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(54) PHARMACEUTICAL COMPOSITIONS

(71) We, HOECHST AKTIENGESELLSCHAFT, a Body Corporate organised under the laws of the Federal Republic of Germany of 6230 Frankfurt/Main 80, Germany, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:–

This invention relates to pharmaceutical compositions for oral administration containing xanthine derivatives.

It is well known that certain pharmaceutically active compounds, e.g. xanthine derivatives, particularly dimethylxanthines and derivatives thereof, have a rather high incompatibility with the gastro-intestinal tract. Pharmaceutical products containing these compounds are thus frequently presented in the form of injection solutions, solution for infusion or coated tablets resistant to gastric juices. In the latter pharmaceutical form, the dosage has had to be kept low to avoid incompatibility reactions and this has heretofore restricted the usefulness of oral therapy.

The irritant effect on the gastric mucous membrane is particularly strong when large quantities of the active ingredient are released in and come into contact with a narrowly circumscribed area of the mucous membrane, as is the case, for example, when a tablet rests on the gastric mucous membrane and disintegrates there within a short time, e.g. in about 1 to 2 minutes. The problem is only partially solved by administration of pharmaceutical preparations which are resistant to gastric juices, since the disintegration of the pharmaceutical form does not then take place until it reaches the small intestine. Moreover, with subacid and anacid patients, the pharmaceutical preparation nevertheless decomposes in the stomach itself. For the reasons described above, the use of oral therapy with such pharmaceuticals, which is generally preferred because of its convenience, has been severely restricted because of the limitations imposed by the low dosage levels which can be administered safely.

The present invention is based upon the discovery that the incompatibility of certain pharmaceutically active agents with the gastro-intestinal tract may be considerably reduced by admixture of the active agent with a sufficient amount of a swelling agent (as herein defined), thereby permitting safe oral administration of such active agents in considerably higher dosages than has been possible heretofore.

Thus according to the present invention there is provided a pharmaceutical composition for oral administration in dosage unit form which comprises at least one xanthine derivative selected from

a) [(φ-1)-hydroxyalkyl]-dialkylxanthines wherein the (φ-1)-hydroxyalkyl group contains 5 or 6 carbon atoms and is in the 1- or 7-position, the alkyl group in the other of the 1- and 7-positions contains from 1 to 12 carbon atoms and the alkyl group in the 3-position contains from 1 to 4 carbon atoms,

b) [(φ-1)-oxoalkyl]-dimethylxanthines wherein the (φ-1)-oxoalkyl group contains 5 or 6 carbon atoms and is in the 1- or 7-position, and

c) dimethylxanthine derivatives having a further alkyl group containing from 4 to 12 carbon atoms or a benzyl group in the 1- or 7-position,

and a swelling agent (as herein defined), each dosage unit containing at least 300mg, preferably at least 400mg, of xanthine derivative and the weight ratio of xanthine derivative to swelling agent being in the range from 1:2 to 10:1, preferably from 1:1 to 6:1.

The term "swelling agent" as used herein is intended to mean a physiologically acceptable substance which when brought into contact with an aqueous liquid such as for example saliva or gastric juices, forms a viscous liquid resembling mucus.

The invention is particularly valuable for administration of water-soluble xanthine derivatives but is also useful for administration of xanthine derivatives which are not soluble in water. The invention makes it possible for pharmaceutically active xanthine derivatives which are water-soluble and badly tolerated by the stomach to be administered orally in considerably higher doses than has been possible heretofore, whilst avoiding incompatibility reaction in the gastro-intestinal tract. This has been demonstrated as follows:

Where 400 mg of 1-(5-oxohexyl)-3,7-dimethylxanthine were administered together with carriers and excipients, but without a swelling agent, the level of this active ingredient in the blood was found to rise rapidly but then fall again very rapidly. This indicates that the substance is well resorbed and quickly eliminated by the body.

In contrast, where 400 mg of the same active ingredient were administered in the form of a pharmaceutical composition according to the invention, a relatively constant level of the active ingredient was sustained in the blood for a long period. This indicated a gradual release of the active ingredient from the pharmaceutical composition. Although decomposition products of the active ingredient are constantly eliminated in the urine, the level of the active ingredient in the blood remained relatively constant over a long period. This thus confirms that there is a prolonged release of the active ingredient into the gastro-intestinal tract.

