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NO DRAWINGS

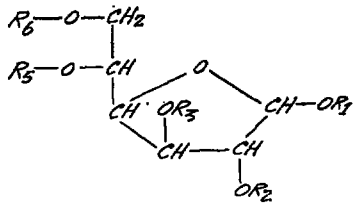
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(54) A GRANULAR MATERIAL COMPRISING OILY OR LIQUID PHARMACOLOGICALLY ACTIVE GLUCOFURANOSIDES AND A PROCESS FOR ITS MANUFACTURE

(71) We, CIBA-GEIGY AG., (formerly known as CIBA Limited), a body corporate organised according to the laws of Switzerland, of Basle, Switzerland, 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 a granular material obtained from an oily or liquid pharmacologically active glucofuranoside of the formula specified below, and to a process for the manufacture of the granular material. The granular material used for the manufacture of a pharmaceutical solid oral administration form, for example tablets or dragées.

Pharmacologically active glucofuranosides of general formula



wherein R_1 denotes a hydrogen atom or a cycloalkyl, benzyl, lower alkyl, lower alkenyl or hydroxy-lower alkyl residue, primarily an ethyl, hydroxyethyl, dihydroxypropyl, allyl or butyl residue, R_2 primarily represents a hydrogen atom, but may represent a lower alkanoyl residue, R_3 represents an allyl residue, a lower alkyl residue, primarily a propyl residue, or a benzyl, methyl benzyl or halogeno - benzyl residue, and R_5 and R_6 each represents a benzyl, methyl - benzyl or halogenobenzyl residue, primarily a benzyl residue or a *p*-methyl benzyl or *p* - chlorobenzyl residue, and one of the symbols R_3, R_5 and R_6 may denote a hydrogen atom, are mostly oily or liquid in nature and possess an unpleasant flavour. These orally highly active compounds, of which ethyl - 3,5,6 - tri - O - benzyl - D - glucofuranoside or ethyl - 3 - O - propyl-5,6 - di - *p* - chlorobenzyl - D - gluco - furanoside are especially valuable, therefore had to be enclosed in capsules or administered in a liquid form. Administration in a liquid form or in a capsule form however presents various disadvantages; for example, accurate dosing is practically impossible in the case of the liquid form, and the capsules present manufacturing difficulties. Because these glucofuranosides possess very good solvent properties and plasticiser properties and are furthermore not very stable in most media it has not so far proved possible to manufacture solid oral dispensing forms which could be kept for prolonged periods and which would at the same time permit accurate dosing.

The term "lower" in qualifying an organic residue is used throughout this specification to indicate that the residue should have not more than 5 carbon atoms.

The present invention provides a process for the manufacture of a granular material wherein an oily or liquid, pharmacologically active glucofuranoside of the above formula is mixed with a film-forming agent and a lower alkanol, for example, methanol, isopropanol or primarily ethanol, the mixture so obtained is worked up into a plastic mass with magnesium trisilicate adsorbent, together, if desired, with a further adsorbent for example colloidal silica or cellulose, especially microcrystalline cellulose, and the mass is granulated whilst drying it, for example with warm air. The granular material produced by the process of the invention is, in general, free flowing and can relatively easily be processed into a solid oral administration form.

As a film-forming agent it is preferable to use one which will also act as a binding agent, for example, especially shellac, a poly-

acrylic or methacrylic ester, an ethylene oxide polymer (Carbowaxes; "Carbowax" is a Trade Mark), a polyvinyl alcohol or ester, for example a polyvinyl acetate, or primarily a polyvinyl pyrrolidone, for example polyvinylpyrrolidone or polyvinylpyrrolidone - poly - vinyl acetate copolymers. A further possible film-forming agent is, for example, an alcohol-soluble or water-soluble cellulose derivative, especially cellulose acetate - phthalate, hydroxypropyl - methyl - cellulose, ethyl - cellulose, ethyl - hydroxyethyl - cellulose, hydroxypropyl - cellulose or carboxymethyl - cellulose.

The process is preferably effected by dissolving the film-forming agent in the lower alkanol, working up the furanoside with this solution, and working up the solution so obtained with the magnesium trisilicate absorbent and, if desired, the further adsorbent to give a plastic mass, and drying and granulating the latter in the usual manner. When working up the solution of the furanoside with magnesium trisilicate, the sugar is adsorbed on the latter.

