PATENT SPECIFICATION (11) 1 589 946

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(21) Application No. 52123/77 (2) Filed 14 Dec. 1977

(44) Complete Specification Published 20 May 1981

(51) INT. CL. [3] A61K 9/08 9/10

(52) Index at Acceptance
A5B 822 823 M

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(19)

(54) ENTERALLY ABSORBABLE PREPARATIONS AND PROCESS FOR THE PRODUCTION THEREOF

(71) We, KALI-CHEMIE PHARMA G.M.B.H, a body corporate organised under the laws of the German Federal Republic, of Hans-Böckler-Allee 20, D-3000, 8 Hanover 1, German Federal Republic, 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 enterally absorbable preparations of medicaments which by themselves are absorbable with difficulty, and to a process for the production of such preparations.

It is known that, certain medicaments are not absorbed, or are absorbed to only a limited extent in the intestinal tract; such medicaments are hereinafter referred to as medicaments which are absorbable with difficulty. The reason for this may, in the case of many medicaments, be their low solubility in water, but even among water-soluble medicaments there are those which are not enterally absorbable to the desired extent.

The absorbability of such enterally difficultly absorbable medicaments may in many cases be increased by technological treatment of the medicament, as for example micronisation, formation of adsorbates or the addition of solubilisers, but the dose to be applied almost always lies considerably above the amount of active substance which would be necessary for achieving a therapeutic effect in the case of complete bio-availability.

However, there exists a need to render enterally absorbable medicaments which are not only in injection form but also in orally or rectally applicable form, and which are absorbable with difficulty.

According to the present invention, there is provided an enterally absorbable preparation of a medicament which is absorbable with difficulty (as hereinbefore defined), wherein the medicament is present in the form of a solution or microcrystalline suspension in one or more partial glycerides of one or more long-chain fatty acids having 12 to 18 carbon atoms.

The partial glycerides of long-chain fatty acids having 12 to 18 carbon atoms possess excellent dissolving properties both for hydrophilic and lipophilic substances and are therefore particularly suitable as a vehicle for medicaments which are absorbable with difficulty. The preferred partial glycerides of long-chain fatty acids are the mono- and/or di-glycerides of saturated and/or unsaturated fatty acids with chain lengths of 12 to 18, preferably 14 to 18, carbon atoms, the mono- and/or di-glycerides of palmitic acid, stearic acid, oleic acid or mixtures of such partial glycerides being preferred.

Depending upon the mode of application, whether oral or rectal, the preparation is brought into a form suitable for this purpose. Such forms, as for example tablets, gelatin capsules or suppositories, may be formed particularly easily because, some of the partial glycerides which may be used are liquid at room temperature while some are solid. By suitable mixing of the partial glycerides, almost any desired consistency may be achieved or the optimum melting point for rectal application may be set up. In an extreme case, the otherwise conventional viscosity-changing or structure-conferring additives or auxiliaries may be added to the present preparation. If, in the case of forms which are to be applied orally, it is desirable that absorption is not caused to commence until in the duodenum, it may be expedient to provide such forms with a coating which is resistant to gastric juices.

Medicaments which may be used in or form an active part of the present preparations, include those which normally show an unsatisfactory enteral absorption. Preferred medicaments include cardiac glycosides which are absorbable with difficulty, as for example

strophanthin G or proscillaridin A, gestogenic hormones which are absorbable with difficulty, as for example progesterone or medrogestone, or preparations for treating varicose veins, or agents for treating or preventing the impairment of the strength of capillary blood vessels, as for example benzarone, which are absorbable with difficulty.

The present preparations may be produced by dissolving the medicament or active substance in the partial glyceride(s). Depending upon solubility and/or speed of dissolving of the active substance in the partial glycerides or the melting point of the partial glycerides, the dissolving may be effected with heating. In so far as, during the cooling of preparations produced by heating, the medicament recrystallises or the partial glyceride re-solidifies, micro-crystalline suspensions or solid solutions form which, in absorption behaviour, behave like true solutions.

