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(72) Inventors HIROITSU KAWADA, HIROO MAENO, SHIGEO KAWAMURA, ISAO OHATA and KUNIHIDE ICHIKAWA

(54) PHARMACEUTICAL COMPOSITION OF INSULIN FOR RECTAL USE

(71) We, YAMANOUCHI PHARMACEUTICAL COMPANY LIMITED, a Japanese Company organised and existing under the laws of Japan, of 5—1, Nihonbashi-Honcho 2-chome, Chuo-ku, Tokyo, Japan, 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 pharmaceutical insulin composition for rectal administration.

Insulin is a medicament particularly useful as a hypoglycaemic agent and has been widely used up until now. Insulin is administered in practice only by injection, and thus since the majority of patients with diabetes mellitus are required to have insulin every day throughout their lives, its administration is very troublesome both for physicians and patients. Injection of insulin particularly leads to mental and physical suffering for the patients, as well as other problems.

In order to overcome the aforesaid difficulties caused by injection of insulin, pharmaceutical compositions of insulin for rectal administration have recently been developed. However, in order to obtain the desired hypoglycaemic activity by such rectal administration, the insulin dose has to be greatly larger than that required by injection, as will be described later. Furthermore, since the necessary amount of insulin differs greatly for each sufferer of diabetes mellitus, it is undesirable to irrespectively administer a pharmaceutical composition of insulin of high unit dose. Such a mode of administration is quite dangerous as hypoglycaemia may occur, if, for any reason, a larger amount of insulin than needed is absorbed. Still further, insulin itself is very expensive and thus the conventional pharmaceutical compositions which require large amounts of insulin are economically disadvantageous.

By way of example we mention that Y. Matsubara tested hypoglycaemic activity by administering through the rectum of a rabbit a pharmaceutical composition prepared by mixing insulin, water, olive oil, and a polyoxyethylene oleic acid ester (Emanone 4115®) (Tokyo Idai Zasshi, *21*, 135(1963)) and Y. Nishioka *et al*, tested hypoglycaemic activity by administering through the rectum of a rabbit a pharmaceutical composition prepared by mixing insulin, water, olive oil (or a water-soluble or oil-soluble base), and a polyoxethylene-hydrogenated castor oil derivative (HCO—60®) (Lecture Summary; Vol. IV, 196(1975) in the 95th Annual Meeting of Nippon Yakugaku Kai). The former reported that when insulin was administered at a dose of 30 I.U./kg of rabbit, the decrease in blood glucose was 30—40%, while the latter reported that when insulin was administered at a dose of 100 I.U./kg of rabbit, the decrease in blood glucose was 40%. Compared with this, it is said that when insulin is injected in a rabbit at a dose of 0.1—1 I.U./kg, the decrease in blood glucose is 40—60%. This is, to achieve similar results, rectal administration of insulin requires doses of about 30—3000 times (in the former case) and about 100—1,000 times (in the latter case) larger than an insulin dose administered by injection.

Thus, conventional pharmaceutical insulin compositions have not in practice been used by rectal administration.

As a result of various investigations with such technical knowledge in mind, the

present inventors have discovered pharmaceutical compositions containing insulin which can be administered through the rectum at an insulin dose almost equivalent to that employed for injection. They have found that with compositions embodying the present invention, the insulin is quickly absorbed in the body through the rectum to provide a high insulin concentration in blood nearly equal to, or, in certain instances, higher than that with administration of insulin by injection. Thus a remarkable reduction in the blood glucose is rendered possible with rectal administration. That is, when pharmaceutical compositions embodying this invention are administered through the rectum of a rabbit at an insulin dose of 0.5—5 I.U./kg, the decrease in blood glucose was found to be 40—60%. Such compositions can thus exhibit a remarkable hypoglycaemic effect per dose of insulin almost equivalent to that with injection.

According to this invention, there is provided a pharmaceutical composition for rectal administration which comprises insulin, a carrier suiting the composition for rectal administration, and an agent for increasing the rate of absorption of the insulin into the body on rectal administration of the composition, the agent comprising at least one material selected from (a) nonionic polyoxyethylene ether surface active agents having an HLB value of 6 to 19 and wherein the average number of polyoxyethylene units is 4 to 30, (b) anionic surface active agents, (c) cationic surface active agents, (d) ampholytic surface active agents, (e) bile acids and (f) alkali metal salts of bile acids, and amounting to 0.001 to 0.5 times the weight of the carrier. The agent may be a mixture of a said nonionic polyoxyethylene ether surface active agent and a bile acid.

The specified nonionic surface active agents can provide the desired effects, while other nonionic surface agents have not shown the desired effects (see Test 1 below). The polyoxyethylene oleic acid ester and the polyoxyethylene-hydrogenated castor oil derivatives use as absorption agents in the aforesaid reports of Y. Matsubara and Y. Nishioka *et al.* respectively are nonionic surface active agents but are distinct from the specific nonionic surface active agents employed for the present purposes. Furthermore, the desired effects have also been obtained when anionic surface active agents, cationic surface active agents, ampholytic surface active agents, bile acids, or the alkali metal salts of bile acids are used as the absorption-accelerating agent, (see Test 1 below).