The film-forming agent is preferably used in a concentration of from 0.2 to 20, especially 1 to 5 and primarily 2 to 4, parts by weight per 10 parts by weight of furanoside. The magnesium trisilicate is used in an amount which permits adsorption of the furanoside, especially in a concentration of from 5 to 20, preferably 8 to 15 or primarily about 10 to 12, parts by weight per 10 parts by weight of furanoside. The further adsorbent, if present, is used in an amount of from 1 to 20, preferably 1 to 10 and primarily 4 to 6, parts by weight per 10 parts by weight of furanoside.

The present invention also provides a granular material obtained by the process of the invention, which material comprises an oily or liquid, pharmacologically active glucofuranoside of the above formula adsorbed on magnesium trisilicate and if desired on a further adsorbent, and a film-forming agent. This granular material is stable for prolonged periods even at temperatures above ambient temperature, for example 60°C, and can be easily processed into any desired oral administration form.

EXAMPLE 1

Composition of the Granular Material:

10 parts by weight of ethyl - 3,5,6 - tri - O - benzyl - D - glucofuranoside (Glyvenol), 10 parts by weight of magnesium trisilicate, 5 parts by weight of colloidal silica and 2.5 part by weight of polyvinylpyrrolidone (PVP).

Manufacture of the Granular Material:

The PVP is dissolved in a fourfold amount of alcohol and mixed with the Glyvenol. This solution is processed into a paste with the magnesium trisilicate in a suitable apparatus and is kneaded with colloidal silica to give a plastic mass. It is then granulated and dried in the usual manner.

Manufacture of Dragées:

5.45 parts by weight of granular material are mixed with 2.0 parts by weight of starch, 1.7 parts by weight of talc and 0.3 parts by weight of magnesium stearate and processed into pressed blanks weighing 585 mg and containing 200 mg of ethyl - 3,5,6 - tri - O - benzyl - D - glucofuranoside.

In order to hide the bad taste, the pressed blanks are, after coating with a protective lacquer, converted into dragées with sugar in the usual manner.

EXAMPLE 2

Composition of the Granular Material:

10 parts by weight of preparation of ethyl-3 - O - propyl - 5,6 - di - O - p - chloro - benzyl - glucofuranoside, 14 parts by weight of magnesium trisilicate, 5 parts by weight of colloidal silica and 2.5 parts by weight of polyvinylpyrrolidone (PVP).

Manufacture of the Granular Material:

The PVP is dissolved in the fourfold quantity of alcohol and mixed with the furanoside. This solution is processed into a paste with magnesium trisilicate in a suitable apparatus and kneaded with colloidal silica to give a plastic mass. The mass is granulated and dried in the usual manner.

Manufacture of Dragées:

31.5 parts by weight of granular material are mixed with 0.8 part by weight of starch, 1.55 parts by weight of microcrystalline cellulose, 1.05 parts by weight of talc and 0.15 part by weight of magnesium stearate and processed into pressed blanks of 350 mg (=100 mg of furanoside).

These cores are given a protective lacquer in the usual manner and then converted into dragées with sugar.

EXAMPLE 3

Composition of the Granular Material:

10 parts by weight of ethyl - 3,5,6 - tri - O - benzyl D - glucofuranoside (Glyvenol), 10 parts by weight of magnesium trisilicate, 5 parts by weight of colloidal silica, 0.5 parts by weight of polyvinylpyrrolidone, and 2 parts by weight of microcrystalline cellulose.

Manufacture of the Granular Material:

The PVP is dissolved in a fourfold amount of alcohol and mixed with the Glyvenol. This solution is processed into a paste with the magnesium trisilicate in a suitable apparatus and is kneaded with colloidal silica to give a plastic mass. It is then granulated and dried in the usual manner.

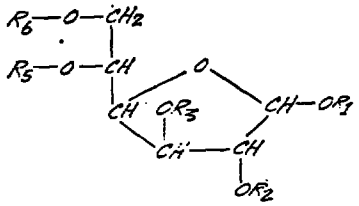
Manufacture of Dragées:

5.45 parts by weight of granular material are mixed with 2.0 parts by weight of starch, 1.7 parts by weight of talc and 0.3 part by weight of magnesium stearate and processed into pressed blanks weighing 585 mg and containing 200 mg of ethyl - 3,5,6 - tri - O - benzyl - D - glucofuranoside.

In order to hide the bad taste, the pressed blanks are, after coating with a protective lacquer, converted into dragées with sugar in the usual manner.

