(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 273 890 B1**

(12) # EUROPEAN PATENT SPECIFICATION

(45) Date of publication of patent specification: **31.03.93** (51) Int. Cl.5: **A61K 9/50**, A61K 9/10

(21) Application number: **87850382.0**

(22) Date of filing: **07.12.87**

(54) **A liquid dosage form for oral administration of a pharmaceutically active substance.**

(30) Priority: **22.12.86 SE 8605515**

(43) Date of publication of application:
06.07.88 Bulletin 88/27

(45) Publication of the grant of the patent:
31.03.93 Bulletin 93/13

(84) Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

(56) References cited:
EP-A- 69 097
EP-A- 101 418
EP-A- 257 915
WO-A-81/00205
WO-A-88/01165
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GB-A- 1 380 206

CHEMICAL ABSTRACTS, vol. 95, 1981, Columbus, OH (US); no. 225549x*

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EP 0 273 890 B1

Description

Technical field

The present invention relates to a liquid dosage form for oral administration containing microspheres or microcapsules of a pharmaceutically active substance which substance has either an unpleasant taste or which substance is unstable in aqueous solution or both.

The present invention also relates to a method of masking unpleasant taste of a pharmaceutically active substance administered in the form of a solution or suspension and to increase the stability properties of an unstable pharmaceutically active substance administered in the form of a solution or suspension using a pharmaceutically acceptable oil.

Background of the Invention

Many pharmaceutically active substances have a very unpleasant taste, and they are therefore not suited for oral administration in the form of solutions or suspensions. Because the administration by solutions or suspensions is a very suitable one and in some cases the only oral way feasible, (e.g. when a patient can not accept tablets or capsules) the problem is a serious one. Thus, for administration to children and elderly, oral suspensions or solutions may be advantageous. In the former case, taste is very important in order to have a high patient compliance.

The problem of masking the unpleasant taste of a pharmaceutically active substance in connection with a liquid dosage form for oral administration and where the substance is microencapsulated has been tackled in different ways.

In EP 69097 the combination of a microencapsulated active substance with a basic substance prior to preparing a ready to use aqueous suspension is described.

In EP 101418 the combination of a microencapsulated active substance with a high content of sugar prior to preparing a ready to use aqueous suspension is described.

The object of the present invention is to provide a ready to use suspension of a pharmaceutically active substance intended to be administered orally wherein the unpleasant taste of the substance has been masked by combining the principles of microencapsulation and a pharmaceutically acceptable oil wherein the encapsulated drug is practically insoluble.

Many pharmaceutically active compounds degrade when dissolved in aqueous or hydrophilic solvents. In order to delay this mechanism, preparations have been formulated where the active compound is reconstituted with water prior to use. In many cases, the suspensions or solutions need to be stored in a cold place. A great improvement would therefore be to have a stable formulation from the manufacturer where the active compound is already suspended in a liquid vehicle. However, when it is not possible to make an ready to use suspension, due to physicochemical reasons, the application of microencapsulation in a water repellant sphere can be used in order to increase the solid state stability. Thus, the microspheres or microcapsules can also be mixed with a granulation for reconstitution which creates a more stable system compared to a conventional granulation for reconstitution.

A further object of the invention is therefor to increase the stability of a pharmaceutically active substance which is unstable in aqueous or hydrophilic solution or suspension.

A still further object of the invention is to provide controlled release properties of the dosage form according to the invention, thus combining a controlled release with good taste and high stability.

Disclosure of the invention

Aqueous suspensions have been used in all prior attemps to tackle the problem of masking unpleasant taste of a liquid oral formulation using a microencapsulated pharmaceutically active substance.

It has now been found that the unpleasant taste of a pharmaceutically active compound intended to be administered orally in the form of a suspension can be asked if the active compound which must be microencapsulated is mixed with a vehicle which consists of a pharmaceutically acceptable oil, in which the encapsulated drug shows no or extremely low solubility. Hence, it is the combination of a microencapsulated drug and the application of a pharmaceutically acceptable oil which makes this particular invention unique.

