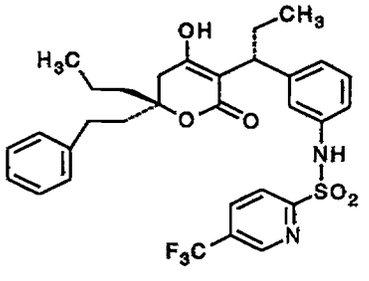
SELF-EMULSIFYING FORMULATION FOR LIPOPHILIC COMPOUNDS

FIELD OF THE INVENTION

The present invention relates to novel pharmaceutical compositions in a form of a self-emulsifying formulation which provide high concentration and high oral bioavailability for pyranone compounds which are inhibitors of retroviral protease.

BACKGROUND OF THE INVENTION

It has recently been discovered that certain pyranone compounds inhibit retroviral protease and thus they are useful for treating patients infected with human immunodeficiency virus (HIV) which results in acquired immunodeficiency syndrome (AIDS). In particular, the pyranone compound of formula I has been found to be especially effective as an inhibitor of retroviral protease.



I

However, like many other HIV protease inhibitors, these compounds are characteristically lipophilic and thus poorly water soluble. For example, the compound of formula I has an aqueous solubility about 1 μg/ml in the buffer of pH 6.5 (close to the pH of the intestine), which is considered as extremely poor aqueous solubility and would be expected to provide very low oral bioavailability in the free acid form. It is well known that an active drug substance or therapeutic moiety administered by any route must possess some aqueous solubility for systemic absorption and therapeutic response. Poorly water soluble compounds often exhibit either incomplete or erratic absorption and thus produce a minimal response at desired dosage.

Attempts were made to identify salts of the pyranone compounds in solid forms which could improve aqueous solubility. An overriding defect which has however remained is that the formulations in the form of salt are prone to

precipitation of the parent free acid in the gastrointestinal tract and hence are not capable to provide a dosage in the desired high concentration to permit convenient use and yet meet the required criteria in terms of bioavailability.

Recognizing the problems, the present invention is directed toward pharmaceutical compositions in a form of self-emulsifying formulations which provide high concentration and high oral bioavailability for pyranone compounds. In particular it has been discovered that the compositions of the present invention allow the preparation of self-emulsifying formulations containing a pyranone inhibitor of retroviral protease in an exceedingly high concentration up to about 400 mg/g to permit convenient oral administration while at the same time achieving improved bioavailability, which is at least two fold higher than the aqueous suspension of the free acid.

INFORMATION DISCLOSURE

The International Publication No. WO 95/30670 discloses pyranone compounds useful to treat retroviral infections.

The International Publication No. WO 96/39142 discloses compositions which increase the bioavailability of protease inhibitors.

UK Patent Application, GB 2,222,770A discloses pharmaceutical compositions comprising a cyclosporin in microemulsion pre-concentrate and microemulsion form.

UK Patent Application, GB 2,228,198A discloses pharmaceutical compositions comprising a cyclosporin as active ingredient, a fatty acid triglyceride, a glycerol fatty acid partial ester or propylene glycol or sorbitol complete or partial ester and a tenside having an HLB of at least 10.

UK Patent, GB 2,257,359B discloses pharmaceutical compositions suitable for oral administration comprising a cyclosporin, 1,2-propylene glycol, a mixed mono-, di-, and tri-glyceride and a hydrophilic surfactant.

U.S. Patent No. 4,230,702 discloses a readily enterally absorbable pharmaceutical composition of pharmacologically active agents, which per se are poorly enterally absorbable.

SUMMARY OF THE INVENTION

One object of the present invention is to provide a pharmaceutical composition comprising a pyranone compound of formulas I, II, III or IV which possesses high oral bioavailability

A further object of the present invention is to provide a pharmaceutical

composition containing a high drug load of a pyranone compound of formulas I, II, III or IV for convenient administration.

Another object of the present invention is to provide pharmaceutical compositions which exhibit adequate physical and chemical stability in self-emulsifying formulations.

Still another object of the present invention is to provide a liquid composition for soft elastic capsules.

The objects of the present invention have been accomplished in that the present invention provides pharmaceutical compositions in a form of a self-emulsifying formulation which allow a high loading of pyranone compounds' (up to about 400 mg/g) while at the same time achieving good oral bioavailability.

The present invention specifically provides a pharmaceutical composition based on the use of a particular oil phase which comprises:

(a) a pyranone compound of formula I, II, III or IV,

(b) a mixture of diglyceride and monoglyceride in a ratio of from about 9:1 to about 6:4 by weight (diglyceride:monoglyceride) wherein the diglyceride and monoglyceride are mono- or di- unsaturated fatty acid esters of glycerol having sixteen to twenty-two carbon atom chain length of from,

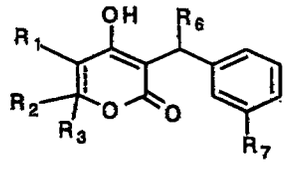
(c) one or more pharmaceutically acceptable solvents, and

(d) one or more pharmaceutically acceptable surfactants.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, there are pharmaceutical compositions comprising a pyranone compound as a pharmaceutically active agent in a self-emulsifying formulation vehicle.

