMC matrices, show an initial burst of drug release rate owing to the time required for the formation of an efficient gel layer. To obtain a zero-order release, the matrix must be prepared by combining HPMC with other polymers which reduce this effect. It is therefore desirable to provide a pharmaceutical dosage form providing a controlled release of memantine without using a composition formed from a swellable polymer. By avoiding the use of a swellable polymer, problems with the initial burst of the release rate may be solved.

The memantine is formulated into the compositions of the present invention in a form of a water-soluble memantine salt. As used herein, a "water-soluble memantine salt" is any acid addition salt of memantine, exhibiting a solubility in water at 25°C higher than 25 mg/ml. Suitable salts of the compound include, but are not limited to, acid addition salts made with hydrochloric, hydrobromic, acetic, propionic, glycolic, lactic, malonic, succinic, maleic, fumaric, maleic, tartaric, citric, benzoic, mandelic, methanesulfonic, ethanesulfonic, benzenesulfonic, p-toluene sulfonic acid. The preferred salt is memantine hydrochloride, but the invention is not limited thereto.

Memantine salts are commercially available or may be made by contacting memantine with a corresponding acid by methods known per se.

The memantine salt is formulated into the composition of the present invention in a solid state, whereby such solid state may represent a crystalline state in any suitable crystal form, or an

amorphous form. The memantine salt is generally used in the form of a powder; i.e. fine particles. The particles can have a variety of particle size distributions but preferably at least 90% of the particles are 150 microns or less in particle size.

The relative amount of the memantine salt present in the composition is advantageously of between 1 and 40 % of the tablet composition. As used herein all percentages refer to weight percent based on the entire weight of the tablet composition.

The composition of the present invention further contains a matrix-forming component/excipient, which is a water-insoluble non-swellable polymer. As used herein, a "non-swellable" polymer is one that does not absorb a significant amount of water (i.e., it absorbs less than about 10 weight percent water). Advantageously, the polymer component is not readily degraded in the body or, if the polymer is biodegradable, the rate at which it degrades is slower than the rate at which the therapeutic agent elutes. Furthermore, such polymer component is sufficiently compressible to permit tablet formation, especially via direct compression, and has sufficient binding properties to bind memantine component in the formed matrix.

In general, the composition of the present invention may contain from 20 to 80 % of the non-swellable polymer.

The advantageous matrix-forming non-swellable polymer in compositions of the present invention is a pharmaceutically acceptable polyvinylacetate (PVA) polymer. Such polymer has suitably good tabletting and binding properties for direct compression. Some other non-swellable polymers, e.g. polyacrylate polymers or polymetacrylate polymers, may be used.

The third component is a pore-forming agent. This pore-forming agent is a solid material that dissolves in the body environment, thereby forming pores in the matrix. The size of the pores can, to some extent, be controlled by the size of the solid particulate material being used.

The particulate material can range from less than about 1 micrometer in diameter to about 1000 micrometers, preferably about 1 micrometer to about 100 micrometers, more preferably about 5 micrometers to about 50 micrometers. For uniformity of pores, the particulate material can be screened through successively finer mesh sieves to produce a desired range of particle sizes.

The particulate material may include inorganic and organic particulate material, including, for example, polyvinylpyrrolidone, sodium chloride, sucrose, glucose, sorbitol, sodium citrate, dextran, poly(ethylene glycol), mannitol, or combinations thereof. Advantageously, the pore forming material is polyvinylpyrrolidone (PVP).

In general, the composition of the present invention may contain from 5 to 25 % of the pore-forming material.

Conveniently a commercially available ready-to-use mixture of polyvinylacetate and polyvinylpyrrolidone, sold under brand name of Kollidon SR® (BASF) may be used for making the controlled release compositions comprising water-soluble memantine salts. This mixture comprises both the matrix-forming component (PVA) and the pore-forming component (PVP) in a single excipient. The Kollidon SR is a spray-dried non-hygroscopic powder of medium particle size of about 100 micrometers. The ratio of PVA and PVP is fixed in Kollidon SR at approx. 80% to approx. 20%, and it further comprises minimal amounts of sodium lauryl sulphate and silica. The excellent flowability and compressibility of Kollidon SR® makes this excipient particularly suitable for the manufacture of sustained release matrix tablets obtained by direct compression.