The present invention provides an improved liquid delivery system for active compounds which have an unpleasant taste. It is also advantageous compared to conventional suspensions or solutions since it prevents the active compound from degrading in the liquid medium. The mechanism behind this phenom-

enon is first the application of a liquid carrier in which the active compound is not soluble or soluble to a very low extent and secondly the fact that the active compound is microencapsulated. Since the active compound is microencapsulated the risk for obtaining an unpleasant taste in the mouth due to dilution or washing of the non-aqueous liquid is reduced due to a delayed release of the active compound from the microcapsules in aqueous media. The combination of these two factors is a solid ground for obtaining the above mentioned properties. However, as mentioned above, the application of microcapsules may also be advantageous for a granulation for aqueous reconstitution in terms of solid state stability before reconstitution.

By replacing the aqueous vehicle with a pharmaceutically acceptable oil and by microencapsulating the active compound the following advantages are obtained:

- The active substance can be prepared in a liquid formulation which is ready to use. These types of formulations are otherwise normally delivered as a dry powder which has to be mixed with water prior to use. Such a product has relatively bad keeping qualities. Besides, this operation is costly in countries where the pharmacies fulfill them. In countries where the patient himself has to add water the risk of mistakes could not be disregarded. In a manufacturing point of view it is often advantageous to handle a liquid product instead of a dry powder and thus avoiding problems in connection with the production environment.
- The formulation of a microencapsulated active substance in a non-aqueous vehicle not only provides risking of an unpleasant taste but affords also enhanced stability. This property is particularly valuable in connection with compounds normally unstable in liquid vehicles, for instance penicillins.
- Furthermore the formulation according to the invention affords controlled release properties to the formulation.

All those pharmaceutically active substances which have an unpleasant taste or which are unstable in solution are well suited for use in connection with this invention. Examples of such active substances are

Chemoterapeutics	**bacampicillin, ampicillin, flucloxacillin, tetracycline, dicloxacillin, chloramphenicol, gentamicin, erythromycin, lincomycin, rifampicin, sulphadiazine, sulphamethoxypyridazine, griseofulvine, nitrofurantoine, penicillin V, penicillin G, cephalosporin derivatives.**
Adrenergic and betareceptor-stimulators	**ephedrine, terbutaline, theophylline, enprophylline**
Expectorants and cough depressants	**Ethylmorphine, dextromethorphan, noscapine, bromhexine**

Heart glucosides and antiarythmics	Digitoxine, digoxin, dispyramide, procainide, tocainide, alprenolol, atenolol, metoprolol pindolol, propranolol
Blood pressure depressants	betanidine, clonidine, guanetidine, methyldopa, reserpine, trimetaphane, hydrolazine, bendrophlumetiazide, furosemide, chlorotiazide
Antihistamines	brompheniramine, chlorcyclizine, chlorpheniramine, diphenhydramine, prometazine
Peroral antidiabetes	carbutamide, chlorpropamide, tolazamide, tolbutamide
Sedatives Hypnotics Antidepressants Antipsychotics	meprobamate, chlordiazepoxide, diazepam,buspirone, flunitrazepam, nitrazepam, oxazepam, chloromethiazol, chlorpromazine, fluphenazine, perphenazeine prochloroperazin, haloperidol, lithium, alaproclate, zimeldine, amitryptiline, imipramine, nortriptyline, remoxipride, raclopride
Antiepileptics	phenytoine, ethotoin, ethosuximide, carbamazepine
Analgetics Anesthetics	codeine, morphine, pentazocine, petidine, dextropropoxyphene, methadone, acetylsalicylic acid, diflunisal, phenazone, phenylbutazon, acetaminophene, indometazine, naproxen, piroxicam, lidocaine, etidocaine
Others	cimetidine, quinidine, dicoumarine, warfarine, potassium chloride, chloroquine

Preferred active substances are remoxipride, raclopride, penicillins, cephalosporins, alaproclate, buspirone, diazepam and other bensodiazepins.