For the purpose of the present invention, the term "pyranone compounds" refers to compounds of formula II

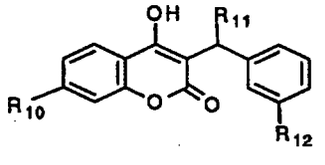


II

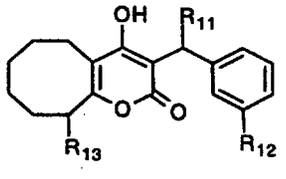
wherein R_1 is H-; R_2 is C_3-C_5 alkyl, phenyl-$(CH_2)_2$-, het-SO_2NH-$(CH_2)_2$-, cyclopropyl-$(CH_2)_2$-, F-phenyl-$(CH_2)_2$-, het-SO_2NH-phenyl-, or F_3C-$(CH_2)_2$-; or R_1

and R_2 taken together are a double bond; R_3 is R_4-$(CH_2)_n$-$CH(R_5)$-, H_3C-$[O(CH_2)_2]_2$-CH_2-, C_3-C_5 alkyl, phenyl-$(CH_2)_2$-, het-SO_2NH-$(CH_2)_2$-, $(HOCH_2)_3C$-NH-C(O)-NH-$(CH_2)_3$-, $(HO_2C)(H_2N)CH$-$(CH_2)_2$-C(O)-NH-$(CH_2)_3$-, piperazin-1-yl-C(O)-NH-$(CH_2)_3$, $HO_3S(CH_2)_2$-$N(CH_3)$-C(O)-$(CH_2)_6$-C(O)-NH-$(CH_2)_3$-, cyclopropyl-$(CH_2)_2$-, F-phenyl-$(CH_2)_2$-, het-SO_2NH-phenyl, or F_3C-$(CH_2)_2$-; n is 0, 1 or 2; R_4 is phenyl, het, cyclopropyl, H_3C-$[O(CH_2)_2]_2$-, het-SO_2NH-, Br-, N_3-, or $HO_3S(CH_2)_2$-$N(CH_3)$-C(O)-$(CH_2)_6$-C(O)-NH-; R_5 is -CH_2-CH_3, or -CH_2-cyclopropyl; R_6 is cyclopropyl, CH_3-CH_2-, or t-butyl; R_7 is -NR_8SO_2-het, -NR_8SO_2-phenyl, optionally substituted with R_9, -CH_2-SO_2-phenyl, optionally substituted with R_9, or -CH_2-SO_2-het; R_8 is -H, or -CH_3; R_9 is -CN, -F, -OH, or -NO_2; wherein het is a 5-, 6- or 7-membered saturated or unsaturated ring containing from one to three heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring or another heterocycle, optionally substituted with -CH_3, -CN, -OH, -$C(O)OC_2H_5$, -CF_3, -NH_2, or -C(O)-NH_2; or a pharmaceutically acceptable salt thereof. The preferred compound of formula II is a compound of formula I.

The term "pyranone compounds" also refers to compounds of formula III and formula IV



III



IV

wherein R_{10} is H-, CH_3O-, or CH_3O-$[(CH_2)_2O]_3$-; R_{11} is cyclopropyl, or -CH_2-$CH(CH_3)_2$; R_{12} is -$NR_{14}SO_2$-phenyl, optionally substituted with R_{15}, -$NR_{14}SO_2$-het, -CH_2-SO_2-phenyl, optionally substituted with R_{15}, or -CH_2-SO_2-het; R_{13} is -H, -$(CH_2)_2$-CH_3, -CH_2-cyclopropyl, or -CH_2-phenyl; R_{14} is -H, or -CH_3; R_{15} is -CN, -F, -CH_3, -COOH, or -OH; het is a 5-, 6- or 7-membered saturated or unsaturated ring containing from one to three heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring or another heterocycle; optionally substituted with one or two -CH_3, -CN, -$C(O)OC_2H_5$, or -OH; or a pharmaceutically acceptable salt thereof.

These compounds inhibit retroviral protease and thus inhibit the replication

of the virus. They are useful for treating patients infected with human retrovirus, such as human immunodeficiency virus (strains of HIV-1 or HIV-2) or human T-cell leukemia viruses (HTLV-I or HTLV-II) which results in acquired immunodeficiency syndrome (AIDS) and/or related diseases. The compounds of formulas I, II, III, and IV are disclosed and claimed in International Application No. PCT/US95/05219, incorporated herein by reference, and may be prepared according to the procedures described in International Publication No. WO 95/30670. In particular, the pyranone compound of formula I has been found to be especially effective as an inhibitor of retroviral protease.

The term "self-emulsifying formulation" used herein refers to a concentrated composition capable of generating emulsions or microemulsions upon mixing with sufficient aqueous media.

The emulsions or microemulsions generated from the present invention are conventional solutions comprising a hydrophilic phase and a lipophilic phase. Microemulsions are also characterized by their thermodynamic stability, optical transparency and small average droplet size, generally less than about 0.15 micron.