WHAT WE CLAIM IS:—

1. A process for the manufacture of a granular material wherein an oily or liquid, pharmacologically active glucofuranoside of the formula



wherein R_1 denotes a hydrogen atom or a cycloalkyl, benzyl, lower alkyl, lower alkenyl or hydroxy-lower alkyl residue, R_2 represents a lower alkanoyl residue or a hydrogen atom, R_3 represents an allyl residue, a lower alkyl residue or a benzyl, methylbenzyl or halogenobenzyl residue and R_5 and R_6 each represents a benzyl, methylbenzyl or halogenobenzyl residue and one of the symbols R_3, R_5 and R_6 may denote a hydrogen atom, is mixed with a film-forming agent and a lower alkanol, the mixture so obtained is worked up with magnesium trisilicate adsorbent to form a plastic mass, and the latter is granulated while drying it.

2. A process as claimed in claim 1, wherein a further adsorbent is added to the magnesium trisilicate.

3. A process as claimed in either of claims 1 or 2, wherein the film-forming agent is shellac, a polyacrylic or methacrylic ester, an ethylene oxide polymer, a polyvinyl alcohol or an ester thereof or a cellulosic derivative which is soluble in alcohol or water.

4. A process as claimed in claim 3, wherein the film-forming agent used is polyvinylpyrrolidone.

5. A process as claimed in any one of claims 1 to 4, wherein the film-forming agent is used in a concentration of from 0.2 to 20 parts by weight for every 10 parts by weight of furanoside.

6. A process as claimed in any one of claims 1 to 4, wherein the film-forming agent is used in a concentration of from 1 to 5 parts by weight for every 10 parts by weight of furanoside.

7. A process as claimed in any one of claims 1 to 4, wherein the film-forming agent is used in a concentration of from 2 to 4 parts by weight for every 10 parts by weight of furanoside.

8. A process as claimed in any one of claims 1 to 7, wherein the magnesium trisilicate is used in a concentration of from 5 to 20 parts by weight for every 10 parts by weight of furanoside.

9. A process as claimed in any one of claims 1 to 7, wherein the magnesium trisilicate is used in a concentration of from 8 to 15 parts by weight for every 10 parts by weight of furanoside.

10. A process as claimed in any one of claims 1 to 7, wherein the magnesium trisilicate is used in a concentration of from 10 to 12 parts by weight for every 10 parts by weight of furanoside.

11. A process as claimed in any one of claims 2 to 10, wherein the further absorbent is colloidal silica or cellulose.

12. A process as claimed in claim 11, wherein the additional absorbent is used in a concentration of from 1 to 20 parts by weight for every 10 parts by weight of furanoside.

13. A process as claimed in claim 11, wherein the additional absorbent is used in a concentration of from 1 to 10 parts by weight for every 10 parts by weight of furanoside.

14. A process as claimed in claim 11, wherein the additional absorbent is used in a concentration of from 4 to 6 parts by weight for every 10 parts by weight of furanoside.

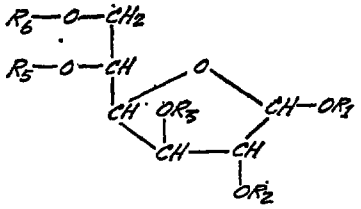
15. A process as claimed in any one of claims 1 to 14, wherein the furanoside used is ethyl - 3,5,6 - tri - O - benzyl - D - glucofuranoside.

16. A process as claimed in any one of claims 1 to 14, wherein the furanoside used in ethyl - 3 - O - propyl - 5,6 - di - O - para - chlorobenzyl - D - glucofuranoside.

17. A process as claimed in claim 1 and conducted substantially as described herein.

18. A granular material whenever prepared by a process as claimed in any one of claims 1 to 17.

19. A solid, free-flowing granular material comprising an oily or liquid pharmacologically active glucofuranoside of the formula



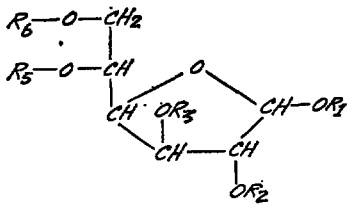
Manufacture of Dragées:

5.45 parts by weight of granular material are mixed with 2.0 parts by weight of starch, 1.7 parts by weight of talc and 0.3 part by weight of magnesium stearate and processed into pressed blanks weighing 585 mg and containing 200 mg of ethyl - 3,5,6 - tri - O - benzyl - D - glucofuranoside.

In order to hide the bad taste, the pressed blanks are, after coating with a protective lacquer, converted into dragées with sugar in the usual manner.