Particularly preferred compounds are remoxipride, acetaminophen, phenoxymethylpenicillin, bacampicillin, bensylpenicillin, flucloxacillin and cephalosporin derivatives.

The active substances mentioned above are used in neutral or salt form.

Any salts of the active substances mentioned above can be used, for instance
Acetate, benzenesulfonate, benzoate, bicarbonate, bitartrate, bromide, calcium edetate, camsylate, carbonate, chloride, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malte, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, pamoate, (embonate), pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulphate, tannate, tartrate, teoclate, triethiodide.

Also the further cationic salts can be used. Suitable cationic salts include the alkali metal, e.g. sodium and potassium, and ammonium salts and salts of amines known in the art to be pharmaceutically acceptable, e.g. glycine, ethylene diamine, choline, diethanolamine, triethanolamine, octadecylamine, diethylamine, triethylamine, 1-amino--2-propanol-2-amino-2-(hydroxymethyl)propane-1,3-diol and 1-(3,4-dihydroxyphenyl)-2-isopropylaminoethanol.

Coating materials

Coating material to be used are ethylcellulose, bees wax and carnauba wax.

Combinations of the above mentioned polymers and waxes can be used for encapsulation purposes. More particular the coating consists of either a single wall encapsulation in which case the coating material is selected from the group consisting of carnauba wax, ethylcellulose and a combination of carnauba wax and bees wax or a dual wall encapsulation in which case the pharmaceutically active substance is encapsulated in ethylcellulose, carnauba wax and bees wax.

The microcapsules useful for the present invention can be prepared by any of several acknowledged microencapsulation processes or microsphere production processes including pan coating, prilling, extrusion and spheronization, fluid bed processes, spray drying, spray chilling coacervation and other processes.

Microspheres or microcapsules in the size range of 10-1000 microns are suitable for being suspended in the liquid carrier. Preferably, the size range of 50-150 µm are used since this size range is small enough in order to give a smooth appearance in the mouth which is especially important for pediatric formulations. This size range can easily be obtained by means of e.g. spray chilling or spray drying and these processes are also suitable for generating controlled release microcapsules in the same size range. The size range of 50-150 µm is also preferred because of the low risk of crushing the spheres between the teeth after administration as it might be for larger beads.

Microcapsules

Microcapsules are defined as a solid or a liquid core enclosed in a coating. The coating may also be referred to as the wall or shell. Various types of microcapsule structures can be obtained depending on the manufacturing process, e.g. mononuclear spherical, multinuclear spherical, multinuclear irregular, encapsulated mononuclear capsules, dual-walled microcapsules etc. When no distinct coating and core region can be observed, the analogous terms are microparticles, microspheres, micromatrices or microbeads (c.f. multinuclear microcapsules above). The microcapsules usually have a particle size between 1 and 2000 µm. The preferred size range for this invention is 50-150 µm.

The microcapsules referred to in the present invention can thus be designed as micromatrices, overcoated micromatices or overcoated homogeneous microsphere cores.

Pharmaceutically acceptable oil

Pharmaceutically acceptable oil is e.g. hydrogenated coconut oil, such as Miglyol® and Viscoleo®, coconut oil, peanut oil, sesam oil, corn oil.

Emulsifying agents

Emulsifying agents (super active agents) to be used are for instance:

- bile salts or derivatives thereof
- propyl gallat
- sorbitan fatty acid esters
- polyoxyethylene sorbitan fatty acid esters
- polyoxyethylene sorbitol esters
- polyoxyethylene acids
- polyoxyethylene alcohols
- polyoxyethylene adducts not otherwise classified
- mono and diglycerides
- polyoxyethylene glyceryl fatty acid esters
- fusidic acid derivatives
- sodium lauryl sulphate

Preferred embodiments

A preferred embodiment of the present invention is obtained when remoxipride is encapsulated in carnauba wax and mixed with a vehicle consisting of hydrogenated coconut oil.