The term "self-emulsifying formulation vehicle" refers to a composition comprising a mixture of diglyceride and monoglyceride in a ratio of from about 9:1 to about 6:4 by weight (diglyceride:monoglyceride) wherein the diglyceride and monoglyceride are mono- or di- unsaturated fatty acid esters of glycerol having sixteen to twenty-two carbon chain length, one or more pharmaceutically acceptable solvents, and one or more pharmaceutically acceptable surfactants. Optionally, the self-emulsifying formulation vehicle may further comprise a basic amine.

Diglyceride of the present invention refers to a fatty acid ester of glycerol having structureal formula $HOCH_2$-$CH(O_2CR)$-$CH_2(O_2CR)$ or $(RCO_2)CH_2$-$CH(OH)$-$CH_2(O_2CR)$, wherein R is mono-unsaturated or di-unsaturated alkyl group having fifteen to twenty-one carbon atoms. The preferred diglyceride is diolein (R is mono-unsaturated alkyl group with seventeen carbon atoms), dilinoleate (R is di-unsaturated alkyl group with seventeen carbon atoms), or a mixture of diolein and dilinoleate. The most preferred diglyceride is diolein.

Monoglyceride of the present invention refers to a fatty acid ester of glycerol having structureal formula $HOCH_2$-$CH(OH)$-$CH_2(O_2CR)$ or $HOCH_2$-$CH(O_2CR)$-CH_2OH, wherein R is a mono-unsaturated or di-unsaturated alkyl group having fifteen to twenty-one carbon atoms. The preferred monoglyceride is monoolein (R is mono-unsaturated alkyl group with seventeen carbon atoms), monolinoleate (R is di-unsaturated alkyl group with seventeen carbon atoms), or a mixture of monoolein

and monolinoleate. The most preferred monoglyceride is monoolein.

The mixture of diglyceride and monoglyceride may be prepared by mixing individual diglyceride and monoglyceride in appropriate relative proportion or by partial hydrolysis of triglyceride, or transesterification reaction of triglycerides, diglycerides with glycerol.

All of the glycerides of the present invention are known and can be prepared by conventional methods.

The amount of active ingredient in the composition may vary or be adjusted widely depending on the intended route of administration, the potency of the particular active ingredient being used, the severity of the retroviral infection and the required concentration. If desired, however, a pyranone compound as an inhibitor of retroviral protease can be present in the self-emulsifying formulation vehicle of the present invention in an amount up to about 400 mg/g with excellent dispersability and high oral bioavailability *in vivo* typically reaching 70-84% in rats.

The compositions of the present invention with high oral bioavailability (84% in rats) demonstrate an almost transparent or translucent solution upon dilution with water, which indicates that a microemulsion is formed.

The compositions of the present invention with moderately high bioavailability (60-70% in rats) usually show a visible fine white emulsion without precipitation of the drug upon dilution with water, which indicates that an emulsion is formed.

In one aspect, the present invention specifically provides a pharmaceutical composition based on the use of particular oil phase which comprises:

(a) a pyranone compound of formulas I, II, III or IV as a pharmaceutically active agent,

(b) a mixture of diglyceride and monoglyceride in a ratio of from about 9:1 to about 6:4 by weight (diglyceride:monoglyceride) wherein the diglyceride and monoglyceride are mono- or di- unsaturated fatty acid esters of glycerol having sixteen to twenty-two carbon chain length,

(c) one or more pharmaceutically acceptable solvents, and

(d) one or more pharmaceutically acceptable surfactants.

In addition, the composition may further comprise a pharmaceutically acceptable basic amine.

The term "pharmaceutically acceptable" used herein refers to those properties which are biologically compatible with the treated subjects from a pharmacological and toxicological point of view.

Solvents of the present invention refer to propylene glycol, polypropylene glycol, polyethylene glycol (such as PEG300, 400, 600, etc.), glycerol, ethanol, triacetin, dimethyl isosorbide, glycofurol, propylene carbonate, water, dimethyl acetamide or a mixture thereof.

The preferred solvent is propylene glycol or a mixture comprising propylene glycol and 95% (v/v) ethanol (hereinafter ethanol). In the mixture of propylene glycol and ethanol, propylene glycol is in an amount of from about 50% to about 95%.

Surfactants of the present invention refer to non-ionic surfactants including Polyoxyl 40 hydrogenated castor oil sold under the trade name, among the others, Cremophor RH40; Polyoxyl 35 castor oil sold under the trade name, among the others, Cremophor EL or Cremophor EL-P; Polysorbates; Solutol HS-15; Tagat TO; Peglicol 6-oleate; Polyoxyethylene stearates; Saturated Polyglycolyzed Glycerides; or Poloxamers; all of which are commercially available. The preferred surfactant is Cremophor RH40 or Cremophor EL.

Saturated Polyglycolyzed Glycerides used herein include Gelucire 44/14 or Gelucire 50/13.

Polyoxyethylene stearates used herein include Poloxyl 6 stearate, Poloxyl 8 stearate, Poloxyl 12 stearate and Poloxyl 20 stearate.

Poloxamers used herein include Poloxamer 124 and Poloxamer 188.

Polysorbates used herein include Polysorbate 20, Polysorbate 40, Polysorbate 60 and Polysorbate 80.

