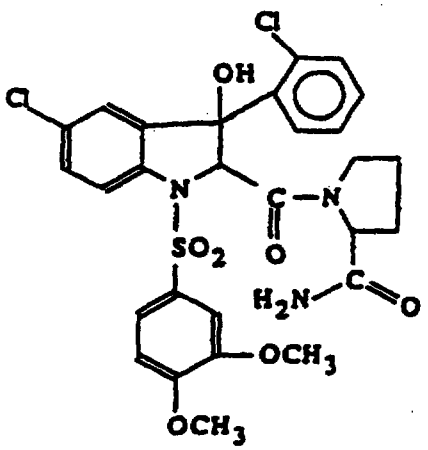
Pharmaceutical compositions containing N-sulphonyl-indoline derivatives

The present invention relates, in a general manner, to new pharmaceutical compositions containing, as active ingredient, N-sulphonylindoline derivatives.

In particular, the invention relates to pharmaceutical compositions either for parenteral administration or for oral administration containing, as active ingredient, one or more isomers of N-[5-chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxyphenylsulphonyl)-3-hydroxy-2,3-dihydro-1H-indole-2-carbonyl]pyrrolidine-2-carboxamide of formula:



These compounds of formula I above exist, indeed, in the form of cis-trans isomers around the 2,3 bond of indoline.

By convention, cis isomer refers to the compounds of formula I in which the 2-chlorophenyl and 2-carbamoyl-pyrrolidinocarbonyl groups are on the same side of the ring.

In contrast, trans isomer refers to the compounds of formula I in which these 2-chlorophenyl and 2-carbamoyl-pyrrolidinocarbonyl groups are each on one side of the ring.

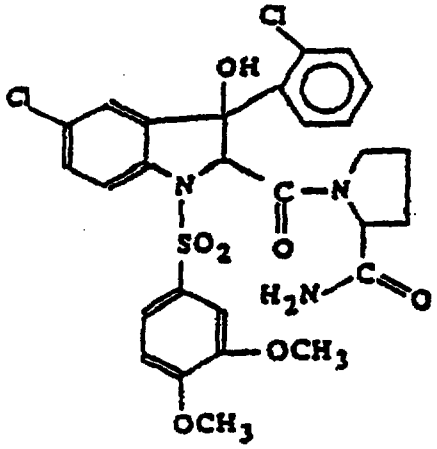
In addition, these compounds of formula I exist in the form of optical isomers because of the asymmetric carbon represented by the asterisk.

The various isomers mentioned above as well as mixtures thereof form part of the formula I.

The N-sulphonylindoline derivatives in question are known compounds which have been described in Patent Application EP 0,526,348. These compounds have revealed an affinity for the vasopressin and ocytocin receptors and are consequently useful particularly in the treatment of the central nervous system, of the cardiovascular system and of the gastric sphere.

Among the isomers which are the most representative of this series, there may be mentioned:

(2S)-1-[(2R,3S)-(5-chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxyphenylsulphonyl)-3-hydroxy-2,3-dihydro-1H-indole-2-carbonyl]pyrrolidine-2-carboxamide corresponding to the structural formula:



This compound will be called hereinafter "Compound α".

The active ingredients of formula I, in particular Compound α, are highly hydrophobic products and, for this reason, are found to be very poorly soluble in aqueous medium at physiological pH values, that is to say of between 1.2 and 7.5.

Now, it is known that medicinal substances are absorbed better if they are in dissolved form in pharmaceutical compositions.

However, this solubilization, which may be obtained in organic solvents specific for the substance considered, should, in order to preserve its maximum efficiency, maintain (stabilize) this solubilized state of the molecule during dilution of the pharmaceutical

composition in aqueous medium. Certain formulations of the microemulsion type make it possible to cause such an organic phase, containing the solubilized hydrophobic pharmaceutical substance, and an aqueous phase to coexist.

However, when they are introduced into pharmaceutical envelopes such as soft capsules, liquid pharmaceutical compositions require the absence of water, the gelatin-based membrane being incompatible with an aqueous formulation.

Moreover, the volume of pharmaceutical composition to be administered should be minimized for such a presentation, in hard gelatin capsule or soft gelatin capsule, to be feasible.

Indeed, a pharmaceutical envelope of this type cannot be too large in size for easy swallowing by the patient.

There have already been described in the literature systems allowing the solubilization of particularly hydrophobic pharmaceutical substances for the purpose of formulating pharmaceutical compositions which can be administered as hard gelatin capsules or as soft gelatin capsules.

To this effect, there have already been proposed lipophilic matrices such as vegetable or animal oils which, if necessary, can be combined with lubricating agents such as fats, waxes or mineral oils.

There may be mentioned for example Patent EP 107 085 which teaches the use of an oily phase consisting of vegetable oil and a water-soluble anhydrous hydrophilic phase consisting, for example, of polyethylene glycols having a molecular mass of 300 to 20,000 or of propylene glycol, glycerol or mixtures thereof.

Likewise, there have been described in Patent GB 1,132,518, pharmaceutical compositions containing an active ingredient soluble in benzyl benzoate, whose matrix consists of a unit formed by benzyl benzoate and a nonionic hydrophilic surfactant such as polysorbate

80 and optionally a mineral or vegetable oil and a cosolvent such as a polyethylene glycol.

However, it is well known that matrices already proposed for use in pharmaceutical compositions to be introduced into capsules cannot be generalized regardless of the active substance to be combined.

As proof, orientation tests carried out within the framework of the invention have shown that the active ingredients of formula I, particularly Compound α, are not very or are very poorly soluble in oils.

Consequently, the systems recommended by the state of the art for the solubilization of hydrophobic compounds should, a priori, be excluded as regards the active ingredients in question.

Consequently, the development of an anhydrous pharmaceutical composition concentrated in the hydrophobic compound of formula I, for example Compound α, appears to be highly desirable and remains of fundamental interest.

However, it has now been shown that it is possible to prepare, without a hydrophobic oily phase, an emulsifiable or microemulsifiable, anhydrous pharmaceutical composition containing the active ingredients of formula I, this composition making it possible to arrive at a presentation in particular in the form of a tablet, a hard gelatin capsule or a soft gelatin capsule in which this active ingredient is present in a form dissolved in a solubilizing/stabilizing system spontaneously microdispersible in water.

Consequently, a first subject of the invention relates to an anhydrous solubilizing/stabilizing system, emulsifiable or microemulsifiable in water, for the solubilization of the N-sulphonylindoline derivatives of formula I, comprising one or more constituents selected from amphiphilic compounds, nonionic hydrophilic surfactants and nonionic hydrophilic compounds endowed with both amphiphilic and surfactant proper-

ties, it being understood that the said system comprises either at least one mixture of an amphiphilic compound and of a nonionic hydrophilic surfactant, or at least one nonionic hydrophilic compound endowed with both surfactant and amphiphilic properties.

In particular, the invention relates to a solubilizing/stabilizing system as above, comprising:

- either one or more constituents selected from glycol-type amphiphilic compounds, namely propylene glycol, polyethylene glycols and glycol ethers, (preferably polyethylene glycols and glycol ethers), the system comprising, in addition, one or more nonionic hydrophilic surfactants,
- or one or more nonionic hydrophilic compounds which are both amphiphilic and surfactant, selected from saturated polyglycolysed glycerides, the system optionally comprising one or more nonionic hydrophilic surfactants, and optionally one or more glycol-type amphiphilic compounds, namely polyethylene glycols.

The solubilizing/stabilizing system of the invention refers in particular to a system comprising at least two different compounds, one acting as solvent or amphiphilic solubilizing agent, the other as nonionic hydrophilic surfactant.

However, this system can combine more than two compounds, for example several compounds acting as amphiphilic cosolvents or several nonionic hydrophilic surfactant compounds.

It is also possible to envisage that among this set of at least two different compounds, either of them is capable of acting both as amphiphilic solvent and as nonionic hydrophilic surfactant.

In particular, this solubilizing/stabilizing system may be limited to a single nonionic hydrophilic compound acting both as solvent or amphiphilic solubilizer and as surfactant.