Other preferred embodiments are obtained when phenoxymethyl penicillin, bacampicillin, bensylpenicillin, flucloxacillin or acetaminophene are encapsulated in carnauba wax and mixed with a vehicle consisting of hydrogenated coconut oil.

Still other preferred embodiments are obtained when the active substance is encapsulated in either carnauba wax and beeswax or in ethyl cellulose, carnauba wax and bees wax and mixed with a vehicle consisting of hydrogenated coconut oil.

Still another preferred embodiment is obtained when the active substance is encapsulated in either carnauba wax, bees wax, carnauba wax and bees wax or ethyl cellulose and mixed with a vehicle consisting of hydrogenated coconut oil and a suitable emulsifying agent, e.g. bile salts.

The preparation is preferably made by adding the solid powders (i.e, flavouring agents and sugars) to the fluid component by mixing until a homogeneous suspension is obtained. Finally the microcapsules are added and gently mixed. The suspension can then be added to glass or plastic bottles. In some cases, a thickening agent is preferable to prevent a too rapid sedimentation of the suspended particles (e.g. aluminum monostearate, stearic acid, bees wax etc.)

Best mode of carring out the invention

Example 1

Remoxipride substance with a particle size less than 10 µm was suspended in a carnauba wax melt at 100 °C. The slurry was spray chilled into microspheres with a diameter between 50 and 125 µm.

Remoxipride microspheres consist of:

Remoxipride hydrochloride monohydrate	40 %
Carnauba wax	60 %

Composition of an oral suspension:

Remoxipride microcapsules	13.5 g
Sodium bicarbonate	0.84 g
Caramel flavour	0.50 g
Sucrose powder	35.50 g
Hydrogenated coconut oil	60.00 g

In a beaker the oil was added and the sucrose powder was added in small portions while stirring vigorously. Sodium bicarbonate and the flavouring component were added and finally the remoxipride microcapsules were added. The resulting product was a free flowing suspension with a nice appearance.

The taste of this product was judged by 10 people and was compared to an aqueous solution with the same concentration of remoxipride. The people was asked to judge if the product was acceptable from a taste point of view compared to the plain remoxipride solution.

Results:

	Acceptable	Not acceptable
The composition according to ex 1	10	0
Remoxipride aqueous solution	0	10

The invented product was superior to a non taste masked aqueous product. Thus the invented product has a very high degree of taste masking as the plain solution has a very bitter taste, which was the main comment from the test panel for the plain remoxipride solution.

Example 2

A suspension according to the present invention, containing remoxipride micromatrices (40 % remoxipride and 60 % wall material) was filled in no. 1 hard gelatin capsules. The capsules were administered to two male beagle dogs, and plasma was collected. As reference a solution of remoxipride was used. The dose of the oil suspension (the invented product) was 215 µmol and the solution was 250 µmol of remoxipride. The plasma concentrations of remoxipride were analyzed with a high pressure liquid chromatography method.

The maximum plasma concentration obtained (C_{max}) and the extent of bioavailability (AUC) are shown in the Table.

The C_{max} reflects the highest concentration of the drug. A drug that absorbs rapidly reaches a higher C_{max}-value than if it absorbs slowly. The area under the plasma concentration vs. time curve (AUC) reflects the amount of the drug that has been absorbed during the experimental period.

Results:

	C_{max} µmol/l		AUC µmolxh/l	
	Dog 1	Dog 2	Dog 1	Dog 2
The invented product	10.5	9.4	72	56
Remoxipride solution	11.9	11.2	72	58

It can easily be seen that the invented product is bioequivalent to a plain solution of remoxipride. As a matter of fact, if corrections are made for the dosing difference the invented product has 9 and 4 percent better bioavailability in the two dogs respectively. Thus, the taste masking efforts have no negative effect upon the biopharmaceutical properties of the drug.

Example 3

Controlled release microcapsules were prepared by means of spray chilling. The particles consisted of 16 % remoxipride hydrochloride monohydrate and 84 % carnauba wax/bees wax. Particles with a size between 53 and 106 µm were collected and used for further experiments.