Any insulin such as, for example, the insulin obtained from cows (bovine), pigs or whales can be used as the insulin for compositions of this invention. Furthermore, metal complexes of insulin such as the zinc complex of insulin as well as protamine zinc insulin and globin zinc insulin may be also used as the insulin in compositions of this invention.

The carrier (also referred to herein as a base) used in this invention can be one conventionally employed for preparing pharmaceutical compositions for rectal use, e.g. an oily (fatty) base, an aqueous bases, or water.

The oily (fatty) bases useable are exemplified by sesame oil, olive oil, soybean oil, rapeseed oil, cottonseed oil, rice bran oil, tsubaki oil (from *Camellia japonica* L), corn oil, arachis oil, coconut oil, cocoa butter, Isocacao MO—5 (Trade Mark of KAO—SOAP Co., Ltd., higher saturated fatty acid triglyceride), laurin butter, beef tallow, lard, and wool fat; materials obtainable by the modification of the fats and oils mentioned above, e.g. by procedures such as hydrogenation, interesterification, acetylation, or fractional extraction; mineral oils such as "Vaseline" (Trade Mark), paraffin, or silicone oils; ester of fatty acids having 6 to 30 carbon atoms esterified with glycerol, such as glyceryl palmitate, glyceryl laurate, glyceryl stearate, glyceryl myristate; waxes such as esters of fatty acids having 6 to 30 carbon atoms esterified with alcohols having 2 to 8 carbon atoms, e.g., isopropylmyristate [Nikkol IPM®(EX) Nikko Chemicals Co. Ltd.]; higher fatty acids of 6 to 30 carbon atoms, e.g., stearic acid, oleic acid; and artifical suppository bases [e.g., "Witepsol" (Trade Mark) (Dynamit Nobel Aktiengesellschaft: triglyceride of saturated vegetable fatty acids with monoglycerides)]. These oily (fatty) bases may be employed either singly or as mixtures. Particularly preferred oily (fatty) bases are corn oil and olive oil.

The aqueous bases are exemplified by polyethylene glycol (Macrogol in Japanese Pharmacopoeia) 300, 400, 1000, 1500, 4000 and 6000; methyl cellulose (e.g. "Methocel" (Trade Mark) SM, Shinetsu Kagaku Co. Ltd.); sodium carboxy methyl cellulose (e.g., "Celogen" (Trade Mark) PR. Daiichi-Kogyo Co. Ltd.); and glycerogelatin. These aqueous bases may be employed either singly or as mixtures. A particularly preferred aqueous base is a mixture of polyethylene glycol 1500 and 6000.

Where water is to be used as a base it may be employed either alone or as a mixture of water with an oily (fatty) or aqueous base.

There is no particular restriction about the amount of the carrier or base used in this invention but the amount thereof is ordinarily 0.5—4 g, preferably 1—3 g per

administration for an adult.

The nonionic polyoxyethylene ether surface active agents (hereinafter referred to as POE) employed for the purposes of this invention, (hereinafter having an HLB value of 6—19 and an average number of POE units (hereinafter referred to as n) of 4—30 are preferably POE higher alcohol ethers wherein the higher alcohol has 6 to 22 carbon atoms, POE higher alkyl phenol ethers wherein hither alkyl means 6 to 18 carbon atoms, POE polyoxypropylene (hereinafter referred to as POP) higher alkyl ethers wherein higher alkyl means 6 to 22 carbon atoms and the average number of POP units (hereinafter referred to as m) is 1 to 16, or block copolymers of propylene oxide and ethylene oxide.

Practical examples of such POE higher alcohol ethers are POE lauryl ether (HLB = 8.0, n = 4.2), POE lauryl ether (HLB = 9.5, n = 6), POE lauryl ether (HLB = 11.5, n = 9), POE lauryl ether (HLB = 15.5, n = 21), POE lauryl ether (HLB = 16.5, n = 25), POE cetyl ether (HLB = 10.5, n = 5.5), POE cetyl ether (HLB = 11.5, n = 7), POE cetyl ether (HLB = 13.5, n = 10), POE cetyl ether (HLB = 15.5, n = 15), POE cetyl ether (HLB = 17.7, n = 20), POE stearyl ether (HLB = 7.5, n = 4), POE stearyl ether (HLB = 11.5, n = 10), POE stearyl ether (HLB = 18.0, n = 20), POE oleyl ether (HLB = 10.5, n = 7), POE oleyl ether (HLB = 14.0, n = 10), POE oleyl ether (HLB = 16.0, n = 15), POE oleyl ether (HLB = 17.0, n = 20), POE octyl ether (HLB = 15.8, n = 15). Practical examples of the POE higher alkyl phenol ethers are POE nonyl phenyl ether (HLB = 8, n = 5), POE nonyl phenyl ether (HLB = 14, n = 7.5), POE nonyl phenyl ether (HLB = 16.5, n = 10), POE nonyl phenyl ether (HLB = 18.0, n = 15), POE nonyl phenyl ether (HLB = 19.0, n = 18), POE octyl phenyl ether (HLB = 11.5, n = 10), POE octyl phenyl ether (HLB = 13.5, n = 15), POE octyl phenyl ether (HLB = 17.0, n = 30). Practical examples of the POE—POP higher alkyl ethers are POE—POP cetyl ether (HLB = 8.7, m = 4, n = 5), POE—POP cetyl ether (HLB = 10.6, m = 4, n = 10), POE—POP cetyl ether (HLB = 16.4, m = 8, n = 20), POE—POP cetyl ether (HLB = 9.0, m = 8, n = 5), POE—POP cetyl ether (HLB = 9.9, m = 8, n = 10), POE—POP cetyl ether (HLB = 12.5, m = 8, n = 20). Practical examples of the block copolymers of propylene oxide and ethylene oxide are those currently marketed under the Trade Names Pluronic L44®, L61®, L62®, L64®, F68®, F88® (Wyandotte Chem. Co.).