The term "basic amine" used herein refers to lower alkylamines such as, for example, ethanolamine, diethanolamine, triethanolamine, dimethylaminoethanol, tris(hydroxymethyl)aminomethane or ethylenediamine; quaternary ammoniums such as, for example, choline hydroxide; basic amino acids such as, for example, arginine lysine or guanidine. The preferred lower alkylamine is dimethylaminoethanol or tris(hydroxymethyl)aminomethane.

A typical composition of the invention comprises:

(a) a pyranone compound of formulas I, II, III or IV in an amount of from about 1% to about 40% by weight of the total composition,

(b) a mixture of diglyceride and monoglyceride in a ratio of from about 9:1 to about 6:4 by weight (diglyceride:monoglyceride) wherein the diglyceride and monoglyceride are mono- or di- unsaturated fatty acid esters of glycerol having sixteen to twenty-two carbon chain length in an amount of from about 5% to about 35% by weight of the total composition,

(c) one or more pharmaceutically acceptable solvents in an amount of from about 10% to about 30% by weight of the total composition, and

(d) a pharmaceutically acceptable surfactant in an amount of from about 10% to about 50% by weight of the total composition.

Optionally, the above composition further comprise a basic amine in an amount of from about 0.1% to 10% by weight of the total composition.

A preferred composition of the invention comprises:

(a) a pyranone compound of formulas I, II, III or IV in an amount of from about 20% to about 30% by weight of the total composition,

(b) a mixture of diolein and monoolein in a ratio of about 9:1 by weight (diolein:monoolein) in an amount of from about 5% to about 20% by weight of the total composition,

(c) a solvent comprising propylene glycol or a mixture of propylene glycol and ethanol in an amount of from about 15% to about 25% by weight of the total composition, and

(d) a surfactant comprising Cremophor RH40 or Cremophor EL in an amount of from about 30% to about 45% by weight of the total composition .

Another preferred composition of the invention comprises:

(a) a pyranone compound of formulas I, II, III or IV in an amount of from about 20% to about 30% by weight of the total composition,

(b) a mixture of diolein and monoolein in a ratio of about 8:2 by weight (diolein:monoolein) in an amount of from about 5% to about 20% by weight of the total composition,

(c) a solvent comprising propylene glycol or a mixture of propylene glycol and ethanol in an amount of from about 15% to about 25% by weight of the total composition, and

(d) a surfactant comprising Cremophor RH40 or Cremophor EL in an amount of from about 30% to about 45% by weight of the total composition.

Optionally, the preferred compositions may further comprise a basic amine in an amount of about 0.1% to about 7% by weight of the total composition.

In the preferred compositions of the present invention, an even more preferred composition comprises a pyranone compound of formula I in an amount of from about 20% to about 30% by weight to the total composition.

In the preferred compositions of the present invention, the mixture of propylene glycol and ethanol is in a ratio of about 1:1.

In the preferred compositions of the present invention, an even more

preferred composition comprises a tris(hydroxymethyl)aminomethane or dimethylaminoethanol in an amount of from about 0.1% to 7% by weight of the total composition.

In the preferred compositions of the present invention, an even more preferred composition comprises a mixture of diolein and monoolein in a ratio of about 8:2 by weight.

In particular, the most preferred composition of the present invention comprises the pyranone compound of formula I.

The composition of the present invention may take the form of liquid for soft elastic capsules or hard gelatin capsules by oral application. The composition may also be in the form of a liquid solution for oral, parenteral, rectal or topical application. The preferred dosage form is in the form of liquid for soft elastic capsules.

If desired, the compositions of the present invention may further comprise conventional pharmaceutical additives such as co-surfactants (for example, sodium lauryl sulfate), coloring agents, flavoring agents, fragrances, preserving agents, stabilizers, anti-oxidant and/or thickening agents.

The compositions of the present invention may be prepared in a conventional manner, for example, by dissolving an active agent in the solvent, then adding the oil phase, the surfactant, and optionally the basic amine. The resulting solution is then formulated into the desired dosage form such as, for example, soft elastic capsules or hard gelatin capsules by known manufacturing technology.

The pharmaceutical compositions of the present invention will be better understood in connection with the following examples, which are intended as an illustration of and not a limitation upon the scope of the invention. Without further elaboration, it is believed that one skilled in the art can, using the preceding description and the information provided in the examples below, practice the present invention to its fullest extent.

A. General Procedure for Preparing the Compositions of the Present Invention.

Drug is placed in a container. A solvent comprising propylene glycol or a mixture of solvents selected from ethanol (95%) and propylene glycol (1:1 by weight) is added and the cap is tightened. The container is put in a water bath at about 60 °C and shaken gently until all of the drug material is dissolved. After the container is cooled to room temperature, appropriate amounts of a mixture of diglyceride (such as diolein) and monoglyceride (such as mononoolein), a surfactant (such as Cremophor RH40 or Cremophor EL) and optionally a basic amine (such as

ethanolamine or diethanolamine) are added into the container. The container is sealed and put in a water bath at about 60 °C and shaken gently until a clear solution is formed. The container is usually left at ambient conditions for future use.