The release rate of remoxipride from the microcapsules in water at 37 ° C is given below:

Percent (%) remoxipride released				
1h	2h	4h	6h	8h
56	66	80	86	92

The controlled release microcapsules were added to an oil formulation.

Composition:

Remoxipride controlled release microcapsules described above:	8.3g
Caramel flavour	0.5 g
Peppermint oil	0.5 g
Sucrose powder	41.0 g
Hydrogenated coconut oil	60.0 g

Caramel flavour, peppermint oil and sucrose powder were added to the oil and mixed vigorously. Then the controlled release microcapsules were added and gently mixed. The resulting product has thus controlled release properties and it is also taste masked.

Example 4

Dual-walled controlled release microcapsules were prepared by means of spray drying and spray chilling. The microcapsule core consisted of remoxipride hydrochloride monohydrate and ethyl cellulose. The cores were then overcoated with carnauba wax and bees wax, respectively. Particles with a size between 50 and 150 µm were collected and used for further experiments. The final content of remoxipride hydrochloride monohydrate was found to be 16 %.

The release rate of remoxipride from the microcapsules in water at 37 °C is given below:

Percent (%) remoxipride released							
2h	4h	6h	8h	10h	15h	20h	24h
30	38	45	53	58	70	76	81

The controlled release microcapsules were added to an oil formulation.

Composition:

Dual-walled remoxipride controlled release microcapsules	15.6 g
Caramel flavour	0.5 g
Peppermint oil	0.5 g
Sucrose powder	35.4 g
Hydrogenated coconut oil	60.0 g

Caramel flavour, peppermint oil and sucrose powder was added to the oil and mixed vigorously. Then the controlled release microcapsules were added and gently mixed. The resulting product has controlled release properties and it is also taste masked.

Example 5

Phenoxymethyl penicillin -K microcapsules consist of

Phenoxymethyl penicillin -K	40 %
Carnauba wax	60 %

The penicillin powder with a particle size less than 10 µm was suspended in a carnauba wax melt at 105 °C. The slurry was spray chilled into microspheres with a diameter between 50 and 125 µm.

Composition of an oral suspension:

Phenoxymethyl penicillin -K microcapsules	11.6 g
Lemon flavour	0.42 g
Strawberry flavour	0.70 g
Maltol	0.28 g
Sucrose powder	30.4 g
Hydrogenated coconut oil	56.5 g

The taste of this product was judged by seven people and was compared to a phenoxymethyl penicillin -K suspension on the market with the same dosage strength (KÅVEPENIN 50 mg/ml). The table summarizes the taste scores obtained where 0 denotes a very bad taste and 100 denotes a perfect taste.

Subject no.	New suspension	Market suspension
1	91	80
2	92	54
3	93	79
4	78	31
5	91	74
6	91	47
7	77	82
x	87.6	63.9

The data demonstrate a much better acceptance for the new type of suspension of phenoxymethyl penicillin -K. Also, the taste profile is more irregular for the market suspension and more uniform for the new one which shows that the new suspension has a much better taste in general.

Example 6

Bacampicillin hydrochloride substance with a particle size less than 10 µm was suspended in a carnauba wax melt at 100 °C. The slurry was spray chilled into microcapsules with a diameter between 50 and 125 µm.

Bacampicillin hydrochloride microcapsules consist of

Bacampicillin hydrochloride	25 %
Carnauba wax	75 %

Composition of an oral suspension

Bacampicillin microcapsules	14.14 g
Strawberry flavour	1.30 g
Lemon flavour	0.69 g
Maltol	0.29 g
Sucrose powder	25.08 g
Hydrogenated coconut oil	58.51 g

Example 7

Bacampicillin hydrochloride substance with a particle size less than 10 µm was suspended in a carnauba wax melt at 100 °C. The slurry was spray chilled into microcapsules with a diameter between 50 and 125 µm.