The amphiphilic solvents in question above are generally selected among glycol-type compounds.

Preferably, they are selected among one or more polyethylene glycols (PEG) having a mean molecular weight of between about 400 and 10,000, in particular between about 400 and about 2000.

In addition, a polyethylene glycol of a given molecular weight may be used alone or mixed with one or more polyethylene glycols of varied molecular weights.

The polyethylene glycols used within the framework of the invention exist at room temperature either in liquid form or in semisolid form according to their molecular weights. Consequently, these polymers will be appropriately selected according to whether the desired solubilizing/stabilizing system should exist in liquid form or on the contrary in semisolid form.

Among the polyethylene glycols preferred according to the invention, there may be mentioned for example polyethylene glycol 400 or "PEG 400" which is liquid at room temperature, polyethylene glycol 1000 or "PEG 1000", polyethylene glycol 1500 or "PEG 1500", polyethylene glycol 2000 or "PEG 2000", polyethylene glycol 6000 or "PEG 6000", as well as a 50/50 mixture by weight of polyethylene glycol 600 or "PEG 600" and polyethylene glycol 1500 or "PEG 1500", all these polyethylene glycols being semisolid at room temperature, with the exception of PEG 400 as indicated above.

It is also possible to use, within the framework of the invention, specific polyethylene glycol derivatives resulting from the esterification of the fatty acid residues with polyethylene glycol and glycerol. The structure of this type of compound, which is semisolid at room temperature, confers on it first an amphiphilic character, capable of solubilizing the active ingredients of formula I, in particular Compound α, because of the fatty chains and the polyethylene glycol unit constituting it, then an appro-

priate hydrophilic surfactant character to stabilize the solution formed during its introduction into an aqueous medium.

Such compounds are selected from saturated polyglycolysed glycerides, also designated as macrogol glycerides, that is to say compounds consisting of a mixture of monoesters, diesters and triesters of glycerol and fatty acids, and of mono- and diesters of polyethylene glycol and fatty acids. The most advantageous among them are those which possess a melting point close to body temperature and whose hydrophilic/lipophilic balance, commonly defined by its "HLB" value indicating the proportion of the hydrophilic groups compared with the lipophilic groups of the molecule according to the GRIFIN WC system [J. Soc. Cosm. Chem., 1, 311 (1949)], is between 12 and 22, preferably between 12 and 18.

Compounds which are particularly representative of this series are those marketed under the trademarks GELUCIRE® 44-14 and GELUCIRE® 50-13. The product GELUCIRE® 44-14 is in fact found to be an excellent solubilizer of Compound α. At 60°C, the solubility of this active ingredient of formula I, determined by the addition method, is 226 mg/g.

Other glycol-type derivatives can be used as solvent or cosolvent within the framework of the invention, that is to say amphiphilic compounds endowed with a solubilizing power. Such glycol derivatives are selected from glycol ethers, in general from diethylene glycol ethers such as diethylene glycol mono(C_1-C_4 alkyl) ether.

Among the monoethers of diethylene glycol, the commercially available methyl and ethyl ethers are preferred, particularly diethylene glycol monoethyl ether.

These products may contain a few impurities consisting, in most cases, of small quantities of diethers and other compounds produced during their

synthesis. They can nevertheless be used in this form to prepare pharmaceutical compositions.

The product with the trademark TRANSCUTOL®, an extremely pure diethylene glycol monoethyl ether sold by the company Gattefosse (FR), constitutes a particularly preferred glycol ether for the purposes of the invention.

Such glycol ethers can be used alone as amphiphilic solvent in the solubilizing/stabilizing system of the invention or preferably combined in any proportion with one or more polyethylene glycols of low molecular weight, that is to say of between 400 and 600 as described above where this glycol ether then acts as cosolvent and even as cosurfactant.

As for the surfactant, it is generally selected from nonionic hydrophilic compounds whose HLB value is between 12 and 22, preferably between 12 and 18.

Surfactants of this type may be, for example, an ethylene oxide/propylene oxide copolymer such as those marketed under the trademarks PLURONIC® P94 (HLB: 13.5) and PLURONIC® F127 (HLB: 22), a polyethoxylated castor oil such as that marketed under the trademark CREMOPHOR® EL (HLB: 13), a nonethoxylated polysorbate, an ethoxylated polysorbate such as polysorbate 80 (HLB: 15) marketed under the trademark TWEEN® 80 or MONTANOX® 80 DF or polysorbate 20 marketed under the trademark TWEEN® 20 (HLB: 16.5), or a polyethylene hydroxystearate such as polyethylene hydroxystearate - 660 (HLB: 13) marketed under the trademark SOLUTOL® HS15.

In addition, the surfactant used within the framework of the present invention may alternatively consist of a mixture of such nonionic hydrophilic surfactant compounds, a mixture whose HLB value would also be between 12 and 22, preferably between 12 and 18.

By way of a preferred surfactant mixture, there may be mentioned a mixture of ethoxylated polysorbate

and nonethoxylated polysorbate such that the final HLB value would be between 12 and 22, preferably between 12 and 18, for example a mixture of polysorbate 80 (HLB: 15) and of nonethoxylated polysorbate marketed under the trademark SPAN® 20 (HLB: 8.6).

Among the solubilizing/stabilizing systems of the invention generally preferred are those consisting:

a) either of an amphiphilic compound selected from polyethylene glycols having a molecular weight of between 400 and 600, the system comprising, in addition, a nonionic hydrophilic surfactant and optionally a diethylene glycol ether

b) or an amphiphilic compound selected from polyethylene glycols having a molecular weight of between 600 and 10,000, for example between 600 and 2000 or else between 2000 and 10,000, the system comprising, in addition, a nonionic hydrophilic surfactant

c) or a solubilizing/surfactant compound selected from saturated polyglycolysed glycerides, the system optionally comprising a nonionic hydrophilic surfactant.

By way of preferred solubilizing/stabilizing systems according to the invention, there may be envisaged the systems consisting:

- either of PEG 400 and polysorbate 80
- or of PEG 400, TRANSCUTOL® product and polysorbate 80
- or of PEG 2000 and polysorbate 80
- or of a 50/50 mixture by weight of PEG 600/PEG 1500 and of polysorbate 80
- or of saturated polyglycolysed glycerides of GELUCIRE® 44-14 or GELUCIRE® 50-13 trademark.

Consequently, the invention relates to an anhydrous solubilizing/stabilizing system, emulsifiable or microemulsifiable in water, for the solubilization of N-sulphonylindoline derivatives of formula I comprising:

- either one or more glycol-type amphiphilic compounds selected from propylene glycol and polyethylene glycols having an average molecular weight of between 400 and 600, preferably such polyethylene glycols, and comprising, in addition, one or more nonionic hydrophilic surfactants having an HLB value of between 12 and 22, preferably between 12 and 18, and optionally a diethylene glycol ether, such that the solubilizing/stabilizing system thus formed is in liquid form,
- or one or more glycol-type amphiphilic compounds selected from propylene glycol, polyethylene glycols having an average molecular weight of between 400 and 600 and diethylene glycol ethers such as a diethylene glycol mono(C_1-C_4 alkyl) ether, preferably the said polyethylene glycols and the said diethylene glycol ethers, the system comprising, in addition, one or more nonionic hydrophilic surfactants having an HLB value of between 12 and 22, preferably between 12 and 18, such that the solubilizing/stabilizing system thus formed is in liquid form,
- or one or more glycol-type amphiphilic compounds selected from polyethylene glycols having an average molecular weight of between 600 and 2000, the system comprising, in addition, one or more nonionic hydrophilic surfactants having an HLB value of between 12 and 22, preferably between 12 and 18, such that the solubilizing/stabilizing system thus formed is in semisolid form,
- or one or more glycol-type amphiphilic compounds selected from polyethylene glycols having an average molecular weight of between 2000 and 10,000, the system comprising, in addition, one or more nonionic hydrophilic surfactants having an HLB value of between 12 and 22, preferably between 12 and 18, such that the solubilizing/stabilizing system thus formed is in semisolid form,

- or one or more nonionic hydrophilic compounds which are both amphiphilic and surfactant, which are saturated polyglycolysed glycerides consisting of mixtures of monoesters, diesters and triesters of glycerol and fatty acids, and of mono- and diesters of polyethylene glycol and fatty acids, the system optionally comprising one or more nonionic hydrophilic surfactants having an HLB value of between 12 and 22, preferably between 12 and 18, and optionally one or more glycol-type amphiphilic compounds selected from polyethylene glycols having an average molecular weight of between 600 and 10,000, for example between 600 and 2000 or else between 2000 and 10,000, such that the solubilizing/stabilizing system thus formed is in semisolid form.