Optionally, the composition of the present invention may further contain a water-insoluble inert filler. While not required, the presence of a filler in the tablet composition is generally advantageous. The role of the filler is mostly practical, e.g., to assure the desired

concentration of the active and the necessary amount of the composition in making tablets. Water insoluble pharmaceutically acceptable fillers are well known in the art. A suitable filler is microcrystalline cellulose as it also aids in achieving good content uniformity of the tablet blends. Other suitable fillers include methyl cellulose and/or starch.

The composition may also contain some non-functional excipients, such a colourants, glidants, lubricants, as known in the art of making pharmaceutical tablet compositions. In general, their amounts are very low and do not affect the release rate.

The composition of the present invention can be in the form of a powder blend or, more preferably as a tablet. The tablets of the present invention can be made by any known tabletting technique including wet granulation, direct compression, etc. Processes in which a liquid is absent, i.e., the tablets are formed by a dry process, are commercially more attractive due to ease of manufacture. It is an advantage of the compositions of the present invention that they may be formulated into tablets by such dry process. The advantageous tabletting process is a direct compression process, which is a simple process comprising preparing the blend by careful mixing of the components and compressing the blend, including a lubricant and/or glidant, to form a tablet in a tablet press by a suitable compression force. The compression force used in the tabletting process may, in certain extent, modify the overall release rate. A suitable compression force is from 10 to 20 kN.

The overall mass of the tablet is generally from 50 to 1000mg. The amount of the memantine drug (calculated as the free base) in a tablet is preferably from 1 to 100 mg, Preferably, the tablets contain 7 mg, 10 mg, 20 mg, 28 mg, 40 mg, or 80 mg active ingredient.

Enteric coating of the tablets is, in essence, not necessary. However, if desired, a tablet may be film-coated to improve its appearance and/or handling, using conventional film-coating

materials and techniques. Such a film-coat does not substantially affect the release rate. Also, the weight of such a cosmetic coating, if present, is not included in the overall or total mass of the tablet for purposes of calculating the above-mentioned component percentages.

By selecting the matrix-forming and pore-forming components, including the species and their relative amounts, as well as the overall amount in the composition in the tablet, the controlled release of memantine can be manipulated to a desired release profile. To provide a tablet that releases memantine for a long time, the tablet typically has an *in vitro* dissolution profile such that less than 80 % of memantine is released at 6 hours and 90-100% is released at 12 hours, when measured by an in vitro dissolution test in USP or Ph.Eur. paddle apparatus at 50 rpm at 37 $\pm$ 5° C, in 900 ml of simulated gastric fluid (typically without enzymes as is common in the art). More advantageously, the tablets should provide the same release profile also when tested in a dissolution medium of pH 4.5 (simulated gastric fluid of a fasten state) and pH 6.8 (simulated intestinal fluid). This would indicate none or minimal influence of pH of various places of the intestinal tract.

The composition of the present invention does not assure the proper slow release rate of memantine in a body environment by a diffusion from a formed viscous gel, as common at swellable compositions, but by a slow diffusion after permeation of water through the eroded pores in the tablet matrix, whereby the erosion/diffusion rate may be modulated by the choice of mutual amounts of the matrix-forming nonswellable polymer and the pore-forming agent, as well as by the nature of the polymer. Advantageously, particularly by using the Kollidone SR excipient, the diffusion rate, and thus also the release rate of the memantine drug, is generally pH-independent, which is an advantage as the release of memantine is not affected by the actual place of release (stomach vs. intestines) and/or by the physiological state of the patient (fasten or

fed at the administration). The release rate is also not dependent on the ionic strength of the body fluid. As the tablet composition of the present invention is not swellable, it does not substantially increase its volume in the stomach. Accordingly, the compressed tablet of this composition may be more easily transported into the intestines and continue in slow releasing the memantine after many hours.

