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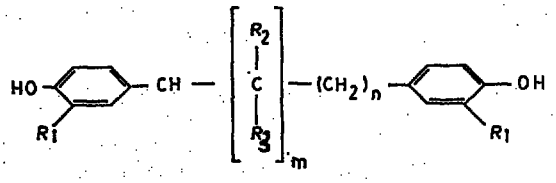
(19)

(54) PHARACEUTICAL ANTILIPIDEMIC COMPOSITIONS

(71) We, SANDOZ LTD., of 35 Lichtstrasse, 4000 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 pharmaceutical compositions comprising diphenylalkane derivatives, and, more particularly, comprising 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 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,
(iv) when m signifies 2 and each radical R_2 signifies methyl, then at least one of the radicals R_3 signifies methyl,
and
(v) when m signifies 2 and each radical R_3 signifies methyl, then at least one of the radicals R_2 signifies methyl.

The present invention is based on the discovery that the compounds of formula I 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 30 mg per kg of body weight *per diem* of the compound of six days. At the end of this period, the animals are anaesthetized with sodium hexobarital and bled from the carotid arteries. Serium 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 triglycerid determination, blood samples are collected as above and 1.0 ml 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

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(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 compounds of formula I are therefore indicated for use as hypolipidemic agents. An indicated, suitable daily dosage is from 150 mg to 2000 mg, preferably administered in divided dosages of from 37.5 mg to 1000 mg, preferably from 50 mg to 1000 mg, more preferably from 50 mg to 500 mg, two to four times daily, or in unit retard form.

The compounds of formula I are known or may be prepared in conventional manner from available starting materials.

According to the present invention, there is provided a pharmaceutical composition comprising 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 solution or suspension.

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

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

The compositions may be administered orally, suitably in such forms as tablets, or capsules or parenterally in the form of sterile injectable solutions or suspensions. The oral compositions may contain 1 or more conventional adjuvants, such as sweetening agents, flavoring agents, coloring 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, injectable suspensions, may contain the active ingredient in admixture with any of the conventional excipients utilized for the preparation of such compositions, e.g. suspending agents (methylcellulose, tragacanth and sodium alginate), wetting agents (lecithin, polyoxyethylene stearate and polyoxyethylene sorbitan mono-oleate) and preservatives (ethyl-*p*-hydroxybenzoate). 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 from 50 mg to 500 mg of the compound of formula I. The preferred compound of formula I is bis(*p*-hydroxyphenyl)methane.

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.)
Bis-(*p*-hydroxyphenyl)methane	50
Tragacanth	10
Lactose	197.5
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.)
Bis-(*p*-hydroxyphenyl)methane	100
Inert solid diluent (starch, lactose, kaolin)	200

EXAMPLES 3 and 4

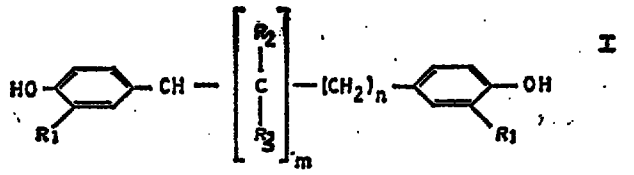
Sterile Suspension for Injection

The following pharmaceutical composition is formulated with the indicated amount of active agent using conventional techniques. The injectable suspension represents a formulation indicated for use as a unit dose in the treatment of lipidemia. The injectable suspension is indicated as suitable for administration once or twice a day.

Ingredients	Weight (mg.)
Bis-(*p*-hydroxyphenyl)methane	50
Sodium carboxy methylcellulose U.S.P.	1.25
Methylcellulose	0.4
Polyvinylpyrrolidone	5
Lecithin	3
Benzyl alcohol	0.01
Buffer agent to adjust pH for desired stability	q.s.
Water	for injection, q.s. to 1 ml.

WHAT WE CLAIM IS:—

1. A pharmaceutical composition comprising a compound of formula I,



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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,
(iv) when m signifies 2 and each radical R_2 signifies methyl, then at least one of the radicals R_3 signifies methyl,
and
(v) when m signifies 2 and each radical R_3 signifies methyl, then at least one one of the radicals R_2 signifies methyl,
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 1000 mg of the compound of formula I.

3. A pharmaceutical composition according to Claim 2, containing from 50 mg to 1000 mg of the compound of formula I.

4. A pharmaceutical composition according to Claims 2 or 3, containing from 50 mg to 500 mg of the compound of formula I.

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.)
Bis-(*p*-hydroxyphenyl)methane	100
Inert solid diluent (starch, lactose, kaolin)	200

EXAMPLES 3 and 4

Sterile Suspension for Injection

The following pharmaceutical composition is formulated with the indicated amount of active agent using conventional techniques. The injectable suspension represents a formulation indicated for use as a unit dose in the treatment of lipidemia. The injectable suspension is indicated as suitable for administration once or twice a day.

Ingredients	Weight (mg.)
Bis-(*p*-hydroxyphenyl)methane	50
Sodium carboxy methylcellulose U.S.P.	1.25
Methylcellulose	0.4
Polyvinylpyrrolidone	5
Lecithin	3
Benzyl alcohol	0.01
Buffer agent to adjust pH for desired stability	q.s.
Water	for injection, q.s. to 1 ml.

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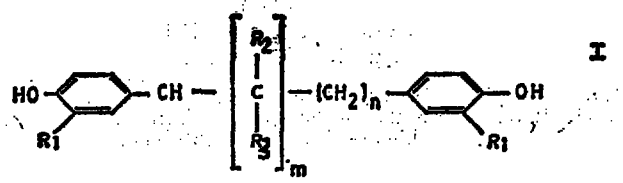

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in which the radicals R_1 are the same and signify a hydrogen atom or a hydroxy group,
R_2 and R_3, which may be the same or different, each signifies a hydrogen atom or a methyl radical,
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in association 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 1000 mg of the compound of formula I.

3. A pharmaceutical composition according to Claim 2, containing from 50 mg to 1000 mg of the compound of formula I.

4. A pharmaceutical composition according to Claims 2 or 3, containing from 50 mg to 500 mg of the compound of formula I.

5. A pharmaceutical composition according to any preceding Claim, in which the compound of formula I is bis(*p*-hydroxyphenyl)methane.

6. A pharmaceutical composition according to any one of Claims 1 to 5, in the form of a tablet.

7. A pharmaceutical composition according to any one of Claims 1 to 5, in the form of a capsule.

8. A pharmaceutical composition according to Claim 1, in the form of a sterile injectable solution or suspension.

9. A pharmaceutical composition according to any one of Claims 1 to 7, in the form suitable for oral administration, which comprises one or more of a sweetening agent, a flavouring agent, a colouring agent and a preserving agent.

10. A pharmaceutical composition according to any one of Claims 1 to 9, comprising up to 90% by weight of the compound of formula I.

11. A pharmaceutical composition according to any one of Claims 1 to 10, comprising at least 1% by weight of the compound of formula I.

12. A pharmaceutical composition according to Claim 1, in which n, m and R_1 are as defined in Claim 1, provided that when m and n each signifies 0, then R_1 signifies hydrogen.

13. A pharmaceutical composition comprising a compound of formula I, 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.

14. A process for the production of a pharmaceutical composition according to Claim 1, which comprises working up an appropriate quantity of a compound of formula I, stated in Claim 1, in a state of purity sufficient for pharmaceutical acceptability, with a suitable quantity of an appropriate pharmaceutically acceptable diluent or carrier.

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

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