The anionic surface active agents used in this invention are preferably higher alkyl sulfates wherein higher alkyl means 8 to 18 carbon atoms POE higher alcohol ether sulfates (n = 1—6) wherein higher alcohol means 8 to 18 carbon atoms, POE higher alkyl phenol ether sulphates (n = 1—6) wherein higher alkyl means 8 to 18 carbon atoms, higher alkyl benzene sulfonates wherein higher alkyl means 8 to 18 carbon atoms, higher alkyl naphthalene sulfonates wherein higher alkyl means 3 to 10 carbon atoms, di-higher alkyl sulfosuccinates wherein higher alkyl means 4 to 10 carbon atoms, higher alkyl phosphates wherein higher alkyl means 8 to 18 carbon atoms, POE higher alcohol ether phosphates (n = 2—15) wherein higher alcohol means 8 to 18 carbon atoms, POE higher alkyl phenol ether phosphates (n = 2—15) wherein higher alkyl means 8 to 12 carbon atoms, and amino acid derivatives. Practical examples of such anionic surface active agents are sodium lauryl sulfate, sodium decyl sulfate, potassium lauryl sulfate, potassium myristyl sulfate, ammonium lauryl sulfate, triethanolamine cetyl sulfate, triethanolamine lauryl sulfate, sodium cetyl sulfate, sodium POE lauryl ether sulfate (n = 4), ammonium POE lauryl ether sulfate (n = 4), triethanolamine POE lauryl ether sulfate (n = 4), potassium POE lauryl ether sulfate (n = 4), sodium POE myristyl ether sulfate (n = 2), sodium POE cetyl ether sulfate (n = 2), sodium POE stearyl ether (n = 2), sodium POE octyl phenyl ether sulfate (n = 4), sodium POE nonyl phenyl ether sulfate (n = 4), sodium dodecyl benzene sulfonate, sodium tetradecyl benzene sulfonate, sodium hexadecyl benzene sulfonate, sodium tert-butyl naphthalene sulfonate, diamyl sodium sulfosuccinate, diisobutyl sodium sulfosuccinate, dioctyl sodium sulfosuccinate, sodium laurylphosphate, sodium oleyl phosphate, POE oleyl ether phosphate (n = 12), POE stearyl ether phosphate (n = 8), POE cetyl ether phosphate (n = 10), POE lauryl ether phosphate (n = 12), sodium POE eleyl ether phosphate (n = 8), sodium POE stearyl ether phosphate (n = 6), sodium POE cetyl ether phosphate (n = 5), sodium POE lauryl ether phosphate (n = 10), sodium di POE oleyl ether phosphate (n = 6), POE octyl phenyl ether phosphate (n = 8), triethanolamine POE octyl phenyl ether phosphate (n = 4), sodium POE octyl phenyl ether phosphate (n = 2), di POE nonyl phenyl ether phosphate (n = 4), monosodium N-lauroyl-L-glutamate, monosodium N-stearoyl-L-glutamate, monotriethanolamine N-lauroyl-L-glutamate, disodium N-stearoyl-L-glutamate, sodium N-lauroyl sarcosinate, sodium N-myristoyl sarcosinate, and sodium N-palmitoyl sarcosinate.