As indicated above, the solubilizing/stabilizing systems of the invention can advantageously serve to solubilize the compounds of formula I so as to form compositions which can be diluted or dispersed in an aqueous medium.

In the case of such solubilizing/stabilizing systems involving one or more amphiphilic solvents such as propylene glycol, a polyethylene glycol of low molecular weight, a diethylene glycol ether or mixtures thereof and comprising, in addition, a nonionic hydrophilic surfactant, it is possible to determine the appropriate proportions of the various constituents on a pseudoternary phase diagram so as to predict the behaviour, in an aqueous medium, of compositions consisting of a compound of formula I and of a solubilizing/stabilizing system according to the invention.

Figures 1 and 2 in the annex represent such diagrams in which:

a) there is represented in Figure 1 the behaviour of compositions consisting of 20 mg/ml of Compound α in solubilizing/stabilizing systems of the inven-

tion, for example PEG 400/TRANSCUTOL® product and polysorbate 80 mixtures,

b) there is represented in Figure 2 the behaviour of compositions consisting of 60 mg/ml of Compound α in solubilizing/stabilizing systems similar to those envisaged in Figure 1.

In these diagrams, the relative concentrations of water, of solubilizer and of stabilizing agent increase from 0 to 100% in the directions indicated by the arrows.

From the diagram of Figure 1, it is observed in particular that the relative proportions by weight of solubilizer/Compound α mixtures, on the one hand, and of stabilizer on the other, determine a homogeneous zone "A" and a heterogeneous zone "B" corresponding to low concentrations of surfactant.

The tangent to this heterogeneous zone "B" materialized by the straight line "d", drawn from the vertex "WATER 100%", determines on the opposite side a point "P" representing the anhydrous mixtures of solubilizer/Compound α and, additionally, of stabilizer or surfactant.

Above this point "P", that is to say for increased concentrations of surfactant, it will be possible to dilute these anhydrous mixtures in water since the line "d" corresponding to each of these concentrations of surfactant, that is to say the line representative of their dilution path, will not cut the heterogeneous zone "B".

In this case, it will be possible to obtain a purely organic formulation of a hydrophobic active ingredient behaving like a true solution, infinitely dilutable in water.

This upper zone "A", relative to the line "d", consequently defines solubilizing/stabilizing systems likely to form concentrated solutions of Compound α.

These solutions of high stability are capable, in the presence of water, of providing microemulsions

which are stable in the temperature ranges generally used for pharmaceutical compositions.

In these concentrated solutions, as represented in Figure 1, the quantity of Compound α may reach 20 mg/ml when the amphiphilic solubilizer is a PEG 400/TRANSCUTOL® product mixture and the stabilizer is polysorbate 80.

If on the other hand it is sought to increase the proportion of active ingredient of formula I, particularly of Compound α, and to reduce that of stabilizer, as represented in Figure 2, it is observed, on the one hand, that the multiphase zone becomes bigger, that is to say "B'", and, on the other hand, that the line for dilution in water "d'" cuts this heterogeneous zone.

Consequently, the preparation of dilutable concentrated solutions of Compound α (Compound α in a solubilizing/stabilizing system of the invention) would require large quantities of stabilizing agents (greater than 20%) not very compatible with a pharmaceutical application.

The concentrated solutions of Compound α whose dilution line cuts the heterogeneous zone "B'" no longer appear as being completely dilutable, but dispersible in an aqueous medium, that is to say as concentrated solutions spontaneously forming an emulsion which is fine to a greater or lesser degree during dispersion in water.

Surprisingly, it was observed that concentrated dispersible solutions (zone B or B') which are qualitatively identical but comprising, nevertheless, lower concentrations of surfactant than the concentrated dilutable solutions, possess qualities similar to those demonstrated with these concentrated dilutable solutions in that they all lead to an improvement in membrane permeability resulting in an identical increase in the transepithelial passage of the compound of formula I, particularly of Compound α.

This alternative consequently allows greater flexibility since it is not necessary to take into account only the systems capable of giving micro-emulsifiable solutions in order to obtain particularly advantageous concentrated solutions.

In this manner, the concentration of active ingredient of formula I may be substantially increased.

In the case of water-dispersible solutions containing Compound α, the concentration of active ingredient may be increased up to 60 mg/ml, that is to say a concentration 3 times greater than that of the solution which is dilutable in water.

Moreover, it will be noted that even in the case of water-dispersible solutions, these exhibit good aqueous tolerance since they can practically incorporate their weight of water while remaining completely homogeneous. This characteristic is highly useful during the introduction of such solutions into soft gelatin capsules for the preparation of pharmaceutical dosage forms because it is known that exchanges between content and envelope can occur during this manufacture.

Consequently, water momentarily incorporated into the solution does not risk causing phase separation in the latter since the quantity exchanged is less than 10%. The same characteristic of homogeneity being maintained is observed when the solution contains up to 5% of glycerol, which may be the case during the use of certain processes for preparing pharmaceutical compositions employing this triol. After drying, the initial solution will be present without these variations having modified the properties thereof.

The solubilizing/stabilizing system of the invention capable of solubilizing the hydrophobic active ingredients of formula I can be justifiably used for the purpose of introducing these active ingredients into pharmaceutical compositions.

Consequently, another subject of the invention relates to a pharmaceutical composition, which is

microemulsifiable or emulsifiable in an aqueous medium, comprising:

- a hydrophobic active ingredient of formula I
- a solubilizing/stabilizing system as described above
- optionally an appropriate pharmaceutical excipient or vehicle.

In particular, the invention relates to an injectable pharmaceutical composition comprising:

- a hydrophobic active ingredient of formula I
- a solubilizing/stabilizing system in liquid form consisting of one or more glycol-type amphiphilic compounds selected from propylene glycol, polyethylene glycols having an average molecular weight of between 400 and 600, and comprising, in addition, one or more nonionic hydrophilic surfactants having an HLB of between 12 and 22, preferably between 12 and 18, such as for example polysorbate 80, and optionally a diethylene glycol ether such as the product TRANSCUTOL®
- an appropriate pharmaceutical vehicle.

Appropriate pharmaceutical vehicle is essentially understood to mean water or a physiologically acceptable ketone derivative, the active ingredients of formula I, particularly Compound α, having proved to be particularly soluble in these organic compositions.

For this reason, a polyvinylpyrrolidone (PVP), preferably the polyvinylpyrrolidone marketed under the trademark KOLLIDON® 12PF or the polyvinylpyrrolidone marketed under the trademark KOLLIDON® 17PF, constitutes a ketone derivative of choice for further enhancing the solubility of the active ingredient of formula I in injectable compositions.

In this manner, pharmaceutical compositions for administration by injection can be prepared, these compositions not exceeding 10 mg/ml, that is to say 1% by weight of compound of formula I.

For example, such compositions may contain from 2 to 6 mg/ml of Compound α.

They will contain, in addition, a nonionic hydrophilic surfactant such as polysorbate 80 at a concentration not exceeding 4% by weight of the final composition.

Such isotonic compositions have proved to be physically stable and dilutable in physiological saline or in glucose-containing saline solution.

According to another of its features, the invention relates to a liquid pharmaceutical composition for oral administration, comprising:

- a hydrophobic active ingredient of formula I
- a solubilizing/stabilizing system in liquid form, consisting of one or more glycol-type amphiphilic compounds selected from propylene glycol, polyethylene glycols having an average molecular weight of between 400 and 600, and diethylene glycol ethers, (preferably the said polyethylene glycols and the said diethylene glycol ethers), the system comprising, in addition, one or more nonionic hydrophilic surfactants having an HLB of between 12 and 22, preferably between 12 and 18, such as for example polysorbate 80 or the product of the trademark PLURONIC® P 94.