EXAMPLE 1

Component	Weight (mg)	% w/w
The compound of formula I	302	26.4
EtOH/Propylene Glycol (1:1)	197	17.3
Diolein/monoolein (8:2)	259	22.7
Cremophor RH40	307	26.9
Ethanolamine	61	5.3
Sodium lauryl sulfate	16	1.4

EXAMPLE 2

Component	Weight (mg)	% w/w
The compound of formula I	302	27.9
EtOH/Propylene Glycol (1:1)	280	19.2
Diolein/monoolein (8:2)	250	23.1
Cremophor RH40	304	28.0
Sodium lauryl sulfate	18	1.6

EXAMPLE 3

Component	Weight (mg)	% w/w
The compound of formula I	202	20.4
EtOH/Propylene Glycol (1:1)	198	20.0
Diolein/monoolein (9:1)	90	9.0
Cremophor EL	502	50.6

EXAMPLE 4

Component	Weight (mg)	% w/w
The compound of formula I	302	29.0
EtOH/Propylene Glycol (1:1)	210	20.2
Diolein/monoolein (9:1)	60	5.8
Cremophor EL	450	43.4
Diethanolamine	16	1.5

EXAMPLE 5

Component	Weight (mg)	% w/w
The compound of formula I	200	16.6
EtOH/Propylene Glycol (1:1)	212	17.6
Diolein/monoolein (8:2)	380	31.5
Cremophor RH40	365	30.2
α-tocopherol	48	4.0

EXAMPLE 6

Component	Weight (mg)	% w/w
The compound of formula I	298	25.8
EtOH/Propylene Glycol (1:1)	198	17.2
Diolein/monoolein (8:2)	287	24.8
Cremophor RH40	325	28.2
dimethylaminoethanol	45	3.9

EXAMPLE 7

Component	Weight (mg)	% w/w
The compound of formula I	299	27.9
EtOH/Propylene Glycol (1:1)	152	14.2
Diolein/monoolein (8:2)	249	23.2
Cremophor RH40	304	28.4
Choline hydroxide	66	6.2

EXAMPLE 8

Component	Weight (mg)	% w/w
The compound of formula I	298	27.6
EtOH/Propylene Glycol (1:1)	150	13.9
Diolein/monoolein (8:2)	257	23.8
Cremophor EL	309	28.7
Ethanolamine	62	5.8

EXAMPLE 9

Component	Weight (mg)	% w/w
The compound of formula I	197	19.7
EtOH/Propylene Glycol (1:1)	208	20.8
Diolein/monoolein (8:2)	271	27.1
Cremophor EL	329	32.9

EXAMPLE 10

Component	Weight (mg)	% w/w
The compound of formula I	202	20.0
EtOH/Propylene Glycol (1:1)	208	20.6
Diolein/monoolein (9:1)	279	27.6
Cremophor EL	321	31.8

EXAMPLE 11

Component	Weight (mg)	% w/w
The compound of formula I	202	19.8
EtOH/Propylene Glycol (1:1)	201	19.7
Diolein/monoolein (9:1)	96	9.4
polysorbate 80	522	51.1

EXAMPLE 12

Component	Weight (mg)	% w/w
The compound of formula I	213	21.0
EtOH/Propylene Glycol (1:1)	200	19.8
Diolein/monoolein (9:1)	86	8.5
Cremophor EL	514	50.7

EXAMPLE 13

Component	Weight (mg)	% w/w
The compound of formula I	301	29.3
EtOH/Propylene Glycol (1:1)	200	19.5
Diolein/monoolein (8:2)	204	19.9
Cremophor EL	261	25.4
Diethanolamine	61	5.9

EXAMPLE 14

Component	Weight (mg)	% w/w
The compound of formula I	400	40
EtOH	100	10
Diolein/monoolein (8:2)	70	7
Cremophor EL	330	33
Diethanolamine	80	8
H_2O	20	2

EXAMPLE 15

Component	Weight (mg)	% w/w
The compound of formula I	200	20
EtOH/Propylene Glycol (1:1)	200	20
Diolein/monoolein (8:2)	120	12
Gelucire 44/14	480	48

EXAMPLE 16

Component	Weight (mg)	% w/w
The compound of formula I	300	30
EtOH/Propylene Glycol (1:1)	190	19
Diolein/monoolein (8:2)	180	18
Cremophor EL	250	25
Water	28	2.8
Popyl Gallate	2	0.2
Diethanolamine	50	5

EXAMPLE 17

Component	Weight (mg)	% w/w
The compound of formula I	200	20
EtOH/Propylene Glycol (1:1)	200	20
Diolein/monoolein (8:2)	120	12
Polysorbate 80	480	48

EXAMPLE 18

Component	Weight (mg)	% w/w
The compound of formula I	200	20
EtOH/Propylene Glycol (1:1)	200	20
Diolein/monoolein (7:3)	120	12
Cremophor EL	480	48

EXAMPLE 19

Component	Weight (mg)	% w/w
The compound of formula I	200	20
EtOH/Propylene Glycol (1:1)	200	20
Diolein/monoolein (6:4)	120	12
Cremophor EL	480	48

EXAMPLE 20

Component	Weight (mg)	% w/w
The compound of formula I	300	30
95%EtOH	95	9.5
Propylene glycol	80	8
Diolein/monoolein (8:2)	70	7
Cremophor EL	455	45.5