Proof of the high enteral absorption of the present preparations was conducted by means of toxicity investigations, blood-level measurements and determination of the renal excretion.

In the toxicity investigations, to female guinea-pigs of 250 to 300 g. weight there were administered orally, by tubular sound, strophanthin G, proscillaridin A and medrogestone dissolved invarious partial glycerides of long-chain fatty acids and, in comparison thereto, suspended in methyl cellulose. The lethal doses found are stated in the following Table and show the improved absorption of the active substance dissolved in partial glycerides.

	LD_{50} (mg./kg.)			
	in "Tylose" 1)	in "Witafrol" 7470[2]	in "Pécéol"[3]	in "Rilanit" GMO[4]
strophanthin-G	34.8	8.28	8.38	–
proscillaridin A	12.3	6.81	7.77	–
medrogestone	>1470	–	850	862

1. methyl cellulose, obtainable from the firm of Hoechst: "Tylose" is a registered Trade Mark.

2. mono-diglyceride mixture of oleic acid, containing about 40% monoester and about 60% diester, obtainable from the first of Dynamit-Nobel: "Witafrol" is a registered Trade Mark.

3. mono-di-triglyceride mixture of oleic acid, containing about 30% monoester, obtainable from the firm of Gattefosse.

4. mono-diglyceride mixture of oleic acid, containing about 40% monoester and 60% diester, obtainable from the firm of Henkel: "Rilanit" is a registered Trade Mark.

In blood-level measurements, a dose of 1000 mg./kg. benzarone dissolved in "Rilanit" GMO and, in comparison thereto, suspended in water, was administered orally to rats by oesophageal sound. Thereafter, every 2 hours up to and including the 10th hour, in each case 8 animals were killed and, after 15 hours, in each case 4 further animals were killed and the blood was obtained by cardiotomy. The benzarone was determined spectrophotometrically in the serum and recorded graphically. The comparison of areas below the curves showed for the benzarone dissolved in "Rilanit" GMO an increase of the serum concentration of 257% compared to the benzarone suspended in water.

For the determination of renal excretion, ^{14}C– labelled progesterone dissolved in various partial glycerides of long-chain fatty acids and, in comparison thereto, suspended in "Tylose", was administered orally, by oesophageal sound, in a dose of 20 mg./kg. to female guinea-pigs of an average weight of 300 g. the urine of the animals was collected in 24-hour fractions and the activity was determined in aliquot parts of the urine. The cumulative percentage excretion of the dose administered is stated in the following Table and reaches, in the case of the progesterone dissolved in "Pécéol", at about 83% almost twice the value of the excretion of the progesterone suspended in "Tylose".

Renal excretion of progesterone in % (cumulative) of the dose administered

Time	"Tylose"	"Tegin" 0[1]	"Tegomuls" X10[2]	"Tegomuls" X17[3]	"Pécéol" X1[4]	"Softigen" 701[5]
1st day	29.7	37.9	42.5	43.7	46.0	51.6
2nd day	39.1	48.7	58.3	55.0	64.6	63.2
3rd day	43.0	51.6	69.2	62.0	71.6	66.2
4th day	44.0	52.3	75.2	66.6	76.1	66.9
5th day	44.5	52.6	78.8	70.0	79.1	67.4
6th day	46.2	52.8	80.6	71.9	81.1	67.6
7th day	46.4	52.9	81.9	73.9	82.9	67.7

1) mono-diglyceride mixture of oleic acid, about 60% mono- and 40% diester, obtainable from the firm of Goldschmidt: "Tegin" is a registered Trade Mark.

2) mixture of 50 parts by weight of "Tegomuls" SO and 10 parts by weight of "Rilanit" GDO; "Tegomuls" SO is a partially hydrolysed soya bean oil containing about 35 - 40% monoglyceride, obtainable from the firm of Goldschmidt; "Rilanit" GDO is an oleic acid partial glyceride containing about 20% monoester and 50% diester, obtainable from the firm of Henkel.

