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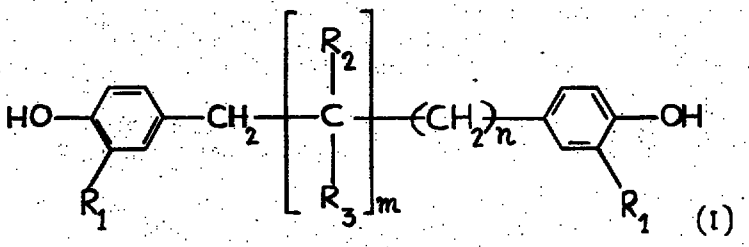
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(19)

(54) PHARMACEUTICAL HYPOLIPIDEMIC COMPOSITIONS

(71) We, SANDOZ LTD., of 35 Lichtstrasse, 4002 Basle, Switzerland, a Swiss Body Corporate, 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 diphenylalkane derivatives, and, more particularly, relates to pharmaceutically acceptable salts of compounds of formula I,



(I)

in which the radicals R_1 are the same and signify a hydrogen atom or a hydroxy group,

R_2 and R_3, which may be the same or different, each signifies a hydrogen atom or a methyl radical,

n signifies 0 or 1, and

m signifies 0, 1 or 2,

provided that

(i) when m signifies 0, then n signifies 0,

(ii) when m signifies 2, the radicals R_2 and the radicals R_3 may be the same or different,

(iii) when m signifies 1 or 2, then n signifies 1 and each radical R_1 signifies a hydroxy group,

and (iv) when m signifies 2 and both the radicals R_2 or both the radicals R_3 signify a methyl group, then at least one of the radicals R_3 or at least one of the radicals R_2, respectively, signifies a methyl group.

The compounds of formula I and salt forms thereof are known or may be prepared in conventional manner. The use of the compounds of formula I as pharmaceuticals is disclosed and claimed in our earlier application British Patent No. 1,361,856.

The present invention is based on the discovery that the pharmaceutically aceptable salts of compounds of formula I also possess pharmacological activity, in particular hypolipidemic activity as indicated by the fall in cholesterol and/or triglyceride levels in male albino Wistar rats weighing 110 to 130 g initially. The rats are maintained on a drug-free laboratory chow diet for several days and then divided into groups of 8 to 10 animals. Each group, with the exception of the control, is then given orally 7,5,30,0, 250 or 500 mg per kg of body weight *per diem* of the salt for six days. At the end of this period, the animals are anaesthetized with sodium hexobarbital and bled from the carotid arteries. Serum or plasma samples are then extracted with isopropanol, and the cholesterol content of the extracts is estimated on a Technicon Autoanalyzer by standard methodology. The mean total serum cholesterol levels are then computed and the hypocholesterolemic activity is expressed as the fall in cholesterol levels as a percentage of the control level. For the triglyceride determination, blood samples are collected as above and 1.0 ml

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samples of the serum are added to 9.0 ml of redistilled isopropanol. Two autoanalyzer cupsful of a mixture of zeolite-copper hydroxide and Lloydds reagent (Kessler, G., and Lederer, H., 1965, Technicon Symposium, Mediad Inc., New York, 345—347) are added, and the mixture is shaken for one hour. After centrifugation, 2 ml of the clear supernates are evaporated to dryness and saponified by addition of 0.1 ml of 10% KOH in 90% ethanol and 1.0 ml of Skelly B (petroleum ether, bp. 60°—70°). After acidification and the removal of fatty acids with petroleum ether, the aqueous phases are neutralized, suitably diluted with water, and analyzed for glycerol by the method of Lofland [Anal. Biochem. 9, 393 1964)] using the Technicon Autoanalyzer. The change in serum triglyceride levels induced by the drug is computed as a percentage of the control triglyceride levels.

The pharmaceutically acceptable salts of compounds of formula I are therefore indicated for use as hypolipidemic agents. An indicated, suitable daily dosage is from about 150 mg to about 4000 mg, preferably 600—4000 mg, preferably administered in divided dosages of from about 37.5 mg to about 2000 mg, preferably 150 to 2000 mg, two to four times daily, or in a sustained release.

According to the present invention, there is provided a pharmaceutical composition comprising a pharmaceutically acceptable salt of a compound of formula I, stated above, in association with a pharmaceutically acceptable diluent or carrier, in solid unit dosage form or in the form of a sterile injectable aqueous solution or suspension.

The invention also provides a process for the production of such pharmaceutical compositions, which comprises working up a pharmaceutically acceptable salt of a compound of formula I, stated above, in a state of purity sufficient for pharmaceutical acceptability, with a pharmaceutically acceptable diluent or carrier.

The compositions may, for example, contain up to 90% by weight of the salt form of the compound of formula I. Preferably, they contain at least 1% by weight of the salt form.