Generally, one or more polyethylene glycols of low molecular weight, that is to say of between about 400 and about 600, are used in the context of such oral compositions. The polyethylene glycol preferably used is PEG 400.

When such polyethylene glycols are used, they are generally combined with one or more diethylene glycol ethers such as methyl or ethyl ethers. Diethylene glycol monoethyl ether is nevertheless recommended as preferred diethylene glycol ether, that is to say the product having the trademark TRANSCUTOL®.

These diethylene glycol ethers will be used, nevertheless, at concentrations preferably not exceeding 50% by weight, or better still 20% by weight of the final composition.

As for the nonionic hydrophilic surfactant, it is preferably selected from the compounds having an HLB of 15 or close to 15, and it is generally used at concentrations not exceeding 20%, preferably not exceeding 12%, by weight of the final composition. In this regard, polysorbate 80 constitutes a surfactant of choice for the purposes of the invention.

Thus, a particularly preferred solubilizing/stabilizing system according to the invention consists of a PEG 400/TRANSCUTOL® product/polysorbate 80 mixture.

The compositions of the invention thus formed are provided in the form of homogeneous and transparent liquids. They may contain high concentrations of active ingredient of formula I because of their anhydrous character, it being possible for these concentrations to be as high as 150 mg/ml or 15% by weight, more particularly 60 mg/ml or 6% by weight of Compound α.

For this reason, small administerable volumes may be envisaged, for example 0.5 ml containing up to 30 mg of this same active ingredient.

These pharmaceutical compositions, spontaneously dispersible in an aqueous medium, while being capable of accepting water without phase separation, consequently become compatible with being put in a gelatin capsule of the soft gelatin capsule type.

Moreover, these liquid pharmaceutical compositions for oral administration have proved capable of increasing the speed of transepithelial transport as well as the bioavailability of the active ingredients of formula I.

According to another of its features, the invention relates to a semisolid pharmaceutical composition for oral administration, comprising:

- a hydrophobic active ingredient of formula I, generally at a concentration not exceeding 15% by weight of the composition,

- a semisolid solubilizing/stabilizing system comprising:

either one or more glycol-type amphiphilic compounds selected from polyethylene glycols having an average molecular weight of between 600 and 2000, the system comprising, in addition, one or more nonionic hydrophilic surfactants having an HLB value of between 12 and 22, preferably between 12 and 18,

or one or more glycol-type amphiphilic compounds selected from polyethylene glycols having an average molecular weight of between 2000 and 10,000, the system comprising, in addition, one or more nonionic hydrophilic surfactants having an HLB value of between 12 and 22, preferably between 12 and 18, such that the solubilizing/stabilizing system thus formed is in semisolid form,

or one or more nonionic hydrophilic compounds which are both amphiphilic and surfactant, and which are saturated polyglycolysed glycerides consisting of mixtures of monoesters, diesters and triesters of glycerol and fatty acids, and mono- and diesters of polyethylene glycol and fatty acids, the system optionally comprising one or more nonionic hydrophilic surfactants having an HLB value of between 12 and 22, preferably between 12 and 18, and optionally one or more glycol-type amphiphilic compounds selected from polyethylene glycols having an average molecular weight of between 600 and 10,000, for example between 600 and 2000 or else between 2000 and 10,000.

Generally, in the context of such oral compositions, one or more polyethylene glycols having a molecular weight of between 600 and 2000 are used.

In this regard, PEG 1000, PEG 2000, PEG 6000 or a 50/50 mixture by weight of PEG 600/PEG 1500 constitute preferred amphiphilic solvents according to the invention.

In the case of mixtures of various polyethylene glycols, it is possible to use small proportions of these polymers, situated outside the range set above in combination with polyethylene glycols included in the range in question.

However, these polyethylene glycols will be selected such that the resulting oral composition is compatible, particularly as regards viscosity, with filling equipment, for example, for the preparation of soft gelatin capsules.

As for the nonionic hydrophilic surfactant, it is preferably selected from compounds having an HLB close to 15. In this regard, polysorbate 80 constitutes a surfactant of choice for the purposes of the invention.

This surfactant will be, however, incorporated into the semisolid compositions in question at a concentration not exceeding 20%, preferably not exceeding 12%, by weight thereof.

Thus, a solubilizing/stabilizing system preferably used consists of PEG 1000 and polysorbate 80 or a 50/50 mixture by weight of PEG 600/1500 as well as of polysorbate 80 or of PEG 2000 and polysorbate 80.

Moreover, the polyglycolysed glycerides, of solid and waxy consistency at room temperature, will be selected such that their melting temperature is close to body temperature.

In this regard, the products having the trademarks GELUCIRE® 44-14 and GELUCIRE® 50-13 constitute mixtures of polyglycolysed glycerides of choice because of their melting temperature of 44°C and 50°C respectively, their amphiphilic character conferred by fatty acid chains and the polyethylene glycol unit and by

their favourable hydrophilic surfactant character (HLB: 14 and 13 respectively).

As in the case of the above liquid pharmaceutical compositions for oral administration, it will be possible to administer semisolid pharmaceutical compositions in a small volume given the high solubility of the active ingredients of formula I in this type of mixture of polyglycolysed glycerides.

In addition, it has been observed during experimental tests that the product GELUCIRE® 44-14, in particular, enhances membrane permeability and allows a speed of transepithelial transport of Compound α about twice as high as that obtained with the liquid compositions of the invention introduced into a soft gelatin capsule.

Likewise, a very marked improvement in bioavailability was observed, this improvement being similar to that recorded with the liquid compositions of the invention which can be used in a soft gelatin capsule.

Consequently, another subject of the invention relates to a pharmaceutical soft gelatin capsule containing a liquid pharmaceutical composition for oral administration as described above, that is to say containing a hydrophobic active ingredient of formula I and a solubilizing/stabilizing system.

The pharmaceutical compositions of the invention containing as solubilizer/stabilizer the saturated polyglycolysed glycerides as described above are formed at high temperature in the liquid state and then solidify on cooling. Consequently, these anhydrous and liquid compositions can be introduced at high temperature into hard gelatin capsules to finally form a semisolid pharmaceutical composition.

Consequently, another subject of the invention relates to a pharmaceutical gelatin capsule containing a semisolid pharmaceutical composition for oral administration as described above.

The pharmaceutical compositions of the invention may be prepared in a conventional manner by solubilizing the active ingredient of formula I in the selected solvent(s) or solubilizer(s) to which the nonionic hydrophilic surfactant is added, these various constituents being in liquid form.

Consequently, the solubilizing/stabilizing system will be heated, if necessary, until a liquid mixture is obtained.

This heating operation is particularly appropriate when polyethylene glycols of molecular weight > 600 or mixtures of monoesters, diesters and triesters of glycerol and fatty acids, and of mono- and diesters of polyethylene glycol and fatty acids, particularly the products GELUCIRE® 44-14 and GELUCIRE® 50-13, are used.

The pharmaceutical compositions of the invention may also be in solid form, such as a powder, granule or tablet.

Consequently, another subject of the invention relates to a solid pharmaceutical composition for oral administration comprising :

- a hydrophobic active ingredient of formula 1, generally at a concentration not exceeding 15% by weight of the composition
- a solubilizing/stabilizing system comprising:

- either one or more glycol-type amphiphilic compounds selected from polyethylene glycols having an average molecular weight of between 2000 and 10,000, the system comprising, in addition, one or more nonionic hydrophilic surfactants having an HLB value of between 12 and 22, preferably between 12 and 18,

- or one or more nonionic hydrophilic compounds which are both amphiphilic and surfactant, and which are saturated polyglycolysed glycerides consisting of mixtures of monoesters, diesters and triesters of glycerol and fatty acids, and mono- and diester of polyethylene glycol and fatty acids, the system

optionally comprising one or more nonionic hydrophilic surfactants having an HLB value of between 12 and 22, preferably between 12 and 18, and optionally one or more glycol-type amphiphilic compounds selected from polyethylene glycols having an average molecular weight of between 600 and 10,000

- an appropriate pharmaceutical excipient or vehicle.