B. Oral Bioavailability Test.

(i) Sprague-Dawley male rats were selected for the *in vivo* oral bioavailability study. Each rat was prepared by the surgical implantation of an indwelling cannula in the superior vena cava. Each rat, in the weight range of 300 - 400 g, was fasted overnight prior to dosing. Each formulation was orally administered to a group of rats (n=3) at a 20 mg/kg dose. The formulations with high concentration of the compound of formula I (typically 200-300 mg/g) was diluted by 100-fold with water and injected directly into the rat's stomach using oral gavage. Serial blood samples of 0.25 ml were obtained from the indwelling cannula at 0.25, 0.5, 1, 2, 4, 6, 8, 12, and 24 hours after dosing. These blood samples were analyzed using a HPLC assay specific for the compound of formula I. Drug concentrations in the blood of the test rats are plotted against the time after the drug is administered through an intravenous (i.v.) or oral route and the AUCs (the Area Under the Pasma

Concentration-Time Curve) are integrated using the trapezoidal rule to calculate the absolute bioavailability as shown in Table 1.

$$Absolute\ bioavailability\ (F) = \frac{(AUC)_{oral} / Dose_{oral}}{(AUC)_{iv} / Dose_{iv}}$$

(ii) Male Beagle dogs were also selected for the *in vivo* oral bioavailability study. Each dog, in the weight range of 13.5 - 17.5 kg, was fasted overnight prior to dosing. Each formulation was orally administered to a group of dogs (n=4) at a 20 mg/kg dose. The formulation of high concentration of the compound of formula I (300 mg/g) was encapsulated in gelatin capsules and administered. Serial blood samples of 2 ml were obtained from the jugular vein at 20, 40 minutes and 1, 2, 4, 6, 8, 12, and 24 hours after dosing. These blood samples were analyzed using a HPLC assay specific for the compound of formula I. The blood concentrations of the compound of formula I are plotted against the time and the AUCs are obtained to calculate the absolute bioavailability. The results are shown in Table 2.

(iii) Ten healthy volunteers were orally administered with eight 150 mg (1200 mg single dose) disodium salt of compound of the formula I encapsulated in hard gelatin capsules as reference. Weeks later, the same group were orally administered with four 300 mg (1200 mg single dose) compound of the formula I in a formulation as exhibited in Example 15. Serial blood samples of the volunteers were obtained at 30 minutes and 1, 2, 4, 6, 8, 12, and 24 hours after dosing. These blood samples were analyzed using a HPLC assay specific for the compound of formula I. The blood concentrations of the compound of formula I are plotted against the time and the AUCs are obtained to calculate the relative bioavailability. The results are shown in Table 3.

$$\textbf{\textit{Relative bioavailability}} = AUC_{test} / AUC_{ref} \times 100\%$$

The present invention achieves the desired results as demonstrated by the increased absolute or relative oral bioavailabilities in Tables 1, 2 and 3.

TABLE 1

Absolute Mean Oral Bioavailability in Rats

Example No.	Absolute Mean Oral Bioavailability (%)
1	84
2	37
3	71
4	71
Aqueous suspension of free acid of the compound of formula I	< 20

TABLE 2

Absolute Mean Oral Bioavailability in Dogs

Example No.	Absolute Mean Oral Bioavailability (%)
12	42.7
13	38.6
Free Acid of the compound formula I in Hard Gelatin Capsules	1.5

TABLE 3

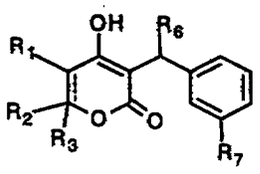
Relative Bioavailability in Human (1200 mg Single Dose)

Formulation	Relative Bioavailability (%)
Example 15	230
Disodium salt of the compound of formula I in Hard Gelatin Capsules	100

We claim

1. A pharmaceutical composition comprising:

(a) a pyranone compound of formula II as a pharmaceutically active agent,



II

(b) a mixture of diglyceride and monoglyceride in a ratio of from about 9:1 to about 6:4 by weight (diglyceride:monoglyceride) wherein the diglyceride and monoglyceride are mono- or di- unsaturated fatty acid esters of glycerol having sixteen to twenty-two carbon chain length,

(c) one or more pharmaceutically acceptable solvents, and

(d) one or more pharmaceutically acceptable surfactants;

wherein R_1 is H-;

R_2 is C_3-C_5 alkyl, phenyl-$(CH_2)_2$-, het-SO_2NH-$(CH_2)_2$-, cyclopropyl-$(CH_2)_2$-, F-phenyl-$(CH_2)_2$-, het-SO_2NH-phenyl-, or F_3C-$(CH_2)_2$-; or

R_1 and R_2 taken together are a double bond;

R_3 is R_4-$(CH_2)_n$-$CH(R_5)$-, H_3C-$[O(CH_2)_2]_2$-CH_2-, C_3-C_5 alkyl, phenyl-$(CH_2)_2$-, het-SO_2NH-$(CH_2)_2$-, $(HOCH_2)_3C$-NH-C(O)-NH-$(CH_2)_3$-, $(HO_2C)(H_2N)CH$-$(CH_2)_2$-C(O)-NH-$(CH_2)_3$-, piperazin-1-yl-C(O)-NH-$(CH_2)_3$, $HO_3S(CH_2)_2$-$N(CH_3)$-C(O)-$(CH_2)_6$-C(O)-NH-$(CH_2)_3$-, cyclopropyl-$(CH_2)_2$-, F-phenyl-$(CH_2)_2$-, het-SO_2NH-phenyl, or F_3C-$(CH_2)_2$-;

n is 0, 1 or 2;