The compositions may be administered orally, suitably in such forms as tablets, dispersible powders, granules, capsules, suspensions syrups and elixirs, or parenterally in such forms as injectable solutions or suspensions. The compositions may contain 1 or more conventional adjuvants, such as sweetening agents, flavoring agents, colouring agents and preserving agents, in order to provide an elegant and palatable preparation. Tablets may contain the active ingredient in admixture with conventional pharmaceutically acceptable excipients, e.g. inert diluents, such as calcium carbonate, sodium carbonate, lactose and talc, granulating and disintegrating agents, e.g., starch and alginic acid, binding agents, e.g., starch, gelatin and acacia, and lubricating agents, e.g., magnesium stearate, stearic acid and talc. The tablets may be uncoated or coated by known techniques to delay disintegration and absorption in the gastro-intestinal tract and thereby provide a sustained action over a longer period. Similarly, suspensions, syrups and elixirs may contain the active ingredient in admixture with any of the conventional excipients utilized for the preparation of such compositions, e.g. suspending agents (methyl-cellulose, tragacanth and sodium alginate), wetting agents (lecithin, polyoxyethylene stearate and polyoxyethylene sorbitan mono-oleate) and preservatives (ethyl-*p*-hydroxybensoate). Capsules may contain the active ingredient admixed with an inert solid diluent, e.g., calcium carbonate, calcium phosphate and kaolin.

The preferred compositions from the standpoint of preparation and ease of administration are solid compositions, particularly hard-filled capsules and tablets containing 300 mg of the salt of the compound of formula I. The preferred compound of formula I is bis (*p*-hydroxyphenyl)methane. Preferred pharmaceutically aceptable salts include alkali metal salts, eg. sodium and potassium salts, and alkaline earth metal salts, eg. magnesium and calcium salts. The compounds of formula I possess two centres for salt formation and may therefore form mono- or di- salts. The invention is intended to embrace both mono- and di- salts but the di-salts are preferred.

The following Examples illustrate the invention.

Example 1.

Tablets

Tablets suitable for oral administration which contain the following ingredients may be prepared by conventional tabletting techniques. Such tablets are indicated for use in treating lipidemia at a dose of one tablet 2 to 4 times a day.

Ingredients	Weight (mg)
Disodium salt of Bis-(*p*-hydroxyphenyl)methane	300
Tragacanth	10
Lactose	297.5
Corn starch	25
Talcum	15
Magnesium stearate	2.5

Example 2.

Dry Filled Capsules

Capsules suitable for oral administration which contain the following ingredients are prepared in a conventional manner. Such capsules are indicated for use in treating lipidemia at a dose of one capsule 2 to 4 times a day.

Ingredients	Weight (mg)
Disodium salt of Bis-(*p*-hydroxyphenyl)methane	300
Inter solid diluent (starch, lactose, kaolin)	300

Examples 3 and 4.

Sterile Suspension for Injection and Oral Liquid Suspension

The following pharmaceutical compositions are formulated with the indicated amount of active agent using conventional techniques. The injectable suspension and the oral liquid suspension represents formulations indicated for use as unit doses in the treatment of lipidemea. The injectable suspension is indicated as suitable for administration twice a day whereas the oral liquid suspension is indicated as suitable for administration 2 to 4 times per day.

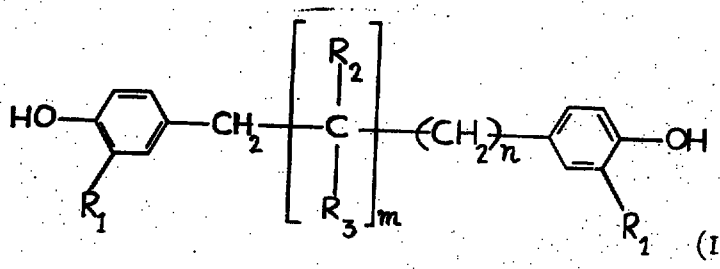
Ingredients	Weight (mg) sterile injectable suspension	Weight (mg) oral liquid suspension
Disodium salt of Bis-(*p*-hydroxyphenyl)methane	300	300
Sodium carboxy methylcellulose U.S.P.	1.25	12.5
Methylcellulose	0.4	–
Polyvinylpyrrolidone	5	–
Lecithin	3	–
Benzyl alcohol	0.01	–
Magnesium aluminum silicate	–	47.5
Flavor	–	q.s.
Color	–	q.s.
Methyl paraben U.S.P.	–	4.5
Propyl paraben U.S.P.	–	1.0
Polysorbate 80 U.S.P.	–	5
Sorbitol solution 70% U.S.P.	–	2,500
Buffer agent to adjust pH for desired stability	q.s.	q.s.
Water	for injection q.s. to 1 ml.	q.s. to 5 ml.

Example 5.

Analogous compositions to those of Examples 1 to 3 are formulated employing, in place of the sodium salt of bis-(*p*-hydroxy phenyl)methane, the dipotassium, calcium or magnesium salt thereof.