3) mixture of 45 parts by weight of "Tegomuls" SO, 45 parts by weight of "Tegomuls" SB and 10 parts by weight of "Miglyol" 812; "Tegomuls" SB is a partially hydrolysed sunflower oil, containing about 60% monoglyceride, obtainable from the firm of Goldschmidt; "Miglylol" 812 is a triglyceride mixture of medium-chain fatty acids, obtainable from the firm of Dynamit-Nobel: "Miglycol" is a registered Trade Mark.

4) mixture of 50 parts by weight of "Pécéol" and 10 parts of "Rilanit" GDO.

5) partial glyceride mixture of an unsaturated fatty acid which is rich in hydroxyl groups and which is obtainable from the firm of Dynamit-Nobel.

In addition, benzarone dissolved in "Rilanit" GMO and, in comparison thereto, suspended in water, was administered orally, by oesophageal sound, in a dose of 100 mg./kg. to rats and the urine of the animals was collected in 2-hour fractions over 15 hours and the amount of renally excreted benzarone was determined spectrophotometrically. The measured values were recorded graphically and the areas below the curves were compared. There resulted in the case of the benzarone dissolved in "Rilanit" GMO, in comparison with benzarone suspended in water, an increase of renal excretion by 437%.

The invention will now be illustrated by the following Examples in which, unless otherwise indicated "parts" are parts by weight.

EXAMPLE 1

Gelatin capsules

A mixture to be filled into gelatin capsules has the following composition:

progesterone	10 parts
"Tegomuls" SO	400 parts
"Rilanit" GDO	90 parts
TOTAL	500 parts

Preparative instruction: the progesterone is dissolved at 40°C. with stirring, in a mixture of "Tegomuls" SO and "Rilanit" GDO. Of this solution, 500 mg. portions are filled into gelatin capsules so that each capsule contains 10 mg. of progesterone.

EXAMPLE 2

Gelatin capsules

progesterone	10 parts
"Péceol"	400 parts
"Rilanit" GDO	90 parts
TOTAL	500 parts

Preparative instruction: the progesterone is dissolved at 40°C. with stirring, in a mixture of "Pécéol" and "Rilanit" GDO. of this solution, 500 mg. portions are filled into gelatin capsules so that each capsule contains 10 mg. of progesterone.

EXAMPLE 3
Gelatin capsules

benzarone	100 parts
"Rilanit" GMO	900 parts
TOTAL	1000 parts

Preparative instruction: the benzarone is dissolved, with stirring, in the "Rilanit" GMO which is liquefied at 60°C.. Of this solution, 1000 mg. portions are filled into gelatin capsules so that each capsule contains 100 mg. of benzarone.

EXAMPLE 4
Gelatin capsules

strophanthin-G	0.25 part
"Witafrol" 7470	199.75 parts
TOTAL	200 parts

Preparative instruction: the strophanthin-G is dissolved at 40°C. with stirring, in "Witafrol" 7470. Of this solution, 200 mg. portions are filled into gelatin capsules so that each capsule contains 0.25 mg. of strophanthin-G.

EXAMPLE 5
Gelatin capsules

propscillaridin A	0.1 parts
"Witafrol" 7470	99.9 parts
TOTAL	100 parts

Preparative instruction: the proscillaridin A is dissolved at 40°C. with stirring, in "Witafrol" 4740. Of this solution, 100 mg. portions are filled into gelatin capsules so that each capsule contains 0.1 mg. of proscillardin A.

EXAMPLE 6
Rectal capsules

benzarone	100 parts
"Softigen" 701	1300 parts
"Tegin" 0	600 parts
TOTAL	2000 parts

preparative instruction: the benzarone is dissolved at 50°C. in a melt of "Softigen" 701 and "Tegin" 0. After cooling, 2000 mg. portions of this solution are filled into rectal capsules so that each capsule contains 100 mg. of benzarone.

EXAMPLE 7
Gelatin capsules

medrogestone	25 parts
"Rilanit" GMO	475 parts
TOTAL	500 parts

Preparative instruction: the medrogestone is dissolved, with stirring, in the 'Rilanit" GMO which is molten at 55°C. After cooling the mixture, 500 mg. portions are filled into gelatin capsules so that each capsule contains 25 mg. of medrogestone.