In tests carried out *in vitro* we have shown that constant quantities of the active ingredient are also released per hour into artificial gastric and intestinal juices.

Such *in vitro* and *in vivo* tests show that a constant level of the active ingredient is resorbed from the compositions according to the invention over a long period in the gastro-intestinal tract, thus guaranteeing a long-lasting therapeutic effect.

By means of the invention it is generally possible to administer safely the aforementioned xanthine derivatives in the form of individual dosage units containing up to 800mg of active ingredient.

Typical water-soluble oxoalkyl-dialkylxanthines which may be incorporated into pharmaceutical compositions according to the invention include for example 1-(5-oxohexyl)-3,7- and 7-(5-oxohexyl)-1,3-dimethylxanthines. Other suitable xanthines are for example 3,7-dimethylxanthines and 1,3-dimethylxanthines substituted by a butyl, isoamyl, hexyl, lauryl or benzyl group in the 1- or 7-position, and also homologues of these compounds with a hydroxy or oxo group in the (φ-1)-position of the alkyl group, e.g. 1-(4-hydroxypentyl)- and 1-(5-hydroxyhexyl)-3,7-dimethylxanthines, 7-(4-hydroxypentyl)- and 7-(5-hydroxyhexyl)-1,3-dimethylxanthines, 1-(4-oxopentyl)-, 1-(5-oxohexyl)-, 1-(2-methyl-3-oxobutyl)- and 1-(2-ethyl-3-oxobutyl)-3,7-dimethylxanthines and the corresponding 1,3-dimethyl compounds having the aforementioned (φ-1)-hydroxyalkyl or (φ-1)-oxoalkyl groups in the 7-position. Suitable homologues of the above hydroxyalkyl-dimethylxanthines, are those having in the 1- or 7-position which is not occupied by a hydroxyalkyl group, instead of a methyl group, an alkyl group with 2 to 12 carbon atoms, e.g. 1-ethyl-1-propyl-, 1-butyl- and 1-isobutyl-3-methyl-7-(5-hydroxyhexyl)-xanthines and 7-ethyl-, 7-propyl-, 7-butyl- and 7-isobutyl-1-(5-hydroxyhexyl)-3-methylxanthines, and corresponding compounds having in place of the 3-methyl group an alkyl group with 2 to 4 carbon atoms.

The swelling agent is preferably guar powder, a galactomannan, an alginate, a hydrophilic acrylic acid polymer, for example the commercial product Carbopol (registered Trade Mark), or a cellulose derivative, for example methyl cellulose or more especially hydroxyethyl cellulose.

Further excipients, for example polyvinyl pyrrolidone, mixtures of polyvinyl pyrrolidone with polyvinyl acetate, talc, magnesium stearate and other excipients conventionally used in tablet making, may be incorporated into the compositions as desired.

Compositions according to the invention in the form of tablets and tablet cores may be prepared by the following method, which method constitutes a further feature of the invention: admixing one or more xanthine derivatives as hereinbefore defined with a swelling agent in a weight ratio of xanthine derivative to swelling agent of from 1:2 to 10:1 preferably from 1:1 to 6:1, granulating the mixture thereby produced and compressing the granulate into tablets or tablet cores each containing at least 300 mg, preferably at least 400mg, of xanthine derivative.

One or more further excipients may be incorporated into the compositions prior to, during or after granulation as convenient. Where tablet cores are produced, these can be subsequently coated as desired to prepare coated tablets.

Granulation is preferably carried out as a dry granulation. However, other conventional granulation processes may also be used.

By means of the compositions according to the invention, it is safe to administer orally

the aforespecified xanthine derivatives in the form of solid dosage units having an active ingredient content which is at least twice as high, often from 3 to 6 times as high as the highest dosages of the same active ingredient orally administered hitherto. In individual cases, the dosage which may be safely administered may even be 8 times as high.

When a pharmaceutical composition according to the invention is administered and comes into contact with water, saliva or gastric juices it is thought that a mucous layer is spontaneously formed around it which layer protects the mucous membrane from the direct action of the high concentration of active ingredient. When we tested pharmaceutical compositions according to the invention containing certain oxoalkyldialkylxanthines on humans, we found that dosages of at least 400mg, generally from 800 to 1200 mg, and even as much as 2400 mg could be orally administered daily without the occurrence of any incompatibility reactions. The xanthine derivatives with which this invention is concerned, are used particularly in the treatment of vascular disorders and develop an optimum activity at individual single dosage levels above 300 mg. Such dosages could previously only be administered by infusion but as a result of the present invention may now be administered by the more convenient oral route.