The cationic surface active agents used in the compositions of this invention include higher alkyl trimethyl ammonium halides, di-higher alkyl dimethyl ammonium halides, higher alkyl dimethyl benzyl ammonium halides and higher alkyl pyridinium halides, POE higher alkylamines (n = 1—20), and POE fatty acid amines (n = 1—20) (wherein higher alkyl means 6—18 carbon atoms and the fatty acid has 12—18 carbon atoms). Practical examples of such cationic surface active agents are octyl trimethyl ammonium chloride, decyltrimethyl ammonium chloride, lauryl trimethyl ammonium chloride, lauryl trimethyl ammonium chloride, palmityl trimethyl ammonium chloride, octyl trimethyl ammonium bromide, lauryl trimethyl ammonium bromide, myristyl trimethyl ammonium bromide, dioctyl dimethyl ammonium chloride, didecyldimethyl ammonium chloride, octyl lauryl dimethyl ammonium chloride, dilauryl dimethyl ammonium chloride, dimyristyl dimethyl ammonium chloride, dipalmityl dimethyl ammonium chloride, distearyl dimethyl ammonium chloride, dioctyl dimethyl ammonium bromide, didecyl dimethyl ammonium bromide, octyl lauryl dimethyl ammonium bromide, dilauryl dimethyl ammonium bromide, hexyl dimethyl benzyl ammonium chloride, octyl dimethyl benzyl ammonium chloride, decyl dimethyl benzyl ammonium chloride, lauryl dimethyl benzyl ammonium chloride, myristyl dimethyl benzyl ammonium chloride, palmityl dimethyl benzyl ammonium chloride, stearyl dimethyl benzyl ammonium chloride, hexyl dimethyl benzyl ammonium bromide, octyl dimethyl benzyl ammonium bromide, decyl dimethyl benzyl ammonium bromide, lauryl dimethyl benzyl ammonium bromide, myristyl dimethyl benzyl ammonium bromide, palmityl dimethyl benzyl ammonium bromide, stearyl dimethyl benzyl ammonium bromide octyl pyridinium chloride, decyl pyridinium chloride, lauryl pyridinium chloride, myristyl pyridinium chloride, cetyl pyridinium chloride, stearyl pyridinium chloride, decyl pyridinium bromide, lauryl pyridinium bromide, myristyl pyridinium bromide, cetyl pyridinium bromide, stearyl pyridinium bromide, POE stearyl amine (n = 5), POE stearyl amine (n = 10), POE stearyl amine (n = 15), POE oleyl amine (n = 10), POE oleyl amine (n = 15), POE stearic acid amide (n = 4), POE stearic acid amide (n = 10), POE stearic acid amide (n = 15), POE oleic acid amide (n = 5), POE stearic acid (n = 10), and POE oleic acid amide (n = 15).

The ampholytic surface active agents used in compositions embodying this invention include sodium β-higher alkylamino propionates, higher alkyl dimethyl amino acetic acid betaines, higher alkyl diamino ethyl glycine hydrochlorides, and 2-higher alkyl-N-carboxy methyl-N-carboxy ethyl imidazolinium betaines (where higher alkyl means 6—18 carbon atoms). Practical examples of such ampholytic surface active agents are sodium β-decylamino propionate, sodium β-laurylamino propionate, sodium β-myristyl amino propionate, sodium β-palmityl amino propionate, sodium β-stearyl amino propionate, decy dimethyl amino acetic acid betaine, lauryl dimethyl amino acetic acid betaine, myristyl dimethyl amino acetic acid betaine, palmityl dimethyl amino acetic acid betaine, stearyl dimethyl amino acetic acid betaine, decyl diamino ethyl glycine hydrochloride, lauryl diamino ethyl glycine hydrochloride, myristyl diamino ethyl glycine hydrochloride, palmityl diamino ethyl glycine hydrochloride, stearyl diamino ethyl glycine hydrochloride, 2-decyl-N-carboxymethyl-N-hydroxy ethyl imidazolinium betaine, 2-lauryl-N - carboxymethyl - N - hydroxyethyl imidazolinium betaine, 2-myristyl-N-carboxymethyl-N-hydroxy ethyl imidazolinium betaine, 2-palmityl-N-carboxymethyl-N-hydroxy ethyl imidazolinium betaine, and 2-stearyl-N-carboxymethyl-N-hydroxy ethyl imidazolinium betaine. Practical examples of the bile acids used for this invention are cholic acid, deoxycholic acid, chenodeoxycholic acid, taurocholic acid, taurochenodeoxycholic acid, glycocholic acid, glycochenocholic acid, 3β-monohydroxychloric acid, lithocholic acid, 3α-hydroxy-12-ketocholic acid, 3β-hydroxy-12-ketocholic acid, 12α-3β-dihydrocholic acid, and ursodesoxycholic acid. Practical examples of the alkali metal salts of the bile acids used in embodiments of this invention are the sodium and potassium salts of the above mentioned bile acids.

These absorption-accelerating agents may be employed either singly or as a mixture; particularly preferred absorption-accelerating agents are, for example, POE higher alcohol ethers, POE higher alkyl phenol ethers and bile acid. The amount of the absorption-accelerating agent to be used is 0.001 to 0.5 times, preferably 0.005 to 0.1 times the weight of the base.

It is also possible to incorporate one or more additional ingredients such as anti-oxidants (e.g., butylated hydroxy toluene), chelating agents (e.g., ethylene diamine tetraacetic acid) and preservatives (e.g., methyl paraben, propyl paraben) in an appropriate amount.