As in the case of the semisolid pharmaceutical compositions, the solid pharmaceutical compositions of the invention will comprise a surfactant, preferably selected from compounds having an HLB close to 15. In this regard, the polysorbates 20 or 80 constitute particularly advantageous surfactants for the purposes of the invention.

This surfactant will, however, be introduced into the solid compositions in question at a concentration not exceeding 20% by weight of the latter, preferably not exceeding 12%.

Besides, appropriate excipients will be incorporated into the active ingredient and the selected solubilizing/stabilizing system.

Such excipients may be selected from compounds such as, for example, lactose, starches, polyvinylpyrrolidone, carboxymethylcellulose.

Consequently, the invention also relates to a solid pharmaceutical composition for oral administration, this composition being in the form of a powder, a granule or a tablet.

The solid compositions of the invention may be prepared in various ways, for instance by applying one of the methods below starting from the various selected ingredients :

either

a) all of the ingredients, including the active ingredient, are mixed in the form of a powder, the saturated polyglycolysed glyceride, that is to say the macrogol glyceride, or the polyethylene

glycol/surfactant mixture is melted, then the mixture of powders is granulated with the melted phase and the granules obtained are sieved,

or

b) the macrogol glyceride or the polyethylene glycol/surfactant mixture is melted, the active ingredient is granulated with the melted phase, the granules formed are sieved and mixed with the remaining excipients,

or

c) the macrogol glyceride or the polyethylene glycol/surfactant mixture is melted, the active ingredient is dissolved in this melted phase, the remaining excipients are mixed, this mixture of excipients is granulated with the melted phase, and then the granules formed are sieved.

One step of the above methods consists in obtaining a mixture starting from the active ingredient and the melted macrogol glyceride or melted polyethylene glycol/surfactant, this mixture optionally containing additional excipients.

At this stage, it is possible to use such a mixture for the preparation of semisolid pharmaceutical compositions by introducing it into soft gelatin capsules.

However, it is generally preferred to use the granules formed (paragraph a) or c) above) or the mixture composed of granules and excipients (paragraph c) above) for the preparation of hard gelatin capsules, powders or tablets.

Accordingly, in order to obtain an oral composition in the form of a hard gelatin capsule, the granules in question or the mixture in question of granules and excipients may be used directly by introducing them into hard gelatin capsules.

Likewise, in order to obtain an oral composition in the form of a powder, these granules or this mixture

of granules and excipients may be ground and then the resulting powder distributed into unit sachets.

Finally, tablets may, if necessary, be formed by direct compression of these granules or this mixture of granules and excipients.

However, it was noted, quite unexpectedly, that method c) above is superior to methods a) and b) regarding the formation of tablets in that the tablets obtained display much better kinetics of dissolution than shown by tablets formed by application of the other two methods.

Thus, tests carried out at 37°C in an aqueous medium of pH = 1.2 using tablets obtained according to this method c) showed that 100% of the active ingredient is dissolved after 15 minutes, whereas less than 50% of this active ingredient is dissolved after 60 minutes starting from tablets containing the same amount of active ingredient but obtained according to methods a) or b).

The characteristics and advantages of the compositions according to the invention will emerge in the light of the description below using compositions given by way of examples.

I. Evaluation of the intestinal transepithelium passage of Compound α

An immortalized human cell line of colon origin "Caco-2" as described in Crist. Rev. Ther. Drug Carrier System 8 (4), 105-330, 1991, is used to this effect. These cells, which have the characteristic of becoming differentiated in culture to reconstitute an intestinal epithelium model, are used as model to study the passage of a molecule through an intestinal epithelium and, consequently, to estimate its intestinal absorption.

These Caco-2 cells are inoculated onto microporous polycarbonate filters coated with collagen. The cellular monolayer formed on the filter then makes it

possible to separate an apical compartment (mimicking the intestinal lumen) of a basal compartment (mimicking the bloodstream).

The composition containing the compound to be studied is then placed on the apical side and the passage of this compound, dispersed or solubilized in Hank's medium, across this cell barrier is evaluated by measuring the kinetics of its appearance on the basal side. This aqueous medium, of pH = 7.4, has the following composition: NaCl = 8.0 g/l; KCl = 0.4 g/l; $CaCl_2$ = 0.19 g/l; $MgCl_2$ = 0.1 g/l; $MgSO_4$ = 0.1 g/l; Na_2HPO_4 = 0.09 g/l; KH_2PO_4 = 0.06 g/l; $NaHCO_3$ = 0.35 g/l; glucose = 1 g/l; phenol red = 0.01 g/l.

The coefficient of permeability P, in cm/sec, is then determined which characterizes the speed of passage of the molecule across the membrane, namely:

$$P = \frac{da}{dt.A.Co}$$

in which:

$\frac{da}{dt}$ = variation of the quantity of test compound crossing the cellular monolayer as a function of time (mol/s)

A = surface area of the monolayer (cm^2)

Co = initial concentration of the test compound (mol/l)

It is also possible to express these results as % of test product transported

1st series of tests

An injectable composition (hereinafter Composition A) of the following formulation was tested:

	% by weight
Compound α	0.4
PEG 400	7.49
Polyvinylpyrrolidone	1.87

Polysorbate 80	1.98
Water	qs* 100

qs* = sufficient quantity

and this, in comparison with control compositions placed in the apical compartment, one consisting of a 100 µmolar suspension of Compound α in gum arabic (Composition I), the other of the same Compound α solubilized at the same concentration in dimethyl sulphoxide (Composition II).

The following results were obtained:

Composition	% Compound α transported per hour
I	1.2 ± 0.6
II	6.5 ± 0.4
A	10.5 ± 0.5

These results show a marked improvement in the transepithelial passage for Compound α compared with the control compositions.

2nd series of tests

The following compositions for oral administration, in which the compound to be studied is Compound α, were tested. The compositions below were used such that Compound α is incubated at 50 µmolar in Hank's solution.

a) Dilutable anhydrous concentrated compositions

Composition	C	D	E
Compound α	2%	2%	2%
PEG 400	89%	-	33.5%
TRANSCUTOL®	-	89%	55.5%
Polysorbate 80	9%	9%	9%

b) Dispersible anhydrous concentrated compositions

Composition	F	G
Compound α	6%	6%
PEG 400	33%	33%
TRANSCUTOL®	55%	55%
Polysorbate 80	-	6%
PLURONIC® P94	6%	-

The Compositions C to G were diluted (Compositions C to E) or dispersed (Compositions F and G) in Hank's medium.

By way of comparison, the passage of Compound α into control compositions was also evaluated, that is to say that Compound α is solubilized at the same concentration in dimethyl sulphoxide (Composition II) and then dispersed in Hank's medium or Compound α (Composition III) is suspended in Hank's medium, as well as the passage of Compound α into a surfactant-free composition of formulation:

Composition IV

Compound α	6%
PEG 400	35%
TRANSCUTOL®	59%

The coefficient of permeability of Compound α in the control composition in suspension (Composition III) was brought to 1 whereas the other coefficients were expressed in relation to this control.

The following results were obtained:

	Compositions							
	which are controls		which are dilutable			which are dispersible		
Coefficient of permeability relative to the control	II	III	C	D	E	F	G	IV
	8.33 ± 0.78	1 ± 0.16	10.8 ± 1.1	10.4 ± 1.2	10.8 ± 1.0	10.8 ± 1.0	14.2 ± 1.2	5.08 ± 1.2

These results show that among the compositions studied, the formulation free of surfactant (Composition IV) does not enhance the passage compared with the solution in dimethyl sulphoxide (Composition II). An improvement is nevertheless observed compared with the control in suspension (Composition III). This improvement is particularly marked when the formulations with surfactant are compared with the formulation in suspension (Composition III) since the passage is multiplied by at least 10.