R_4 is phenyl, het, cyclopropyl, H_3C-$[O(CH_2)_2]_2$-, het-SO_2NH-, Br-, N_3-, or $HO_3S(CH_2)_2$-$N(CH_3)$-C(O)-$(CH_2)_6$-C(O)-NH-;

R_5 is -CH_2-CH_3, or -CH_2-cyclopropyl;

R_6 is cyclopropyl, CH_3-CH_2-, or t-butyl;

R_7 is -NR_8SO_2-het, -NR_8SO_2-phenyl, optionally substituted with R_9, -CH_2-SO_2-phenyl, optionally substituted with R_9, or -CH_2-SO_2-het;

R_8 is -H, or -CH_3;

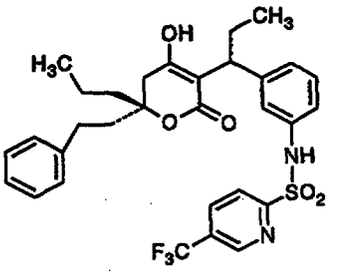
R_9 is -CN, -F, -OH, or -NO_2;

wherein het is a 5-, 6- or 7-membered saturated or unsaturated ring containing from one to three heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur; and including any bicyclic group in which any of the above heterocyclic rings

* C L M S *

is fused to a benzene ring or another heterocycle, optionally substituted with $-CH_3$, -CN, -OH, $-C(O)OC_2H_5$, $-CF_3$, $-NH_2$, or $-C(O)-NH_2$; or a pharmaceutically acceptable salt thereof.

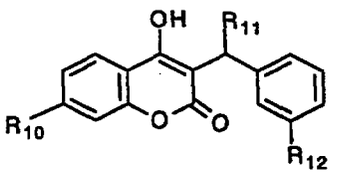
2. The pharmaceutical composition of claim 1 wherein the pyranone compound of formula II is a compound of formula I



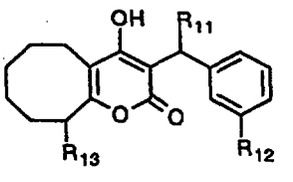
I.

3. A pharmaceutical composition comprising:

(a) a pyranone compound of formula III or IV as a pharmaceutically active agent,



III



IV

(b) a mixture of diglyceride and monoglyceride in a ratio of from about 9:1 to about 6:4 by weight (diglyceride:monoglyceride) wherein the diglyceride and monoglyceride are mono- or di- unsaturated fatty acid esters of glycerol having sixteen to twenty-two carbon chain length,

(c) one or more pharmaceutically acceptable solvents, and

(d) one or more pharmaceutically acceptable surfactants;

wherein R_{10} is H-, CH_3O-, or CH_3O-$[(CH_2)_2O]_3$-;

R_{11} is cyclopropyl, or $-CH_2-CH(CH_3)_2$;

R_{12} is $-NR_{14}SO_2$-phenyl, optionally substituted with R_{15}, $-NR_{14}SO_2$-het, $-CH_2-SO_2$-phenyl, optionally substituted with R_{15}, or $-CH_2-SO_2$-het;

R_{13} is -H, $-(CH_2)_2-CH_3$, $-CH_2$-cyclopropyl, or $-CH_2$-phenyl;

* C L M S *

R_{14} is -H, or -CH_3; R_{15} is -CN, -F, -CH_3, -COOH, or -OH;
het is a 5-, 6- or 7-membered saturated or unsaturated ring containing from one to three heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring or another heterocycle; optionally substituted with one or two -CH_3, -CN, -$C(O)OC_2H_5$, or -OH; or a pharmaceutically acceptable salt thereof.

4. The pharmaceutical composition of claims 1 or 3 wherein the compound of formula II, III or IV is in an amount of from about 1% to about 40% by weight of the total composition.

5. The pharmaceutical composition of claim 2 wherein the compound of formula I is in an amount of from about 20% to about 30% by weight of the total composition.

6. The pharmaceutical composition of claim 1 or 3 wherein said diglyceride is diolein, dilinoleate or a mixture thereof.

7. The pharmaceutical composition of claim 1 or 3 wherein said diglyceride is diolein.

8. The pharmaceutical composition of claim 1 or 3 wherein said monoglyceride is monoolein, monolinoleate or a mixture thereof.

9. The pharmaceutical composition of claim 1 or 3 wherein said monoglyceride is monoolein.

10. The pharmaceutical composition of claim 1 or 3 wherein the mixture of diglyceride and monoglyceride is in an amount of from about 5% to about 35% by weight of the total composition.

11. The pharmaceutical composition of claim 1 or 3 wherein the mixture of diglyceride and monoglyceride is in an amount of from about 5% to about 20% by weight of the total composition.

12. The pharmaceutical composition of claim 1 or 3 wherein the mixture of

* C L M S *

diglyceride and monoglyceride is in a ratio of about 8:2 by weight (diglyceride:monoglyceride) and in an amount of from about 5% to about 35% by weight of the total composition.