The dosage forms which can be adopted in performing the present invention include suppositories which are solid at room temperature but melt at body temperature. Also, an ointment or an enema-type

composition comprising the insulin and the absorption-accelerating agent dispersed in a base of distilled water or other liquid may be formulated for rectal administration as soft capsules or for administration by rectal injection. These dosage forms can be obtained by procedures which are commonly followed in the formulation of ointments, suppositories and the like forms, e.g. by melting or dissolving together the base and absorption accelerating agent, evenly dispersing the insulin in the resulting melt or solution and, if necessary, molding the resultant composition.

The amount of insulin in the pharmaceutical composition for rectal use should be 2—200 I.U., preferably 5—150 I.U. per gram of the total amount of the absorption accelerating agent and the base.

The following sets of tests describe comparative experiments carried out with compositions embodying the present invention and control compositions.

Serum I.R.I. levels and percent decrease in blood glucose Test method:

Male rabbits fasted for 28 hours and weighing about 2 kg each (five rabbits per group) were used for examining the serum I.R.I. (immuno-reactive insulin) and the blood glucose levels after rectal administration and after intramuscular or intravenous administration of insulin. Crystalline bovine insulin (potency 24 I.U./mg) was obtained from Sigma Chemical Company, and the insulin dosages listed below in the Tables I and II were prepared. The compositions for tests Nos. 1—3 and 5—23 are embodiments of the present invention, the remainder are controls.

In more detail, the compositions employed in the Tests comprise those according to the invention Tests Nos. 1—3, 5—23); a conventional dispersion of insulin in a base for rectal use (control: Test No. 24); dispersions of insulin in a base for rectal use and a nonionic surface actrive agent (e.g., POE fatty acid esters and POE hydrogenated caster oil) different from the absorption-accelerating agents of this invention (control: Tests Nos. 25—31); and solutions obtained by adding insulin to distilled water (control: Test No. 4, 32, 33). The compositions of Test No. 1—3 and 5—31 were ointment or enema type compositions.

Rectal administration of each insulin composition was achieved by insertion into the rectum about 3 cm deep from the anus with a small injection syringe. Intramuscular administration was at the thigh and intravenous administration at the ear of the rabbits. In each instance, blood samples were taken from the ear at timed intervals. The serum insulin levels were measured by radioimmunoassay using the two-antibody system of Morgan and Lazarow [Morgan, C. R. & Lazarow, A. Diabetes, *12*, 115 (1963)]. The blood glucose level were estimated by the glucose oxidase method [Schmidt F. H. Internist., *4*, 554 (1963)]. Each value quoted below represents the means of the percent decrease in blood glucose.

The results are shown in Table I and II, wherein the percentages are based on the weight of the composition.

TABLE I

Serum IRI levels

	Test No.	Formulation	serum IRI levels (μI.U./ml)							
			0 min.	5	10	15	30	60	90	120
Compositions of this invention:										
rectal administration	1.	insulin 0.5 I.U./kg POE lauryl ether (HLB=11.5, n=9) 1% corn oil 99%	17.3	29.0	60.0	123.3	74.3	30.2	29.0	20.5
	2.	insulin 1 I.U./kg POE lauryl ether (HLB=11.5, n=9) 1% corn oil 99%	18.8	94.5	149.0	289.0	135.0	33.0	22.3	18.8
	3.	insulin 2 I.U./kg POE lauryl ether (HLB=11.5, n=9) 1% corn oil 99%	18.0	50.8	211.0	296.5	311.5	137.5	46.7	18.8
Control										
I.M.	4.	insulin 0.5 I.U./kg diluent for insulin* 100%	18.4	73.6	80.2	83.6	76.5	68.0	61.9	46.3

*Japanese Pharmacopoeia.

TABLE II

Percent decrease in blood glucose

	Test No.	Formulation	percent decrease in blood glucose			
			30 min.	60	90	120
Compositions of this invention rectal administration	5.	insulin 1 I.U./kg POE lauryl ether 0.5% (HLB=11.5, n=9) corn oil 99.5%	-17.7	-48.8	-42.1	-12.0
	6.	insulin 2 I.U./kg POE lauryl ether 3% (HLB=11.5, n=9) corn oil 97%	-40.4	-58.3	-59.1	-52.1
	7.	insulin 5 I.U./kg POE lauryl ether 3% (HLB=11.5, n=9) corn oil 97%	-32.5	-58.8	-50.8	-40.3
	8.	insulin 5 I.U./kg POE lauryl ether 3% (HLB=11.5, n=9) distilled water 97%	-25.5	-38.5	-37.0	-26.6
	9.	insulin 5 I.U./kg POE nonyl phenyl ether 3% (HLB=16.5, n=10) corn oil 97%	-28.9	-54.8	-54.5	-51.1
	10.	insulin 5 I.U./kg Sodium lauryl sulfate 3% corn oil 97%	-16.2	-48.8	-58.2	-53.7
	11.	insulin 5 I.U./kg Sodium N-lauryl-L-glutaminate 3% corn oil 97%	-42.1	-54.4	-61.4	-57.8
	12.	insulin 5 I.U./kg Sodium N-lauryl-sarcosinate 3% corn oil 97%	-31.5	-35.9	-48.6	-43.7
	13.	insulin 5 I.U./kg Sodium di-2-ethylhexyl sulfosuccinate 3% corn oil 97%	-17.5	-44.8	-48.8	-45.5
	14.	insulin 5 I.U./kg Stearyl trimethyl ammonium chloride 3% corn oil 97%	-10.6	-32.7	-40.9	-47.1