WHAT WE CLAIM IS:—

1. A process for the manufacture of a granular material wherein an oily or liquid, pharmacologically active glucofuranoside of the formula



wherein R_1 denotes a hydrogen atom or a cycloalkyl, benzyl, lower alkyl, lower alkenyl or hydroxy-lower alkyl residue, R_2 represents a lower alkanoyl residue or a hydrogen atom, R_3 represents an allyl residue, a lower alkyl residue or a benzyl, methylbenzyl or halogenobenzyl residue and R_5 and R_6 each represents a benzyl, methylbenzyl or halogenobenzyl residue and one of the symbols R_3, R_5 and R_6 may denote a hydrogen atom, is mixed with a film-forming agent and a lower alkanol, the mixture so obtained is worked up with magnesium trisilicate adsorbent to form a plastic mass, and the latter is granulated while drying it.

2. A process as claimed in claim 1, wherein a further adsorbent is added to the magnesium trisilicate.

3. A process as claimed in either of claims 1 or 2, wherein the film-forming agent is shellac, a polyacrylic or methacrylic ester, an ethylene oxide polymer, a polyvinyl alcohol or an ester thereof or a cellulosic derivative which is soluble in alcohol or water.

4. A process as claimed in claim 3, wherein the film-forming agent used is polyvinylpyrrolidone.

5. A process as claimed in any one of claims 1 to 4, wherein the film-forming agent is used in a concentration of from 0.2 to 20 parts by weight for every 10 parts by weight of furanoside.

6. A process as claimed in any one of claims 1 to 4, wherein the film-forming agent is used in a concentration of from 1 to 5 parts by weight for every 10 parts by weight of furanoside.

7. A process as claimed in any one of claims 1 to 4, wherein the film-forming agent is used in a concentration of from 2 to 4 parts by weight for every 10 parts by weight of furanoside.

8. A process as claimed in any one of claims 1 to 7, wherein the magnesium trisilicate is used in a concentration of from 5 to 20 parts by weight for every 10 parts by weight of furanoside.

9. A process as claimed in any one of claims 1 to 7, wherein the magnesium trisilicate is used in a concentration of from 8 to 15 parts by weight for every 10 parts by weight of furanoside.

10. A process as claimed in any one of claims 1 to 7, wherein the magnesium trisilicate is used in a concentration of from 10 to 12 parts by weight for every 10 parts by weight of furanoside.

11. A process as claimed in any one of claims 2 to 10, wherein the further absorbent is colloidal silica or cellulose.

12. A process as claimed in claim 11, wherein the additional absorbent is used in a concentration of from 1 to 20 parts by weight for every 10 parts by weight of furanoside.

13. A process as claimed in claim 11, wherein the additional absorbent is used in a concentration of from 1 to 10 parts by weight for every 10 parts by weight of furanoside.

14. A process as claimed in claim 11, wherein the additional absorbent is used in a concentration of from 4 to 6 parts by weight for every 10 parts by weight of furanoside.

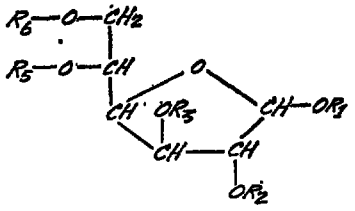
15. A process as claimed in any one of claims 1 to 14, wherein the furanoside used is ethyl - 3,5,6 - tri - O - benzyl - D - glucofuranoside.

16. A process as claimed in any one of claims 1 to 14, wherein the furanoside used in ethyl - 3 - O - propyl - 5,6 - di - O - para - chlorobenzyl - D - glucofuranoside.

17. A process as claimed in claim 1 and conducted substantially as described herein.

18. A granular material whenever prepared by a process as claimed in any one of claims 1 to 17.

19. A solid, free-flowing granular material comprising an oily or liquid pharmacologically active glucofuranoside of the formula



wherein R_1 denotes a hydrogen atom or a cycloalkyl, benzyl, lower alkyl, lower alkenyl or hydroxy - lower alkyl residue, R_2 represents a lower alkanoyl residue or a hydrogen atom, R_3 represents an allyl residue, a lower alkyl residue or a benzyl, methylbenzyl or halogenobenzyl residue and R_5 and R_6 each represents a benzyl, methylbenzyl or halogenobenzyl residue and one of the symbols R_3, R_5 and R_6 may denote a hydrogen atom adsorbed on magnesium trisilicate and, if desired, on a further adsorbing agent, and a film-forming agent.

20. A granular material as claimed in claim 19, wherein the furanoside is ethyl - 3 - O - propyl - 5,6 - di - O - para - chlorobenzyl - D - glucofuranoside.

21. A granular material as claimed in claim 19, wherein the furanoside is ethyl - 3,5,6 - tri - O - benzyl - D - glucofuranoside.

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