The following Examples serve to illustrate the preparation of pharmaceutical compositions according to the invention.

Examples

In each case the various ingredients were admixed, agglomerated in a compactor, granulated and subsequently compressed into tablets or cores for coated tablets having the indicated compositions:

Example 1

a) 400 mg of 1-(5-oxohexyl)-3,7-dimethyl-xanthine
b) 80 mg of hydroxyethyl cellulose
c) 10 mg of polyvinylpyrrolidone
d) 20 mg of talc
e) 5 mg of magnesium stearate

Example 2

a) 300 mg of 1-propyl-3-methyl-7-(5-hydroxyhexyl)-xanthine
b) 200 mg of hydroxyethyl cellulose
c) 20 mg of polyvinylpyrrolidone
d) 10 mg of talc
5 mg of magnesium stearate

Example 3

a) 400 mg of 1,3-dimethyl-7-(4-hydroxypentyl)-xanthine
b) 100 mg of hydroxyethyl cellulose
c) 20 mg of polyvinylpyrrolidone
d) 10 mg of talc
e) 5 mg of magnesium stearate

Example 4

a) 400 mg of 1-(5-hydroxyhexyl)-3,7-dimethylxanthine
b) 100 mg of hydroxyethyl cellulose
c) 20 mg of polyvinylpyrrolidone
d) 10 mg of talc
e) 5 mg of magnesium stearate

Example 5

a) 500 mg of 1-pentyl-3,7-dimethylxanthine
b) 50 mg of hydroxyethyl cellulose
c) 5 mg of polyvinylpyrrolidone
d) 15 mg of talc
e) 5 mg of magnesium stearate

Example 6

a) 800 mg of 1-hexyl-3,7-dimethylxanthine
b) 150 mg of guar powder
c) 20 mg of polyvinylpyrrolidone
d) 15 mg of talc
e) 5 mg of magnesium stearate.

Example 7

a) 800 mg of 1-(5-oxohexyl)-3,7-dimethylxanthine
b) 150 mg of guar powder
c) 20 mg of talc
d) 5 mg of magnesium stearate.

WHAT WE CLAIM IS:–

1. A pharmaceutical composition for oral administration in dosage unit form which

the aforespecified xanthine derivatives in the form of solid dosage units having an active ingredient content which is at least twice as high, often from 3 to 6 times as high as the highest dosages of the same active ingredient orally administered hitherto. In individual cases, the dosage which may be safely administered may even be 8 times as high.

When a pharmaceutical composition according to the invention is administered and comes into contact with water, saliva or gastric juices it is thought that a mucous layer is spontaneously formed around it which layer protects the mucous membrane from the direct action of the high concentration of active ingredient. When we tested pharmaceutical compositions according to the invention containing certain oxoalkyldialkylxanthines on humans, we found that dosages of at least 400mg, generally from 800 to 1200 mg, and even as much as 2400 mg could be orally administered daily without the occurrence of any incompatibility reactions. The xanthine derivatives with which this invention is concerned, are used particularly in the treatment of vascular disorders and develop an optimum activity at individual single dosage levels above 300 mg. Such dosages could previously only be administered by infusion but as a result of the present invention may now be administered by the more convenient oral route.

The following Examples serve to illustrate the preparation of pharmaceutical compositions according to the invention.

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b) 80 mg of hydroxyethyl cellulose
c) 10 mg of polyvinylpyrrolidone
d) 20 mg of talc
e) 5 mg of magnesium stearate

Example 2

a) 300 mg of 1-propyl-3-methyl-7-(5-hydroxyhexyl)-xanthine
b) 200 mg of hydroxyethyl cellulose
c) 20 mg of polyvinylpyrrolidone
d) 10 mg of talc
5 mg of magnesium stearate

Example 3

a) 400 mg of 1,3-dimethyl-7-(4-hydroxypentyl)-xanthine
b) 100 mg of hydroxyethyl cellulose
c) 20 mg of polyvinylpyrrolidone
d) 10 mg of talc
e) 5 mg of magnesium stearate

Example 4

a) 400 mg of 1-(5-hydroxyhexyl)-3,7-dimethylxanthine
b) 100 mg of hydroxyethyl cellulose
c) 20 mg of polyvinylpyrrolidone
d) 10 mg of talc
e) 5 mg of magnesium stearate

Example 5

a) 500 mg of 1-pentyl-3,7-dimethylxanthine
b) 50 mg of hydroxyethyl cellulose
c) 5 mg of polyvinylpyrrolidone
d) 15 mg of talc
e) 5 mg of magnesium stearate

Example 6

a) 800 mg of 1-hexyl-3,7-dimethylxanthine
b) 150 mg of guar powder
c) 20 mg of polyvinylpyrrolidone
d) 15 mg of talc
e) 5 mg of magnesium stearate.