The tablets provided from the composition of the present invention are conventionally packed into suitable dosage forms, such as blisters or bottles. They may be used, in an effective amount, which represents an administration of one or more tablets, in treatment of all memantine-treatable diseases such as Alzheimer's disease or a dementia of Alzheimer type.

The invention is further illustrated by the following non-limiting examples.

Example 1

A batch of tablets of the following composition was prepared

Ingredients	Per tablet	
	(mg)	(%)
Memantine HCl	28.0	9.3
PVA:PVP 80:20 (Kollidon SR)	138.5	46.2
Microcrystalline cellulose (Avicel PH102)	130.5	43.5
Magnesium stearate (MF-2-V)	1.5	0.5
Anhydrous colloidal silica (Aerosil 200)	1.5	0.5
Total	300.0	100.0

Manufacturing process

Memantine hydrochloride was mixed with colloidal silica anhydrous and with microcrystalline cellulose. The blend was sieved over a 0.7 mm sieve and mixed with the Kollidon excipient at 72 rpm for 30 minutes. Magnesium stearate were sieved over 0.71 mm sieve and added to the blend. The whole blend was mixed for another 5 minutes at 72 rpm.

The blend was compressed into round tablets of a 300 mg weight, in a eccentric press machine with a compression force of 10 kN.

The invention having been described it will be obvious that the same may be varied in many ways and all such modifications are contemplated as being within the scope of the invention as defined by the following claims.

CLAIMS

1. A pharmaceutical tablet composition comprising a non-swelling polymer matrix component having dispersed therein a water-soluble memantine salt, preferably memantine hydrochloride, and a pore-forming agent.

2. The composition according to claim 1, wherein said non-swelling polymer matrix component comprises a polyvinylacetate polymer.

3. The composition according to claim 1, wherein said non-swelling polymer matrix component consists of a polyvinylacetate polymer.

4. The composition according to claims 1-3, wherein said pore-forming agent is present in an amount of 5 to 25 wt % based on the total weight of said composition.

5. The composition according to claims 1-4, wherein said pore-forming agent is polyvinylpyrrolidone.

6. The composition according to claim 5, wherein said non-swelling polymer matrix component and said pore-forming component are present in a weight ratio of about 8 to 2, respectively.

7. The composition according to claims 1-6, which further comprises a water-insoluble filler.

8. The composition according to claim 7, wherein the filler is microcrystalline cellulose.

9. The composition according to claim 8, wherein said composition is in the form of a tablet and wherein less than 80 % of the memantine is released from the tablet in 6 hours,

measured by an in vitro dissolution test in USP or Ph.Eur. paddle apparatus at 50 rpm, in 900 ml of simulated gastric fluid at 37 ± 5° C.

10. The composition according to claim 9, wherein said water-soluble memantine salt is contained in an amount of 10 to 50 mg, calculated as free base.

11. A process of making an extended-release tablet of memantine, which comprises subjecting a the composition according to claims 1-8 to direct compression, preferably under compression force of about10 to 20 kN.

12. Use of a polyvinylacetate polymer in a combination with a polyvinylpyrrolidone polymer in making controlled-release composition comprising a water-soluble memantine salt.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2010/002077

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/20 A61K31/13
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 practical, search terms used)
EPO-Internal, WPI Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/005534 A2 (FOREST LABORATORIES [US]; DEDHIYA MAHENDRA G [US]; CHHETTRY ANIL [US];) 10 January 2008 (2008-01-10) examples 3, 6	1,4-11
X	WO 2008/005036 A1 (TEVA PHARMA [IL]; TEVA PHARMA [US]; HRAKOVSKY JULIA [IL]; SEBBAN HAGIT) 10 January 2008 (2008-01-10) tables 4, 8	1,4-11
A	US 2006/062851 A1 (VERGEZ JUAN A [AR] ET AL) 23 March 2006 (2006-03-23) example 1	1-12

☐ 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

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"&" document member of the same patent family

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

International application No
PCT/EP2010/002077

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