WHAT WE CLAIM IS:—

1. A pharmaceutical compositon comprising a pharmaceutically acceptable salt of a compound of formula I,



(I)

in which the radicals R_1 are the same and signify a hydrogen atom or a hydroxy group,

R_2 and R_3, which may be the same or different, each signifies a hydrogen atom or a methyl radical,

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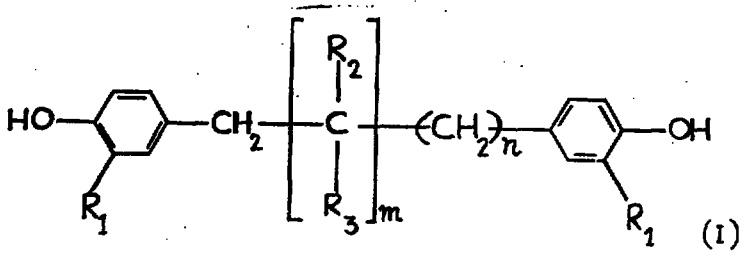
Ingredients	Weight (mg) sterile injectable suspension	Weight (mg) oral liquid suspension
Disodium salt of Bis-(*p*-hydroxyphenyl)methane	300	300
Sodium carboxy methylcellulose U.S.P.	1.25	12.5
Methylcellulose	0.4	–
Polyvinylpyrrolidone	5	–
Lecithin	3	–
Benzyl alcohol	0.01	–
Magnesium aluminum silicate	–	47.5
Flavor	–	q.s.
Color	–	q.s.
Methyl paraben U.S.P.	–	4.5
Propyl paraben U.S.P.	–	1.0
Polysorbate 80 U.S.P.	–	5
Sorbitol solution 70% U.S.P.	–	2,500
Buffer agent to adjust pH for desired stability	q.s.	q.s.
Water	for injection q.s. to 1 ml.	q.s. to 5 ml.

Example 5.

Analogous compositions to those of Examples 1 to 3 are formulated employing, in place of the sodium salt of bis-(*p*-hydroxy phenyl)methane, the dipotassium, calcium or magnesium salt thereof.

WHAT WE CLAIM IS:—

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in which the radicals R_1 are the same and signify a hydrogen atom or a hydroxy group,

R_2 and R_3, which may be the same or different, each signifies a hydrogen atom or a methyl radical,

n signifies 0 or 1, and
m signifies 0, 1 or 2,
provided that
(i) when m signifies 0, then n signifies 0,
(ii) when m signifies 2, the radicals R_2 and the radicals R_3 may be the same or different,
(iii) when m signifies 1 or 2, then n signifies 1 and each radical R_1 signifies a hydroxy group,
and (iv) when m signifies 2 and both the radicals R_2 or both the radicals R_3 signify a methyl group, then at least one of the radicals R_3 or at least one of the radicals R_2, respectively, signifies a methyl group, in association with a pharmaceutically acceptable diluent or carrier, in solid unit dosage form or in the form of a sterile injectable aqueous solution or suspension.

2. A pharmaceutical composition according to Claim 1, in solid unit dosage form, and containing from 37.5 mg to 2000 mg. of the pharmaceutically acceptable salt of the compound of formula I per unit.

3. A pharmaceutical compositon according to Claim 2 containing from 150 mg. to 200 mg. of the pharmaceutically acceptable salt of the compound of formula I per unit.

4. A pharmaceutical composition according to Claim 1, in unit sustained release form, and containing from 150 mg. to 4000 mg. of the pharmaceutically acceptable salt of the compound of formula I per unit.

5. A pharmaceutical composition according to any one of claims 1—4 in which the compound of formula I is bis(*p*-hydroxyphenyl)methane.

6. A pharmaceutical composition according to any one of the preceding claims in which the pharmaceutically acceptable salt is an alkali of alkaline earth metal salt.

7. A pharmaceutical composition according to claim 6 in which the pharmaceutically acceptable salt is the disodium, dipotassium, calcium or magnesium salt.

8. A pharmaceutical composition according to any one of the preceding claims, in the form of a tablet.

9. A pharmaceutical composition according to any one of claims 1—7, in the form of a capsule.

10. A pharmaceutical composition according to any one of claims 1—7 in the form of a sterile injectable solution or suspension.

11. A pharmaceutical composition according to any one of Claims 1 to 9, in a form suitable for oral administration, which comprises one or more of a sweetening agent, a flavouring agent, a colouring agent and a preserving agent.

12. A pharmaceutical composition according to any one of the preceding claims, comprising up to 90% by weight of the compound of formula 1.

13. A pharmaceutical composition according to any one of the preceding claims, comprising at least 1% by weight of the compound of formula 1.

14. A pharmaceutical composition comprising a pharmaceutically acceptable salt of a compound of formula 1, stated in Claim 1, in association with a pharmaceutically acceptable diluent or carrier, substantially as herein described with reference to any one of the Examples.

15. A process for the production of a pharmaceutical composition according to Claim 1, which comprises working up a pharmaceutically acceptable salt of a compound of formula 1, stated in Claim 1, in a state of purity sufficient for pharamaceutical acceptability, with pharmaceutically acceptable diluent or carrier.

16. A pharmaceutical composition according to Claim 1, whenever produced by a process according to Claim 15.

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