In addition, it should be noted that:

- the two cosolvents tested, namely PEG 400 or PEG 400/ TRANSCUTOL® product, present in the dilutable formulations, are not distinguishable from the point of view of the transepithelial passage,
- the fact of having formulations which are practically dispersible and not completely dilutable does not appear to be discriminating,
- the presence of the surfactant favourably influences the passage since the coefficient of permeability is at least twice as high as in the case of the surfactant-free composition (Composition IV). This favourable influence of the surfactant is linked to its stabilizing and/or promoting effect.

3rd series of tests

The Composition H of the invention which can be used in a soft gelatin capsule was tested, namely:

Composition H

Compound α	21 mg
PEG 400	294 mg
TRANSCUTOL®	21 mg
Polysorbate 80	14 mg
	350 mg

and this compared with compositions with a similar concentration of Compound α but not included in the invention:

Composition V: Compound α suspended in Hank's culture medium

Composition VI: Compound α dissolved in dimethyl sulphoxide and then introduced into Hank's culture medium

Composition VII (capable of being used in a gelatin capsule):

Compound α	20.00 mg
Modified maize starch	131.45 mg
Lactose monohydrate (extra fine crystals)	311.75 mg
Talc	9.60 mg
Anhydrous colloidal silica	2.40 mg
Magnesium stearate	4.80 mg
	480.00 mg

The above compositions were used such that Compound α is incubated at 100 µmolar in Hank's solution.

The percentages were then determined relative to Compound α transported on the basal side at time 6 hours and the results were expressed relative to the result for Composition V (suspension) adjusted to 1. The following results were obtained:

Composition	Percentages
V	1.0 ± 0.4
VI	10.1 ± 0.8
VII	2.8 ± 0.3
H	11.2 ± 0.7

These results show that Compositions VI, VII and H improve the passage of Compound α compared with the suspension of this compound (Composition V).

However, the improvement provided by Composition VII which is capable of being used in a gelatin capsule is much less than the improvement recorded with Composition VI which is soluble with the aid of dimethyl sulphoxide. Composition H, which is capable of being used in a soft gelatin capsule, allows for its part a very high improvement in the passage, an improvement which even proves to be greater than that observed with the solution of Compound α in dimethyl sulphoxide (Composition VI).

They confirm, in addition, that the solubilization step has a decisive impact on the transepithelial passage of Compound α and that the surfactant exhibits an absorption-promoting effect while maintaining the solubilized state.

4th series of tests

The compositions below were used on Caco-2 cells in quantities such that Compound α is incubated at 100 µmolar in a Hank's solution supplemented with taurocholic acid and phospholipid at 37°C.

Thus, the semisolid Compositions L, M and N of the invention and a Composition K not included in the invention were tested in comparison with the liquid Composition J of the invention, namely:

Composition	J	K	L	M	N
Compound α	6%	6%	6%	6%	12%
PEG 400	83.9%	-	-	-	-
PEG 600	-	47%	45%	-	-
PEG 1500	-	47%	45%	-	-
GELUCIRE® 44-14	-	-	-	94%	88%
TRANSCUTOL®	6.1%	-	-	-	-
Polysorbate 80	4.0%	-	4%	-	-

The coefficient of permeability of the reference Composition J was adjusted to 1 whereas the other coefficients were expressed relative to this reference composition.

The following results were obtained:

	Composition				
Coefficient of permeability	J	K	L	M	N
	1	0.67	0.98	1.9	2.45

These results show that the passage of PEG 400 to the 50/50 PEG 600/PEG 1500 mixture (Composition L) does not modify the coefficient of permeability measured on Caco-2 cells, when the surfactant, in this case polysorbate 80, remains present in the composition.

In addition, it was observed that Compositions M and N based on GELUCIRE® 44-14 product allow a speed of transepithelial transport about twice as high as that obtained with Composition J which is capable of being used in a soft gelatin capsule.

It even appears that a margin of improvement exists with the GELUCIRE® 44-14 product which allows a higher concentration of Compound α and improves membrane permeability on Caco-2 cells.

From all these tests carried out on these Caco-2 cells, it has been possible, in particular, to conclude that the compositions of the invention allow improvement in transmembrane passage compared with the reference compositions without causing a destructuring effect on this membrane.

II. <u>Kinetics of dissolution of soft gelatin capsules containing Compound α</u>

The kinetics of dissolution of soft gelatin capsules containing 21 mg doses of Compound α was

determined, these capsules containing 350 mg of Composition H compared with that of hard gelatin capsules of the dry form containing 20 mg doses of Compound α and containing 480 mg of Composition VII.

This dissolution was carried out at 37°C in hydrochloric acid pH = 1.2, the stirring speed being 100 revolutions/min.

The results show a marked improvement in the kinetics of dissolution of the soft gelatin capsules compared with that of the hard gelatin capsules: upon opening the capsules, that is to say after 7 min, a complete dissolution of Compound α is observed, whereas only 65% is achieved after 15 min in the case of the hard gelatin capsules as shown in Figure 3 in the annex.

In addition, if the dissolution medium for the soft gelatin capsules is filtered, it is observed that the entire Compound α is in microdispersed form of size < 0.2 micron.

Similar tests carried out with formulations of Compound α in the GELUCIRE® 44-14 product have shown a speed of transport about twice as high as that obtained with the formulation of Composition VII.

III. Tests in vivo in dogs

Plasma assays were carried out in dogs after oral administration of 20 mg of Compound α, that is to say in the form of Composition H introduced in a soft gelatin capsule or in the form of Composition VII introduced in a hard gelatin capsule.

Compared with the hard gelatin capsule, the administration of the soft gelatin capsule containing Composition H results in:

- a decrease in the variability of the plasma levels
- a relative bioavailability increased 3 to 4-fold
- a maximum concentration (Cmax) increased 3-fold

IV. Tests in vivo in man

The microdispersible liquid Composition H was compared with two other formulations having the same Compound α concentration, introduced into a hard gelatin capsule, one with micronized active ingredient, the other with nonmicronized active ingredient.

To this effect, clinical tests were carried out on 24 healthy male volunteers who had received 100 mg of Compound α:

1) on an empty stomach in the form of gelatin capsules containing Composition VII obtained from nonmicronized Compound α (Treatment A)
2) on an empty stomach in the form of gelatin capsules containing Composition VII obtained from micronized Compound α (Treatment B)
3) in the form of gelatin capsules containing Composition VII obtained from micronized Compound α, as well as food (Treatment C)
4) on an empty stomach in the form of soft gelatin capsules containing Composition H (Treatment D).

Blood tests were then carried out 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 24, 48 and 72 hours after administration, then the maximum concentrations of Compound α (Cmax) as well as the area under the curves defined by the concentration of Compound α as a function of time (AUC) were then noted.

The results were expressed in relation to the result of Treatment A taken as 1

Treatment	**Cmax** (ng/ml)	**AUC** (ng.h/ml)	**Ratio** of the Cmax values	**Ratio** of the AUC values
A	5.50	39.47	1	1
B	23.26	93.45	4.2	2.4
C	38.12	142.46	6.9	3.6
D	121.31	231.16	22.1	5.9

These results show a very high increase in bioavailability for Composition H, namely:

- a Cmax multiplied by 22
- a relative bioavailability multiplied by 6

in favour of the composition of the invention.

The following nonlimiting examples illustrate the preparation of pharmaceutical dosage forms according to the invention:

EXAMPLE 1

Injectable composition of Compound α

An injectable composition of the following formulation is prepared

	% by weight
Compound α	0.4
PEG 400	7.49
PVP KOLLIDON® 12 PF	1.87
TWEEN® 80	1.98
WATER for injection sufficient quantity	100

by applying the following process:

The solvent for solubilizing Compound α is first prepared by mixing 50 parts of PVP KOLLIDON® 12 PF containing 25% water with 50 parts of PEG 400 so as to constitute a solvent consisting of 12.5% PVP KOLLIDON® 12 PF, 37.5% water and 50% PEG 400.