TABLE II (Continued)

	Test No.	Formulation	percent decrease in blood glucose			
			30 min.	60	90	120
Compositions of this invention rectal administration	15.	insulin 5 I.U./kg POE oleyl amine (n=5) 3% corn oil 97%	-18.3	-49.0	-58.2	-56.7
	16.	insulin 5 I.U./kg POE oleic acid amide (n=5) 3% corn oil 97%	40.3	45.5	35.8	
	17.	insulin 5 I.U./kg Lauryl dimethylamino acetic acid betain 3% corn oil 97%	-24.6	-35.4	-42.9	-34.3
	18.	insulin 1 I.U./kg POE lauryl ether (HLB=11.5, n=9) 0.25% cholic acid 1% corn oil 98.75%	-26.9	-42.3	-28.9	-19.1
	19.	insulin 2 I.U./kg cholic acid 3% corn oil 97%	-10.6	-53.4	-52.9	-46.7
	20.	insulin 2 I.U./kg Sodium cholate 3% corn oil 97%	-23.2	-47.8	-37.7	-21.4
	21.	insulin 2 I.U./kg Sodium taurocholate 3% corn oil 97%	-39.9	-48.5	-29.3	-17.4
	22.	insulin 2 I.U./kg Glycocholic acid 3% corn oil 97%	-44.0	-56.2	-49.2	-31.6
	23.	insulin 2 I.U./kg Chenodeoxycholic acid 3% corn oil 97%	-29.7	-53.5	-46.7	-32.3
Controls						
rectal administration	24.	insulin 5 I.U./kg corn oil 100%	+2.7	-0.3	+1.3	-1.5
	25.	insulin 5 I.U./kg POE oleate (HLB=13.4, n=15) 3% corn oil 97%	-13.3	-8.3	+2.3	0
	26.	insulin 5 I.U./kg POE sorbitan mono-oleate (HLB=15, n=20) 3% corn oil 97%	+3.6	+9.1	+0.1	-2.7

TABLE II (Continued)

	Test No.	Formulation	percent decrease in blood glucose			
			30 min.	60	90	120
Controls rectal administration	27.	insulin 5 I.U./kg POE hydrogenated caster oil derivative 3% (HLB=14.1, n=60) corn oil 97%	−3.5	+1.1	−1.0	−3.6
	28.	insulin 5 I.U./kg POE lanolin 3% (HLB=14.2, n=30) corn oil 97%	+15.1	+11.7	+17.4	+14.0
	29.	insulin 5 I.U./kg Glycerylmono-stearate 3% (HLB=4.5) corn oil 97%	+15.8	+17.8	+29.4	+18.0
	30.	insulin 5 I.U./kg Sucrose fatty acid ester (HLB=11) 3% corn oil 97%	+4.4	+9.6	+10.3	+16.2
	31.	insulin 5 I.U./kg POE sorbitol hexaoleate 3% (HLB=10.2, n=30) corn oil 97%	+29.9	+36.0	+30.7	+28.3
Controls						
I.M.	32.	insulin 0.5 I.U./kg diluent for insulin* 100%	−15.6	−39.5	−51.7	−53.2
I.U.	33.	insulin 0.5 I.U./kg diluent for insulin* 100%	−41.3	−47.2	−34.0	−33.2

*Japanese Pharmacopoeia.

As is clear from the results shown in Table I, the serum IRI (immuno reactive insulin) levels of rabbits after each of the pharmaceutical compositions (Test Nos. 1—3) of this invention was administered in the rectum of the rabbits at insulin doses of 0.5—2 I.U./kg were almost equal to, or higher than, those when insulin was administered to rabbits by intramuscular injection at a dose of 0.5 I.U./kg. That is, the pharmaceutical compositions for rectal use embodying this invention can provide an insulin concentration in blood as good as that by intramuscular injection of insulin at an insulin dose almost equivalent to that used for intramuscular injection.

Also, as is clear from the results shown in Table II, the percent decreases in blood glucose when the pharmaceutical compositions (Test Nos. 5—23) embodying this invention were administered in the rectum of rabbits at the insulin doses of 1—5 I.U./kg were almost equivalent to those when insulin was administered to rabbits by intramuscular and intravenous injection at a dose of 0.5 I.U./kg (Test Nos. 32 and 33). That is, the pharmaceutical compositions for rectal use of this invention can decrease the blood glucose levels to the same extent as in the case of administering insulin by injection using an insulin dose almost equivalent to that for injection.