Bacampicillin hydrochloride microcapsules consist of

Bacampicillin hydrochloride	40 %
Carnauba wax	60 %

Composition of an oral suspension

Bacampicillin microcapsules	8.81 g
Strawberry flavour	1.30 g
Lemon flavour	0.69 g
Sucrose powder	20.00 g
Hydrogenated coconut oil	58.51 g

Example 8

Phenoxymethyl pencillin -K substance with a particle size less than 10 µm was suspended in a carnauba wax melt at 100 °C. The slurry was spray chilled into microcapsules with a diameter between 50 and 125 µm.

Phenoxymethyl penicillin -K microcapsules consist of

Phenoxymethyl penicillin -K	40 %
Carnauba wax	60 %

Composition of an oral suspension

Phenoxymethyl penicillin microcapsules	15.63 g
Strawberry flavour	0.35 g
Lemon flavour	0.15 g
Sucrose powder	61.91 g
Hydrogenated coconut oil	70.00 g

The stability of this product was investigated during storage at 25 °C and 37 °C for four months. The table shows the assayed quantity of degradation product (mg penicilloic acid/g suspension).

Storage Time	25 °C	37 °C
0	0.20 mg/g	0.20 mg/g
4 months	0.45 mg/g	0.60 mg/g

The result in the table shows that the invented formulation of phenoxymethylpenicillin -K is very stable. An increase of only 0.4 mg/g of penicilloic acid is obtained after 4 months' storage at an accelerated storage condition (37 °C). This corresponds only to about 1% in relation to the phenoxymethylpenicillin -K concentration in the suspension.

Example 9

Bensylpenicillin -K substance with a particle size less than 10 µm was suspended in a carnauba wax melt at 100 °C. The slurry was spray chilled into microcapsules with a diameter between 50 and 125 µm.

Bensylpenicillin -K microcapsules consist of

Bensylpenicillin -K	40 %
Carnauba wax	60 %

Composition of an oral suspension

Bensylpenicillin -K microcapsules	11.6 g
Lemon flavour	2.2 g
Strawberry flavour	2.8 g
Sucrose powder	41.1 g
Hydrogenated coconut oil	54.7 g

Example 10

Flucloxacillin -Na substance with a particle size less than 10 µm was suspended in a carnauba wax melt at 100 °C. The slurry was spray chilled into microcapsules with a diameter between 50 and 125 µm.

Flucloxacillin -Na microcapsules consist of

Flucloxacillin -Na	36 %
Carnauba wax	64 %

Composition of an oral suspension

Flucloxacillin -Na microcapsules	6.41 g
Strawberry flavour	1.32 g
Lemon flavour	0.70 g
Maltol	0.26 g
Sucrose powder	31.95 g
Hydrogenated coconut oil	59.34 g

Example 11

1.0 g of polyisobutylene was dissolved in 200 ml of cyclohexane under stirring and heating up to 80 °C. After the polyisobutylene was dissolved 1.0 g of ethylcellulose was dissolved. To the cyclohexane solution 2.0 g of Remoxipride hydrochloride monohydrate powder was suspended. Under stirring and controlled cooling, the resulting coated particles were collected and filtered off. The coated particles, or microcapsules, were washed with cool cyclohexane and then air-dried.

Composition:

Microcapsules described above	2.0 g
Butterschotch flavour	0.1 g
Sodiumbicarbonate	0.1 g
Sucrose powder	3.0 g
Peanut oil	8.0 g

The microcapsules, flavour, sodium bicarbonate and sucrose were added to the peanut oil and gently mixed. The resulting oral suspension was not tasting any bitterness of remoxipride.

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB IT, LI, LU, NL, SE

1. A liquid dosage form for oral administration of a pharmaceutically active substance comprising a pharmaceutically active substance suspended in a pharmaceutically acceptable oil, wherein the active substance is
   (a) single wall encapsulated wherein the coating material is selected from the group consisting of carnauba wax, ethylcellulose and a combination of carnauba wax and bees wax or
   (b) dual wall encapsulated wherein the pharmaceutically active substance is encapsulated in ethylcellulose, carnauba wax and bees wax.

