(12) PATENT
(19) AUSTRALIAN PATENT OFFICE

(11) Application No. AU 199746193 B2
(10) Patent No. 724802

(54) Title
Oral preparation containing at least one active pharmaceutical substance in a matrix capable of swelling in an aqueous medium

(51)[6] International Patent Classification(s)
A61K 009/20

(21) Application No: 199746193 (22) Application Date: 1997.08.29

(87) WIPO No: WO98/13028

(30) Priority Data

(31) Number	(32) Date	(33) Country
19640062	1996.09.28	DE

(43) Publication Date : 1998.04.17
(43) Publication Journal Date : 1998.06.11
(44) Accepted Journal Date : 2000.09.28

(71) Applicant(s)
LTS Lohmann Therapie-Systeme GmbH

(72) Inventor(s)
Karsten Cremer

(74) Agent/Attorney
DAVIES COLLISON CAVE,GPO Box 3876,SYDNEY NSW 2001

(56) Related Art
US 5456921

OPI DATE 17/04/98 APPLN. ID 46193/97
AOJP DATE 11/06/98 PCT NUMBER PCT/EP97/04717
AU9746193

(51) Internationale Patentklassifikation 6 : A61K 9/20

A1

(11) Internationale Veröffentlichungsnummer: WO 98/13028

(43) Internationales Veröffentlichungsdatum: 2. April 1998 (02.04.98)

(21) Internationales Aktenzeichen: PCT/EP97/04717

(22) Internationales Anmeldedatum: 29. August 1997 (29.08.97)

(30) Prioritätsdaten:
196 40 062.7 28. September 1996 (28.09.96) DE

(71) Anmelder *(für alle Bestimmungsstaaten ausser US)*: LTS LOHMANN THERAPIE-SYSTEME GMBH [DE/DE]; Irlicher Strasse 55, D-56567 Neuwied (DE).

(72) Erfinder; und
(75) Erfinder/Anmelder *(nur für US)*: CREMER, Karsten [DE/DE]; Vorgebirgsstrasse 47, D-53119 Bonn (DE).

(74) Anwalt: FLACCUS, Rolf-Dieter; Sperlingsweg 32, D-50389 Wesseling (DE).

(81) Bestimmungsstaaten: AL, AU, CA, CN, CZ, HU, IL, JP, KR, LT, LV, MX, NO, NZ, PL, RO, SI, SK, US, europäisches Patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Veröffentlicht
Mit internationalem Recherchenbericht.

(54) Title: ORAL PREPARATION CONTAINING AT LEAST ONE ACTIVE PHARMACEUTICAL SUBSTANCE IN A MATRIX CAPABLE OF SWELLING IN AN AQUEOUS MEDIUM

(54) Bezeichnung: ORALE ZUBEREITUNG, ENTHALTEND IN EINER IN WÄSSRIGEM MEDIUM QUELLBAREN MATRIX WENIGSTENS EINEN PHARMAZEUTISCHEN WIRKSTOFF

(57) Abstract

An oral preparation contains in a matrix capable of swelling in an aqueous medium at least one active pharmaceutical substance which is released in the aqueous medium when the matrix swells therein, in a retarded manner, while the matrix is largely resistant to decomposition during the release process. The preparation is characterised in that it consists of a stratified tablet with layers which adhere onto each other and of which at least one layer is the swellable matrix layer and at least another layer is an auxiliary and/or substrate layer. The swellable matrix layer contains a certain proportion of cross-linked amylose.

(57) Zusammenfassung

Eine orale Zubereitung, enthaltend in einer in wäßrigem Medium quellbaren Matrix wenigstens einen pharmazeutischen Wirkstoff, der aus der Matrix bei deren Quellung retardiert in das wässrige Medium freigesetzt wird, während die Matrix beim Freisetzungsprozess weitgehend zerfallsresistent ist, ist dadurch gekennzeichnet, daß sie eine Schichttablette mit aufeinander haftenden Schichten ist, von welchen wenigstens eine Schicht die quellbare Matrixschicht und wenigstens eine weitere Schicht eine Hilfs- und/oder Trägerschicht ist, und daß die quellbare Matrixschicht einen Anteil von quervernetzter Amylose enthält.