EXAMPLE 8
Gelatin capsules

medrogestone	25 parts
"Pécéol"	475 parts
TOTAL	500 parts

Preparative instruction: the medrogestone is dissolved, with stirring, in the "Pécéol" which is molten at 55°C.. After cooling the mixture, 500 mg. portions are filled into gelatin capsules so that each capsule contains 25 mg. of medrogestone.

WHAT WE CLAIM IS:-

1. An enterally absorbable preparation of a medicament which is absorbable with difficulty (as hereinbefore defined), wherein the medicament is present in the form of a solution or microcrystalline suspension in one or more partial glycerides of one or more long-chain fatty acids having 12 to 18 carbon atoms.
2. A preparation as claimed in Claim 1, wherein the fatty acid(s) has (have) 14 to 18 carbon atoms.
3. A preparation as claimed in claim 1 or 2, wherein the fatty acid(s) is (are) saturated and/or unsaturated fatty acid(s).
4. A preparation as claimed in any one of Claims 1 to 3, wherein the partial glyceride(s) is(are) selected from mono- and di-glycerides of palmitic acid, stearic acid and oleic acid, and mixtures of such partial glycerides.
5. A preparation as claimed in any one of Claims 1 to 4, wherein the solution or suspension is filled into gelatin capsules.
6. A preparation as claimed in Claim 5, wherein the gelatin capsules are provided with a coating which is resistant to gastric juices.
7. A preparation as claimed in any one of Claims 1 to 4, wherein the preparation is shaped into suppositories.
8. A preparation as claimed in any one of Claims 1 to 7, wherein the medicament is a cardiac glycoside, a gestogenic hormone or a preparation for treating varicose veins or an agent for treating or preventing the impairment of the strength of capillary bood vessels.
9. A preparation as claimed in Claim 8, wherein the medicament is strophanthin-G, proscillaridin A, progesterone, medrogestone or benzarone.
10. An enterally absorbable preparation in accordance with Claim 1 substantially as hereinbefore described in any one of the foregoing Examples.
11. A process for the production of an enterally absorbable preparation of a medicament which is absorbable with difficulty (as hereinbefore defined), wherein the medicament is dissolved in one or more partial glycerides of one or more long-chain fatty acids having 12 to 18 carbon atoms.
12. A process as claimed in Claim 11, wherein the medicament is dissolved in the partial glycerides with heating.
13. A process as claimed in claims 11 or 12, wherein the medicament is dissolved in one or more partial glycerides of one or more fatty acids having 14 to 18 carbon atoms.
14. A process as claimed in any one of Claims 11 to 13, wherein the medicament is dissolved in one or more partial glycerides of one or more saturated and/or unsaturated fatty acids.
15. A process as claimed in any one of Claims 11 to 14, wherein the medicament is dissolved in one or more mono- and/or diglycerides of palmitic acid, stearic acid or oleic acid or a mixture of such partial glycerides.
16. A process as claimed in any one of Claims 11 to 15, wherein the solution is filled into gelatin capsules.
17. A process as claimed in Claim 16, wherein the gelatin capsules are provided with a coating which is resistant to gastric juices.
18. A process as claimed in any one of Claims 12 to 15, wherein the solution is shaped into suppositories.
19. A process as claimed in any one of Claims 11 to 18, wherein the medicament is a cardiac glycoside, a gestogenic hormone or a preparation for treating varicose veins or an agent for treating or preventing the impairment of the strength of capillary blood vessels.
20. A process as claimed in Claim 19, wherein the medicament is strophanthin-G, proscillaridin A, progesterone, medrogestone or benzarone.
21. A process for the production of an enterally absorbable preparation of a medicament in accordance with Claim 11 substantially as hereinbefore described in any one of the foregoing Examples.

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Printed for Her Majesty's Stationery Office, by Croydon Printing Company Limited, Croydon, Surrey, 1981.
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from
which copies may be obtained.