2. A liquid dosage form according to claim 1, characterized in that the pharmaceutically acceptable oil is hydrogenated coconut oil.

3. A liquid dosage form according to claim 1, characterized in that the pharmaceutically active substance is encapsulated in carnauba wax.

4. A liquid dosage form according to claim 1, characterized in that the pharmaceutically active substance is encapsulated in carnauba wax and bees wax.

5. A liquid dosage form according to claim 1, characterized in that the pharmaceutically active substance is encapsulated in ethyl cellulose, carnauba wax and bees wax.

6. A liquid dosage form according to claim 1, characterized in that the active substance is remoxipride.

7. A liquid dosage form according to claim 1, characterized in that the active substance is selected from the group consisting of bacampicillin, penicillin V, bensylpenicillin and flucloxacillin.

8. A process for the preparation of a liquid dosage form for oral administration of a pharmaceutically active substance comprising a pharmaceutically active substance suspended in a pharmaceutically acceptable oil, wherein the active substance is
(a) single wall encapsulated wherein the coating material is selected from the group consisting of carnauba wax, ethylcellulose and a combination of carnauba wax and bees wax or
(b) dual wall encapsulated wherein the pharmaceutically active substance is encapsulated in ethylcellulose, carnauba wax and bees wax,
characterized in that optionally solid adjuvants are added to a pharmaceutically acceptable oil and mixed therewith until a homogenous suspension is obtained whereafter the pharmaceutically active substance in encapsulated form is added and gently mixed with the suspension.

9. A method of obtaining taste masking/controlled release/improved stability in a liquid oral formulation of a pharmaceutically active substance characterized in adding the pharmaceutically active substance in microencapsulated form to a vehicle consisting of a pharmaceutically acceptable oil, wherein the active substance is
(a) single wall encapsulated wherein the coating material is selected from the group consisting of carnauba wax, ethylcellulose and a combination of carnauba wax and bees wax or
(b) dual wall encapsulated wherein the pharmaceutically active substance is encapsulated in ethylcellulose, carnauba wax and bees wax.

Claims for the following Contracting States : ES, GR

1. A process for the preparation of a liquid dosage form for oral administration of a pharmaceutically active substance comprising a pharmaceutically active substance suspended in a pharmaceutically acceptable oil, wherein the active substance is
(a) single wall encapsulated wherein the coating material is selected from the group consisting of carnauba wax, ethylcellulose and a combination of carnauba wax and bees wax or
(b) dual wall encapsulated wherein the pharmaceutically active substance is encapsulated in ethylcellulose, carnauba wax and bees wax,
characterized in that optionally solid adjuvants are added to a pharmaceutically acceptable oil and mixed therewith until a homogenous suspension is obtained whereafter the pharmaceutically active substance in encapsulated form is added and gently mixed with the suspension.

2. A process for the preparation of a liquid dosage form according to claim 1, characterized in that the pharmaceutically acceptable oil is hydrogenated coconut oil.

3. A process for the preparation of a liquid dosage form according to claim 1, characterized in that the pharmaceutically active substance is encapsulated in carnauba wax.

4. A process for the preparation of a liquid dosage form according to claim 1, characterized in that the pharmaceutically active substance is encapsulated in carnauba wax and bees wax.

5. A process for the preparation of a liquid dosage form according to claim 1, characterized in that the pharmaceutically active substance is encapsulated in ethyl cellulose, carnauba wax and bees wax.

6. A process for the preparation of a liquid dosage form according to claim 1, characterized in that the active substance is remoxipride.

7. A process for the preparation of a liquid dosage form according to claim 1, characterized in that the active substance is selected from the group consisting of bacampicillin, penicillin V, bensylpenicillin and flucloxacillin.