On the other hand, pharmaceutical compositions for rectal use (Test Nos. 24 and 25—31) not containing an absorption agent of this invention (i.e. containing

nonionic surface active agents other than the absorption-accelerating agents of this invention) could not sufficiently decrease the blood glucose levels at insulin doses almost equivalent to that used for injection.

Now, the following examples illustrate practically the pharmaceutical compositions of insulin for rectal use embodying this invention, wherein the dosages of insulin employed are for the human bodies.

Example 1.

After dispersing 2 g of sodium taurocholate and 8,000 I.U. of insulin in 98 g of corn oil with stirring, 1 g of aliquots of the dispersion are filled into soft capsules for rectal application.

Example 2.

After melting 144 g of Witepsol at 45°C., 6 g. of cholic acid and 10,000 I.U. of insulin are dispersed therein with stirring and 1.5 g of aliquots of the dispersion are poured into a mold for suppositories. After solidification, the suppositories formed are released from the mold.

Example 3.

In 145.5 g of corn oil is dissolved 4.5 g of POE lauryl ether (HLB = 11.5, n = 9) with stirring and then after dispersing well 8,000 I.U. of insulin in the solution with stirring, 1.5 g of aliquots of the dispersion are poured into container tubes for rectal application.

Example 4.

After melting 45.5 g of polyethylene glycol 1,500 and 100 g of polyethylene glycol 6,000 together and dispersing well 4.5 g of POE nonyl phenyl ether (HLB = 16.5, n = 10) and 15,000 I.U. of insulin in the molten mixing with stirring, 1.5 g of aliquots of the dispersion are poured into a mold for suppositories. After solidification, the suppositories formed are released from the mold.

Example 5.

In 142.5 g of corn oil is dissolved 7.5 g of POE nonyl phenyl ether (HLB = 16.5, n = 10) with stirring. After dispersing 12,000 I.U. of insulin in the solution with stirring, 1.5 g of aliquots of the dispersion are poured into container tubes for rectal application.

Example 6.

In 94 g of corn oil is dissolved 6 g of POE lauryl ether (HLB = 11.5, n = 9) with stirring. After dispersing 4,000 I.U. of insulin in the solution with stirring, 1 g of aliquots of the dispersion are filled into soft capsules for rectal application.

Example 7.

After melting 145.5 g of Witepsol at 45°C., 4.5 g of sodium lauryl sulfate and 10.000 I.U. of insulin are dispersed in the melt with stirring and 1.5 g of aliquots of the dispersion are poured into a mold for suppositories. After solidification, the suppositories formed are released from the mold.

Example 8.

After melting 144 g of Witepsol at 45°C., 6 g of POE stearylamine is dissolved in the melt and after dispersing 10,000 I.U. of insulin in the solution with stirring, 1.5 g of aliquots of the dispersion are poured into a mold for suppositories. After solidification, the suppositories formed are released from the mold.

Example 9.

After dispersing 4.5 g of lauryl betaine and 8,000 I.U. of insulin in 145.5 g of soybean oil with stirring, 1.5 g of aliquots of the dispersion are filled into soft capsules for rectal application.

Example 10.

In 145.5 g of corn oil is dissolved 3 g of POE lauryl ether (HLB = 11.5, n = 9) and after dispersing well 1.5 g of sodium taurocholate and 10,000 I.U. of insulin in the solution with stirring, 1.5 g of aliquots of the dispersion are filled into soft capsules for rectal application.

Example 11.

After dispersing 4.5 g of stearyltrimethylammonium chloride and 5,000 I.U. of insulin in 145.5 g of corn oil with stirring, 1.5 g of aliquots of the dispersion are poured into container tubes for rectal application.

Example 12.

After melting 147 g of Witepsol at about 45°C., 3 g of distearyldimethylammonium chloride and 3,000 I.U. of insulin are dispersed in the melt and 1.5 g of aliquots of the dispersion are poured into a mold for suppositories. After solidification, the suppositories formed are released from the mold.

Example 13.

After melting 48.5 g of polyethylene glycol 1,500 and 100 g of polyethylene glycol 6,000 together at about 60°C., 1.5 g of stearyldimethylbenzylammonium chloride and 5,000 I.U. insulin are dispersed in the molten mixture with the stirring and 1.5 g of aliquots of the dispersion are poured into a mold for suppositories. After solidification, the suppositories formed are released from the mold.

Example 14.

After dispersing 4.5 g of benzethonium chloride and 5,000 I.U. of insulin in 145.5 g

of corn oil with stirring, 1.5 g of aliquots of the dispersion are filled into soft capsules for rectal application.

Example 15.

After dispersing 3 g of cetylpyridinium chloride and 3,000 I.U. of insulin in 147 g of corn oil with stirring, 1.5 g of aliquots of the dispersion are poured into container tubes for rectal application.

Example 16.

After dispersing 0.5 g of POE lauryl ether (HLB = 11.5, n = 9), 2 g of chloic acid, and then 8,000 I.U. of insulin in 197.5 g of corn oil with stirring, 2 g of aliquots of the dispersion are poured into container tubes for rectal application.