Example 7

a) 800 mg of 1-(5-oxohexyl)-3,7-dimethylxanthine
b) 150 mg of guar powder
c) 20 mg of talc
d) 5 mg of magnesium stearate.

WHAT WE CLAIM IS:–

1. A pharmaceutical composition for oral administration in dosage unit form which

comprises at least one xanthine derivative selected from
a) [(φ-1)-hydroxyalkyl]-dialkylxanthines wherein the (φ-1)-hydroxyalkyl group contains 5 or 6 carbon atoms and is in the 1- or 7-position, the alkyl group in the other of the 1- and 7-positions contains from 1 to 12 carbon atoms and the alkyl group in the 3-position contains from 1 to 4 carbon atoms,
b)[(φ-1)-oxoalkyl]-dimethylxanthines wherein the (φ-1)-oxoalkyl group contains 5 or 6 carbon atoms and is in the 1- or 7-position, and
c) dimethylxanthine derivatives having a further alkyl group containing from 4 to 12 carbon atoms or a benzyl group in the 1- or 7-position,
and a swelling agent (as herein defined), each dosage unit containing at least 300 mg of xanthine derivative and the weight ratio of xanthine derivative to swelling agent being in the range from 1:2 to 10:1.

2. A composition as claimed in claim 1 wherein the weight ratio of xanthine derivative to swelling agent is in the range from 1:1 to 6:1.

3. A composition as claimed in claim 1 or claim 2 wherein the xanthine derivative is water-soluble.

4. A composition as claimed in any of the preceding claims wherein each dosage unit contains at least 400 mg of xanthine derivative.

5. A composition as claimed in any of the preceding claims wherein each dosage unit contains up to 800 mg of xanthine derivative.

6. A composition as claimed in any of claims 1 to 4 wherein each dosage unit contains from 800 to 1200 mg of an (φ-1)-oxoalkyl-dimethylxanthine.

7. A composition as claimed in any of the preceding claims wherein the xanthine derivative is 1-(5-oxohexyl)-3,7-dimethylxanthine or 7-(5-oxohexyl)-1,3-dimethylxanthine.

8. A composition as claimed in any of the preceding claims wherein the swelling agent comprises guar powder, galacto-mannan, an alginate, an hydrophilic acrylic acid polymer, or a cellulose derivative.

9. A composition as claimed in claim 8 wherein the swelling agent is methyl cellulose or hydroxyethyl cellulose.

10. A composition as claimed in any one of the preceding claims which additionally contains a further excipient selected from polyvinyl pyrrolidone, polyvinyl acetate, talcum and magnesium stearate.

11. A composition as claimed in any of the preceding claims in tablet form.

12. A composition as claimed in claim 1 substantially as herein described.

13. A pharmaceutical composition for oral administration in dosage unit form substantially as herein described in any one of the Examples.

14. A method of preparing a pharmaceutical composition according to claim 1 in tablet form which comprises admixing one or more xanthine derivatives as defined in claim 1 with a swelling agent in a weight ratio of xanthine derivative to swelling agent of from 1:2 to 10:1, granulating the mixture thereby produced and compressing the granulate into tablets or tablet cores each containing at least 300 mg of xanthine derivative.

15. A method as claimed in claim 14 wherein prior to, during or after the granulation, at least one further excipient is incorporated.

16. A method as claimed in claim 14 or claim 15 wherein the granulation is effected on a dry mixture.

17. A method as claimed in any of claims 14 to 16 wherein tablet cores thus produced are subsequently coated.

18. A method of preparing a pharmaceutical composition according to claim 1 in the form of coated or uncoated tablets substantially as herein described.

19. Pharmaceutical compositions according to claim 1 in tablet form when prepared by a method as claimed in any of claims 14 to 18.

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