26 mg of Compound α are then incorporated per g of solubilization solvent thus prepared and 0.2 g of this mixture is removed and 0.026 g of polysorbate 80 is added to it, with stirring. 1.074 g of water for injection is then introduced and the mixture is homogenized at room temperature.

EXAMPLE 2

Soft gelatin capsule of Compound α

Soft gelatin capsules containing a composition of the following formulation are obtained:

	% by weight

Compound α	6
PEG 400	83.9
TRANSCUTOL®	6.1
MONTANOX® 80 DF	4

by applying the following procedure:

The solubilizing/stabilizing system is first prepared from:

	% by weight
PEG 400	89.25
TRANSCUTOL®	6.5
MONTANOX® 80 DF	4.25

and then 60 mg of Compound α are incorporated per g of final composition, with mechanical stirring and at room temperature.

After solubilization, the composition formed is introduced into soft gelatin capsules.

EXAMPLE 3

Hard gelatin capsule of Compound α

Hard gelatin capsules containing a composition of the following formulation are obtained:

	% by weight
Compound α	6
GELUCIRE® 44-14	94

by applying the following procedure:

Compound α is solubilized directly in the GELUCIRE® 44-14 product at controlled temperature (about 55°C), with mechanical stirring.

After solubilization, the composition formed is introduced into hard gelatin capsules and cooled.

EXAMPLE 4

Hard gelatin capsule of Compound α

Hard gelatin capsules containing a composition of the following formulation are obtained:

	% by weight
Compound α	6
PEG 600	45
PEG 1500	45

TWEEN® 80 4

by applying the following procedure:

A 50/50 PEG 600/PEG 1500 mixture by weight is prepared, with stirring and at a temperature of 55°C, until homogenization is obtained.

42 g of TWEEN® 80 product are then incorporated per 100 g of PEG 600/PEG 1500 mixture so as to constitute a 4% solution of TWEEN® 80 product in the PEG 600/PEG 1500 mixture.

The mixture is stirred at 55°C until homogenization is obtained, then Compound α is introduced directly into the solubilizing/stabilizing system thus constituted, at 55°C.

By following the methods described in Examples 2 to 4 above, soft gelatin capsules or hard gelatin capsules containing compositions of the following formulations were prepared. The percentages are expressed by weight relative to the weight of the final composition.

EXAMPLE 5

Compound α	12.5%
PEG 2000	79.5%
TWEEN® 20	8%

EXAMPLE 6

Compound α	12.5%
PEG 2000	79.5%
TWEEN® 80	8%

EXAMPLE 7

Compound α	12.5%
PEG 2000	79.5%
TWEEN® 80/SPAN® 20 (69/31)	8%

EXAMPLE 8

Compound α	12.5%

PEG 2000	75.5%
TWEEN® 20	12%

EXAMPLE 9

Compound α	12.5%
PEG 2000	75.5%
TWEEN® 80	12%

EXAMPLE 10

Compound α	12.5%
PEG 2000	75.5%
TWEEN® 80/SPAN® 20 (69/31)	12%

EXAMPLE 11

Compound α	12.5%
PEG 2000	75.5%
GELUCIRE® 44-14	12%

EXAMPLE 12

Compound α	12.5%
PEG 2000	75.5%
GELUCIRE® 50-13	12%

EXAMPLE 13

Compound α	12.5%
GELUCIRE® 44-14	87.5%

EXAMPLE 14

Compound α	12.5%
TWEEN® 80	8%
GELUCIRE® 44-14	79.5%

EXAMPLE 15

Compound α	12.5%
TWEEN® 80	12%
GELUCIRE® 44-14	75.5%

EXAMPLE 16

Compound α	12.5%
GELUCIRE® 50-13	87.5%

EXAMPLE 17

Compound α	12.5%
TWEEN® 80	8%
GELUCIRE® 50-13	79.5%

EXAMPLE 18

Compound α	12.5%
TWEEN® 80	12%
GELUCIRE® 50-13	75.5%

EXAMPLE 19

Compound α	6%
PEG 400	90%
TWEEN® 80	4%

EXAMPLE 20

Compound α	6%
PEG 400	90%
PLURONIC® F127	4%

EXAMPLE 21

Compound α	6%
PEG 400	74%
PLURONIC® F127	20%

EXAMPLE 22

Compound α	15%
PEG 400	81%
PLURONIC® F127	4%

EXAMPLE 23

Compound α	15%
PEG 400	65%
PLURONIC® F127	20%

EXAMPLE 24

Compound α	12.5%
PEG 400	67.5%
TWEEN® 80	20%

EXAMPLE 25

Compound α	12.5%
PEG 400	71.5%
TWEEN® 80	16%

EXAMPLE 26

Compound α	12.5%
PEG 400	71.5%
TWEEN® 80/SPAN®20(69/31)	16%

EXAMPLE 27

Tablet of Compound α

Tablets having the following formulation are obtained:

	mg	% by weight
Compound α	50	2.21
Lactose monohydrate	690	30.46
Pregelatinized starch	1002	44.23
Polyvinylpyrrolidone	58.18	2.57
Sodium carboxymethylcellulose	115.1	5.08
GELUCIRE®44-14	350	15.45
	2265.28	100

by applying the following procedure:

The product GELUCIRE® 44-14 is melted at about 60°C, then compound α is dissolved therein. The remaining excipients are then mixed and the mixture obtained is granulated with the solution of compound α.

EXAMPLE 28

Hard gelatin capsule of compound α

Hard gelatin capsules having a formulation identical to that of Example 27 are obtained by melting the product GELUCIRE® 44-14 at 60°C and then dissolving compound α therein. The remaining excipients are then mixed and the mixture obtained is granulated with the solution of compound α. The granules formed are sieved and introduced into hard gelatin capsules.

EXAMPLE 29

Tablet of Compound α

Tablets having the following formulation are obtained:

	mg	% by weight
Compound α	50	2.21
Lactose monohydrate	690	30.46
Pregelatinized starch	1002	44.23
Polyvinylpyrrolidone	58.18	2.57
Sodium carboxymethylcellulose	115.1	5.08
PEG 2000	302	13.33
TWEEN®20	48	2.12
	2265.28	100

by applying the following procedure:

The mixture PEG 2000/TWEEN®20 is melted at about 60°C, then compound α is dissolved therein.

The remaining excipients are then mixed and the mixture formed is granulated with the solution of compound α. The granules obtained are sieved and compressed.

Dissolution tests carried out at 37°C in an aqueous medium of pH = 1.2 using the tablet thus obtained showed that this compound α is completely dissolved after 15 minutes.

EXAMPLE 30

Using an identical procedure, tablets having the following formulation were prepared:

	mg
Compound α	50
Lactose monohydrate	690
Pregelatinized starch	1002
Polyvinylpyrrolidone	58.18
Sodium carboxymethylcellulose	115.1
PEG 6000	302
TWEEN®20	48
	2265.28

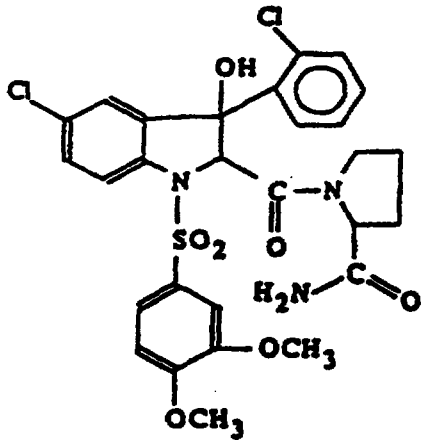
EXAMPLE 31

Hard gelatin capsule of compound α

Hard gelatin capsules having a formulation identical to that of Example 29 are obtained by melting the mixture PEG 2000/TWEEN®20 at about 60°C and dissolving compound α therein. The remaining excipients are mixed and then the mixture formed is granulated with the solution of compound α. The granules obtained are sieved and introduced into hard gelatin capsules.