A B S T R A C T

An oral preparation, comprising at least one pharmaceutical active compound in a matrix which is swellable in aqueous medium, which is released from the matrix into the aqueous medium in a delayed manner on swelling thereof, while the matrix is largely resistant to disintegration during the release process, is characterized in that it is a layered tablet with layers adhering to one another, of which at least one layer is the swellable matrix layer and at least another layer is an auxiliary and/or excipient layer, and in that the swellable matrix layer contains an amount of crosslinked amylose.

Oral preparation, comprising at least one pharmaceutical active compound in a matrix which is swellable in aqueous medium

D E S C R I P T I O N

The invention relates to an oral preparation, comprising at least one pharmaceutically active compound in a matrix which is swellable in aqueous medium, which is released from the matrix into the aqueous medium in a delayed manner, while the matrix remains largely resistant to disintegration.

The delayed release of active compound from oral administration forms serves to avoid undesired plasma level variations. The construction variants with which delayed active compound release can be achieved also include layered tablets, in particular those in which the surface of the active compound-containing layer enlarges in the course of the release, whereby the release rate can be controlled in such a way that it remains largely constant. Depending on the design and the formulation of the layered tablet, this surface layer enlargement can result from the continuous erosion of one or more adjacent layers or from the swelling of the active compound-containing layer. The first-mentioned principle was described in the documents P 43 41 442.7 and P 44 16 926.4, the second, for example, in US 5,422,123.

In the study of commercially available layered tablets having a swellable matrix layer, it was recognized as essential that a satisfactory surface enlargement due to swelling can only be achieved if mechanical stress on the tablet is largely avoided. If, to be precise, swelling takes place on entry of aqueous medium, a semi-solid gel of comparatively low mechanical stability results with increase in volume.

Even the carrying-out of the disintegration test according to GP 10 using applied Plexiglass discs leads to a serious loss of shape of the swollen tablets.

The cause of the lack of mechanical stability of such matrix layers in the swollen state is the use of swellable polymers producing a swelling. They are mainly strongly hydrophilic polymers which, however, are insoluble or slowly soluble due to crosslinking, due to formation of crystalline fields or due to their large chain length. Examples of these types of polymers are croscarmellose, polyvinyl alcohol with a high degree of hydrolysis and high molecular weight hydroxypropylmethylcellulose. These very highly swellable polymers are also employed as disintegration accelerators or disintegrant in tablet formulations on account of this property (Sucker et. al., Pharmazeutische Technologie, Thieme Verlag, 1991, pp 174 et seq.). The preparation of swellable matrices which simultaneously remain mechanically stable when adequately swollen in aqueous medium is extremely problematical using the polymers mentioned, since their swelling-promoting properties cannot be separated from disintegration-promoting properties.

In one aspect of the present invention there is provided an oral preparation having a matrix which is swellable on entry of aqueous medium, from

which active compound is released into the aqueous medium in a delayed manner, and which is mechanically stable and resistant to disintegration in the swollen state up to the extensive end of the release.

In a preparation of the type described in the precharacterising clause of Claim 1, aspects of the invention are defined according to the characterising features of the main claim.

Crosslinked amylose swells in water, but differs from the customary swellable polymers by a surprisingly high mechanical strength in the swollen state. In this way, it is for the first time possible to create markedly improved, disintegration-resistant

layered tablets in which the surface enlargement of the swelling matrix layer is also still effective if mechanical stresses occur, such as, for example, in the disintegration test or after administration in the gastrointestinal tract.

Amylose is a constituent of natural starches, which is contained mainly in the interior of starch grains with a content of approximately 15 to 30%, and consists of unbranched chains with D-glucopyranose units which are linked with one another α-1,4-glycosidically. By reaction with agents such as, for example, epichlorohydrin or 2,3-dibromopropanol, amylose can be effectively crosslinked, for which purpose a proportion of 0.1 to 10% of crosslinker, based on the amylose, is necessary.

It is disclosed in US Patent Specification 5,456, 921 that crosslinked amylose, in particular that with a relatively low degree of crosslinking, is distinguished in particular by a strong tendency to form hydrogen bridges between the molecular chains, which in turn leads to large cohesive forces which can maintain the mechanical stability of a preparation or of a tablet even in the swollen state. In this patent specification, various homogeneous, i.e. single-layered tablets with crosslinked amylose, are also described which release their active compound, e.g. theophylline, in a uniformly delayed manner. Different types of mechanisms for the control of the release rate are discussed here, the favoured type being based on control of the kinetics of the entry of water by intermolecular hydrogen bridges and this being attributed the greatest importance for the release rate.