13. The pharmaceutical composition of claim 1 or 3 wherein the mixture of diglyceride and monoglyceride is in a ratio of about 8:2 by weight (diglyceride:monoglyceride) and in an amount of from about 5% to about 20% by weight of the total composition.

14. The pharmaceutical composition of claim 1 or 3 wherein the mixture of diglyceride and monoglyceride is in a ratio of about 9:1 by weight (diglyceride:monoglyceride) and in an amount of from about 5% to about 20% by weight of the total composition.

15. The pharmaceutical composition of claim 1 or 3 wherein the pharmaceutically acceptable solvent is propylene glycol, polypropylene glycol, polyethylene glycol, glycerol, ethanol, triacetin, dimethyl isosorbide, glycofurol, propylene carbonate, water, dimethyl acetamide, or a mixture thereof.

16. The pharmaceutical composition of claim 1 or 3 wherein the pharmaceutically acceptable solvent is propylene glycol.

17. The pharmaceutical composition of claim 1 or 3 wherein the pharmaceutically acceptable solvent is a mixture comprising propylene glycol and 95% (v/v) ethanol in a ratio of about 1:1.

18. The pharmaceutical composition of claim 1 or 3 wherein the pharmaceutically acceptable solvent is in an amount of from about 10% to about 30% by weight of the total composition.

19. The pharmaceutical composition of claim 1 or 3 wherein the pharmaceutically acceptable solvent is in an amount of from about 15% to about 25% by weight of the total composition.

20. The pharmaceutical composition of claim 1 or 3 wherein the pharmaceutically acceptable surfactant is Polyoxyl 40 hydrogenated castor oil, Polyoxyl 35 castor oil,

* C L M S *

Solutol HS-15, Tagat TO, Peglicol 6-oleate, Polyoxyethylene stearates, Poloxamers, Polysorbates, or Saturated Polyglycolyzed Glycerides.

21. The pharmaceutical composition of claim 1 or 3 wherein the pharmaceutically acceptable surfactant is Polyoxyl 40 hydrogenated castor oil or Polyoxyl 35 castor oil.

22. The Polyoxyl 40 hydrogenated castor oil of claim 21 which is Cremophor RH40.

23. The Polyoxyl 35 hydrogenated castor oil of claim 21 which is Cremophor EL, or Cremophor EL-P.

24. The pharmaceutical composition of claim 1 or 3 wherein the surfactant is in an amount of from about 10% to about 50% by weight of the total composition.

25. The pharmaceutical composition of claim 1 or 3 wherein the surfactant is in an amount of from about 30% to about 45% by weight of the total composition.

26. The pharmaceutical composition of claim 1 or 3 wherein the composition further comprises a basic amine.

27. The pharmaceutical composition of claim 26 wherein the basic amine is lower alkylamine, basic amino acid, or choline hydroxide.

28 The pharmaceutical composition of claim 27 wherein the lower alkylamine is ethanolamine, diethanolamine, triethanolamine, ethylenediamine, dimethylaminoethanol or tris(hydroxymethyl)aminomethane.

29. The pharmaceutical composition of claim 27 wherein the basic amino acid is arginine, lysine, or guanidine.

30. The pharmaceutical composition of claim 26 wherein the basic amine is in an amount from about 0.1% to about 10% by weight of the total composition.

31. A pharmaceutical composition comprising:

(a) a pyranone compound of formula I in an amount of from about 20% to about

* C L M S *

30% by weight of the total composition,

(b) a mixture of diolein and monoolein in a ratio of about 9:1 by weight (diolein:monoolein) and in an amount of from about 5% to about 20% by weight of the total composition,

(c) a solvent comprising propylene glycol or a mixture of propylene glycol and 95% (v/v) ethanol in a ratio of about 1:1 and in an amount of from about 15% to about 25% by weight of the total composition, and

(d) a surfactant comprising Cremophor RH40 or Cremophor EL in an amount of from about 30% to about 45% by weight of the total composition.

32. A pharmaceutical composition comprising:

(a) a pyranone compound of formula I in an amount of from about 20% to about 30% by weight of the total composition,

(b) a mixture of diolein and monoolein in a ratio of about 8:2 by weight (diolein:mono-olein) and in an amount of from about 5% to about 20% by weight of the total composition,

(c) a solvent comprising propylene glycol or a mixture solution of propylene glycol and 95% (v/v) ethanol in a ratio of about 1:1 in an amount of from about 15% to about 25% by weight of the total composition, and

(d) a surfactant comprising Cremophor RH40 or Cremophor EL in an amount of from about 30% to about 45% by weight of the total composition.

33. The pharmaceutical composition of claim 31 or 32 which further comprises a dimethylaminoethanol or tris(hydroxymethyl)aminomethane in an amount of from about 0.1% to 7% by weight of the total composition.

34. The pharmaceutical composition of claim 1, 3, 31 or 32 which is a self-emulsifying formulation capable of generating emulsions or microemulsions upon mixing with sufficient aqueous media.

35. The pharmaceutical composition of claim 1, 3, 32 or 33 which is in a form of liquid for soft elastic capsules.

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