CLAIMS

1. Anhydrous solubilizing/stabilizing system, emulsifiable or microemulsifiable in water, for the solubilization of hydrophobic derivatives of N-sulphonylindoline of formula:



characterized in that it comprises one or more constituents selected from amphiphilic compounds, nonionic hydrophilic surfactants and nonionic hydrophilic compounds endowed with both amphiphilic and surfactant properties, it being understood that the said system comprises either at least one mixture of an amphiphilic compound and of a nonionic hydrophilic surfactant, or at least one nonionic hydrophilic compound endowed with both surfactant and amphiphilic properties.

2. Solubilizing/stabilizing system according to Claim 1, characterized in that it comprises one or more glycol-type amphiphilic compounds selected from propylene glycol, polyethylene glycols and glycol ethers, the system also comprising one or more nonionic hydrophilic surfactants.

3. Solubilizing/stabilizing system according to Claim 1, characterized in that it comprises one or more nonionic hydrophilic compounds which are both amphiphilic and surfactant, selected from saturated polyglycolysed glycerides, the system optionally comprising one or more nonionic hydrophilic surfactants

and optionally one or more glycol-type amphiphilic compounds.

4. Solubilizing/stabilizing system according to Claim 1 or 2, characterized in that it is in liquid form and comprises one or more glycol-type amphiphilic compounds selected from propylene glycol and polyethylene glycols having an average molecular weight of between 400 and 600, the system comprising, in addition, one or more nonionic hydrophilic surfactants having an HLB value of between 12 and 22 and optionally a diethylene glycol ether.

5. Solubilizing/stabilizing system according to Claim 1 or 2, characterized in that it is in liquid form and comprises one or more glycol-type amphiphilic compounds selected from propylene glycol, polyethylene glycols having an average molecular weight of between 400 and 600 and diethylene glycol ethers, the system also comprising one or more nonionic hydrophilic surfactants having an HLB value of between 12 and 22.

6. Solubilizing/stabilizing system according to Claim 1 or 2, characterized in that it is in semisolid form and comprises one or more glycol-type amphiphilic compounds selected from polyethylene glycols having an average molecular weight of between 600 and 2000, the system also comprising one or more nonionic hydrophilic surfactants having an HLB value of between 12 and 22.

7. Solubilizing/stabilizing system according to Claim 1 or 2, characterized in that it is in semisolid form and comprises one or more glycol-type amphiphilic compounds selected from polyethylene glycols having a molecular weight of between 2000 and 10,000, the system also comprising one or more nonionic hydrophilic surfactants having an HLB value of between 12 and 22.

8. Solubilizing/stabilizing system according to Claim 1 or 3, characterized in that it is in semisolid form and comprises one or more nonionic hydrophilic compounds which are both amphiphilic and surfactant and which are saturated polyglycolysed glyceride deriva-

* C L M S *

tives consisting of mixtures of monoesters, diesters and triesters of glycerol and fatty acids, and of mono- and diesters of polyethylene glycol and fatty acids, the system optionally comprising one or more nonionic hydrophilic surfactants having an HLB value of between 12 and 22 and optionally one or more glycol-type amphiphilic compounds selected from polyethylene glycols having an average molecular weight of between 600 and 10,000.

9. Solubilizing/stabilizing system according to one of Claims 1, 2, 4 or 5, characterized in that the amphiphilic compound, which is a polyethylene glycol having an average molecular weight of between 400 and 600, is polyethylene glycol 400.

10. Solubilizing/stabilizing system according to one of Claims 1, 2, 6 or 8, characterized in that the amphiphilic compound, which is a polyethylene glycol having an average molecular weight of between 600 and 2000, is polyethylene glycol 1000, polyethylene glycol 2000 or a 50/50 mixture by weight of polyethylene glycol 600/polyethylene glycol 1500.

11. Solubilizing/stabilizing system according to one of Claims 1 to 8, characterized in that the surfactant is polysorbate 80.

12. Solubilizing/stabilizing system according to one of Claims 1, 2, 4 or 5, characterized in that the amphiphilic compound, which is a glycol ether, is a diethylene glycol mono(C_1-C_4 alkyl) ether.

13. Solubilizing/stabilizing system according to Claim 12, characterized in that the diethylene glycol mono(C_1-C_4 alkyl) ether is diethylene glycol monoethyl ether having the trademark TRANSCUTOL®.

14. Solubilizing/stabilizing system according to one of Claims 1, 3 or 8, characterized in that the compound which is both amphiphilic and surfactant is a mixture of monoesters, diesters and triesters of glycol, and of mono- and diesters of polyethylene

glycol, a mixture of trademark GELUCIRE® 44-14 or GELUCIRE® 50-13.

15. Pharmaceutical composition, which is micro-emulsifiable or emulsifiable in an aqueous medium, characterized in that it comprises:

- a hydrophobic derivative of N-sulphonylindoline according to Claim 1
- a solubilizing/stabilizing system according to one of Claims 1 to 14
- optionally an appropriate pharmaceutical excipient or vehicle.

16. Pharmaceutical composition according to Claim 15 for injectable administration, characterized in that it comprises:

- a hydrophobic derivative of N-sulphonylindoline according to Claim 1
- a solubilizing/stabilizing system as defined in Claim 4 and optionally comprising the additional features of Claims 9, 11, 12 or 13
- an appropriate pharmaceutical vehicle.

17. Pharmaceutical composition according to Claim 16, characterized in that the pharmaceutical vehicle is water and/or a polyvinylpyrrolidone.

18. Pharmaceutical composition according to Claim 16 or 17, characterized in that the hydrophobic derivative of N-sulphonylindoline does not exceed 1% by weight of the composition.

19. Pharmaceutical composition according to Claim 15 in liquid form and for oral administration, characterized in that it comprises:

- a hydrophobic derivative of N-sulphonylindoline according to Claim 1
- a solubilizing/stabilizing system as defined in Claim 5 optionally comprising the additional features of Claims 9, 11 or 13.

20. Pharmaceutical composition according to Claim 15 in semisolid form and for oral administration, characterized in that it comprises:

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- a hydrophobic derivative of N-sulphonylindoline according to Claim 1
- a solubilizing/stabilizing system as defined in one of Claims 6, 7 or 8 and optionally comprising the additional features of Claims 10, 11 or 14.

21. Pharmaceutical composition according to Claim 19 or 20, characterized in that the hydrophobic derivative of N-sulphonylindoline does not exceed 15% by weight of the composition.

22. Pharmaceutical composition according to one of Claims 16 to 18, characterized in that, in the solubilizing/stabilizing system, the diethylene glycol ether does not exceed 50% by weight of the composition.

23. Pharmaceutical composition according to one of Claims 16 to 18, characterized in that the solubilizing/stabilizing system contains a nonionic hydrophilic surfactant at a concentration not exceeding 4% by weight of the composition.

24. Pharmaceutical composition according to Claim 15 in solid form and for oral administration, characterized in that it comprises:

- a hydrophobic derivative of N-sulphonylindoline according to Claim 1
- a solubilizing/stabilizing system according to one of Claims 7 or 8 and optionally comprising the additional features of Claims 11 or 14
- an appropriate pharmaceutical excipient or vehicle

25. Pharmaceutical composition according to one of Claims 19 to 24, characterized in that the solubilizing/stabilizing system contains a nonionic hydrophilic surfactant at a concentration not exceeding 12% by weight of the composition.

26. Pharmaceutical composition according to one of Claims 15 to 25, characterized in that the hydrophobic derivative of N-sulphonylindoline is (2S)-1-[(2R,3S)-(5-chloro-3-(2-chlorophenyl)-1-(3,4-dimethoxyphenyl-

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sulphonyl)-3-hydroxy-2,3-dihydro-1H-indole-2-carbonyl]-pyrrolidine-2-carboxamide.

27. Pharmaceutical soft gelatin capsule, characterized in that it contains a pharmaceutical composition in liquid form for oral administration according to one of Claims 19, 21, 25 or 26.

28. Pharmaceutical hard gelatin capsule, characterized in that it contains a pharmaceutical composition in semisolid form for oral administration according to one of Claims 20, 21, 25 or 26.

29. Pharmaceutical composition according to one of Claims 24 to 26, characterized in that it is in the form of a powder, a granule or a tablet.

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