Surprisingly, it has now been achieved by the invention for the first time that layered tablets having at least one swellable matrix layer, whose release kinetics are controlled by means of the surface growth of the matrix layer due to swelling, with a content of amylose have a distinctly increased measure

of mechanical strength compared with the prior art, whereby reliable control of the release kinetics is guaranteed even on mechanical stress of the tablet, because their surface growth takes place despite this stress without them disintegrating during release.

The term layered tablet in the sense of this invention relates to a tablet made of at least two layers in each case adhering to one another and prepared by compressing powder or granules. A layered tablet can additionally have further features, such as, for example, a coating of a sugar-containing or polymer-containing composition or a coating produced by compressing powder or granules. In these cases, the layered tablet would also be described as a sugar-coated tablet, film-coated tablet or press-coated tablet.

The layered tablet defined in the characterizing part of Claim 1 has an active compound-containing matrix layer, this term being understood as a major term for all layer compositions in which active compound is uniformly dispersed or embedded. A layered tablet according to the invention can also contain more than one active compound-containing matrix layer, for example if more than one active compound is intended to be released in delayed form, or various active compound components are intended to be released from different layers at a different rate.

Accordingly, a layered tablet according to the invention can contain one or more active compounds.

The active compound-containing matrix layer is swellable on entry of aqueous medium, i.e. in contact with water, physiological or artificial gastric or intestinal juice the matrix layer takes up water and constituents optionally dissolved in water with an increase in volume, a large part of the swelling water typically being intercalated between polymer chains which are contained in a matrix preparation.

In the sense of the invention, an extensive resistance to disintegration of a matrix layer during

the release process means that the disintegration is not complete in the disintegration test according to GP 10 as long as at least the greater part of the active compound dose contained in the matrix layer has been released. A delayed release of active compound as a rule takes place over at least several hours, all types of release profiles, i.e. linear and non-linear, but also complex profiles with an initial and a maintenance dose etc., being included.

The layered tablet of the invention according to the main claim is different from known layered tablets of the prior art in that it has a swellable matrix layer with a content of crosslinked amyloses. Preferred contents of crosslinked amylose in the matrix layer are between 30 and 99.5%. While very low-dose active compounds allow a high content of crosslinked amylose, larger active compound doses with respect to a maximum administrable tablet size require a more or less marked reduction in the auxiliary content. In order to be able to allow the positive effects of the crosslinked amylose described above to come to bear, however, as a rule a content of at least 20% will have to be employed. Even lower use amounts are admittedly less preferred, but likewise conform to the invention, since they can likewise lead through the choice of special pharmaceutical technological additive measures such as, for example, the use of special particle forms and particle size distributions, particularly press conditions, agglomeration processes, etc., to a layered tablet according to the invention.

The main advantage of a preparation according to the invention is accordingly to be been in that a layered tablet prepared with it regardless of mechanical tumbling stress proves its cohesive strength in the gastrointestinal tract and thus maintains a uniformly delayed release of its active compound content up to its exhaustion.

Throughout the specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

The reference to any prior art in this specification is not, and should not be taken as, an acknowledgment or any form of suggestion that that prior art forms part of the common general knowledge in Australia.

PATENT CLAIMS

1. Oral preparation, comprising at least one pharmaceutical active compound in a matrix which is swellable in aqueous medium, which is released from the matrix into the aqueous medium in a delayed manner on swelling thereof, while the matrix remains largely resistant to disintegration during the release process, characterized in that it is a layered tablet with layers adhering to one another, of which at least one layer is the swellable matrix layer and at least another layer is an auxiliary and/or excipient layer, and in that the swellable matrix layer contains an amount of crosslinked amylose.

2. Preparation according to Claim 1, characterized in that the amount of crosslinked amylose in the matrix layer is between 20 and 99.5% by weight.

3. Preparation according to Claim 1, characterized in that the release rate over the greater part of the release period is largely constant.

4. Preparation according to Claim 1, charactertized in that it contains more than one active compound.

5. Preparation according to one or more of Claims 1 to 4, characterized in that the layer or layers adjacent to the swellable matrix layer is/are largely resistant to disintegration during the release of active compound.

6. Preparation according to one or more of Claims 1 to 5, characterized in that it is formed as a core of a film-coated or press-coated tablet.

7. An oral preparation as claimed in claim 1 substantially as herein described.

DATED this eighteenth day of July 2000.

LTS LOHMANN THERAPIE-SYSTEME GMBH
By Its Patent Attorneys
DAVIES COLLISON CAVE