Example 17.

After dispersing 4.5 g of sodium N-lauroyl-L-glutamate and 8,000 I.U. of insulin in 145.5 g of corn oil with stirring, 1.5 g of aliquots of the dispersion are poured into container tubes for rectal application.

Example 18.

After dispersing 4.5 g of sodium N-lauroylsarcosinate and 8,000 I.U. of insulin in 145.5 g of corn oil with stirring, 1.5 g of aliquots of the dispersion are poured into container tubes for rectal application.

Example 19.

After dispersing 4.5 g of sodium di-2-ethylhexyl sulfosuccinate and 8,000 I.U. of insulin in 145.5 g of corn oil with stirring, 1.5 g of aliquots of the dispersion are poured into container tubes for rectal application.

Example 20.

After dispersing 4.5 g of stearyltrimethyl ammonium chloride and 8,000 I.U. of insulin in 145.5 g of corn oil with stirring, 1.5 g of aliquots of the dispersion are poured into container tubes for rectal application.

Example 21.

After dispersing 4.5 g of POE oleylamine (n = 5) and 8,000 I.U. of insulin in 145.5 g of corn oil with stirring, 1.5 g of aliquots of the dispersion are poured into container tubes for rectal application.

Example 22.

After dispersing 4.5 g of POE oleic acid amide (n = 5) and 8,000 I.U. of insulin in 145.5 g of corn oil, 1.5 g of aliquots of the dispersion are poured into container tubes for rectal application.

Example 23.

After dispersing 4.5 g of lauryldimethyl-aminoacetate betaine and 8,000 I.U. of insulin in 145.5 g of corn oil with stirring, 1.5 g of aliquots of the dispersion are poured into container tubes for rectal application.

Example 24.

After dispersing 4.5 g of cholic acid and 8,000 I.U. of insulin in 145.5 g of corn oil with stirring well, 1.5 g of aliquots of the dispersion are poured into container tubes for rectal application.

Example 25.

After dispersing 4.5 g of sodium cholate and 8,000 I.U. of insulin in 145.5 g of corn oil with stirring well, 1.5 g of aliquots of the dispersion are poured into container tubes for rectal application.

Example 26.

After dispersing 4.5 g of sodium taurocholate and 8,000 I.U. of insulin in 145.5 g of corn oil, 1.5 g of aliquots of the dispersion are poured into container tubes for rectal application.

Example 27.

After dispersing 4.5 g of glycocholic acid and 8,000 I.U. of insulin in 145.5 g of corn oil with stirring, 1.5 g of aliquots of the dispersion are poured into container tubes for rectal application.

Example 28.

After dispersing 4.5 g of chenodeoxycholic acid and 8,000 I.U. of insulin in 145.5 g of corn oil with stirring, 1.5 g of aliquots of the dispersion are poured into container tubes for rectal application.

WHAT WE CLAIM IS:—

A pharmaceutical composition for rectal administration which comprises insulin, a carrier suiting the composition for rectal administration, and an agent for increasing the rate of absorption of the insulin into the body on rectal administration of the composition, the agent comprising at least one material selected from (a) nonionic polyoxyethylene ether surface active agents having an HLB value of 6 to 19 and wherein the average number of polyoxyethylene units is 4 to 30, (b) anionic surface active agents, (c) cationic surface active agents, (d) ampholytic surface active agents, (e) bile acids and (f) alkali metal salts of bile acids, and amounting to 0.001 to 0.5 times the weight of the carrier.

2. A pharmaceutical composition according to claim 1 wherein the carrier is an oily carrier.

3. A pharmaceutical composition according to claim 1 or 2 wherein the nonionic polyoxyethylene ether comprises a polyoxyethylene ether of an alcohol of 6 to 22 carbon atoms.

4. A pharmaceutical composition according to claim 3 wherein the polyoxyethylene ether is a polyoxyethylene lauryl ether having a HLB value of about 11.5.

5. A pharmaceutical composition according to claim 1 or 2 wherein the nonionic polyoxyethylene ether surface active agent comprises a polyoxyethylene C6 to C18 alkyl phenol ether.

6. A pharmaceutical composition according to claim 5 wherein the polyoxyethylene alkyl phenol ether is a polyoxyethylene nonyl phenyl ether having a HLB value of about 16.5.

7. A pharmaceutical composition according to any preceding claim wherein the bile acid is cholic acid.

8. A pharmaceutical composition according to any preceding claim wherein the agent is a mixture of a nonionic polyoxyethylene ether surface active agent and a bile acid.

9. A pharmaceutical composition according to claim 1 and substantially as employed in any one of the Tests Nos. 1—3 and 5—23.

10. A pharmaceutical composition according to claim 1 and substantially as described in any one of the Examples herein.

11. A soft capsule or tube for rectal administration filed with a pharmaceutical composition according to any preceding claim.

12. A suppository molded from a pharmaceutical composition according to any preceding claim.

REDDIE & GROSE
Agents for the Applicants
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London, WC1X 8PL.

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