8. A method of obtaining taste masking/controlled release/improved stability in a liquid oral formulation of a pharmaceutically active substance characterized in adding the pharmaceutically active substance in microencapsulated form to a vehicle consisting of a pharmaceutically acceptable oil, wherein the active substance is
   (a) single wall encapsulated wherein the coating material is selected from the group consisting of carnauba wax, ethylcellulose and a combination of carnauba wax and bees wax or
   (b) dual wall encapsulated wherein the pharmaceutically active substance is encapsulated in ethylcellulose, carnauba wax and bees wax.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB IT, LI, LU, NL, SE

1. Flüssige Dosierungsform zur oralen Verabreichung einer pharmazeutisch aktiven Substanz umfassend eine in einem pharmazeutisch akzeptablen Öl suspendierte pharmazeutisch aktive Substanz, wobei die aktive Substanz
   (a) von einer einzigen Wand kapselförmig umgeben ist, wobei das Überzugsmaterial ausgewählt ist aus der Gruppe bestehend aus Carnaubawachs, Ethylcellulose und einer Kombination aus Carnaubawachs und Bienenwachs, oder
   (b) von einer Doppelwand kapselförmig umgeben ist, wobei die pharmazeutisch aktive Substanz in Ethylcellulose, Carnaubawachs und Bienenwachs eingekapselt ist.

2. Flüssige Dosierungsform nach Anspruch 1, dadurch gekennzeichnet, daß das pharmazeutisch akzeptable Öl hydriertes Kokosöl ist.

3. Flüssige Dosierungsform nach Anspruch 1, dadurch gekennzeichnet, daß die pharmazeutisch aktive Substanz in Carnaubawachs eingekapselt ist.

4. Flüssige Dosierungsform nach Anspruch 1, dadurch gekennzeichnet, daß die pharmazeutisch aktive Substanz in Carnaubawachs und Bienenwachs eingekapselt ist.

5. Flüssige Dosierungsform nach Anspruch 1, dadurch gekennzeichnet, daß die pharmazeutisch aktive Substanz in Ethylcellulose, Carnaubawachs und Bienenwachs eingekapselt ist.

6. Flüssige Dosierungsform nach Anspruch 1, dadurch gekennzeichnet, daß die aktive Substanz Remoxipride ist.

7. Flüssige Dosierungsform nach Anspruch 1, dadurch gekennzeichnet, daß die aktive Substanz ausgewählt ist aus der Gruppe bestehend aus Bacampicillin, Penicillin V, Benzylpenicillin und Flucloxacillin.

8. Verfahren zur Herstellung einer flüssigen Dosierungsform zur oralen Verabreichung einer pharmazeutisch aktiven Substanz umfassend eine in einem pharmazeutisch akzeptablen Öl suspendierte pharmazeutisch aktive Substanz, wobei die aktive Substanz
   (a) von einer einzigen Wand kapselförmige umgeben ist, wobei das Überzugsmaterial ausgewählt ist aus der Gruppe bestehend aus Carnaubawachs, Ethylcellulose und einer Kombination aus Carnaubawachs und Bienenwachs, oder
   (b) von einer Doppelwand kapselförmig umgeben ist, wobei die pharmazeutisch aktive Substanz in Ethylcellulose, Carnaubawachs und Bienenwachs eingekapselt ist, dadurch gekennzeichnet, daß gegebenenfalls feste Adjuvantien zu einem pharmazeutisch akzeptablen Öl zugegeben und mit diesem bis zum Erhalt einer homogenen Suspension gemischt werden, wonach die pharmazeutisch aktive Substanz in eingekapselter Form zugegeben und mit der Suspension vorsichtig gemischt wird.

9. Verfahren zur Erreichung von Geschmacksmaskierung/gesteuerter Freisetzung/verbesserter Stabilität bei einer flüssigen oralen Formulierung einer pharmazeutisch aktiven Substanz, gekennzeichnet durch die Zugabe der pharmazeutisch aktiven Substanz in mikroverkapselter Form zu einem Träger bestehend aus einem pharmazeutisch akzeptablen Öl, worin die aktive Substanz
   (a) von einer einzigen Wand kapselförmig umgeben ist, wobei das Überzugsmaterial ausgewählt ist aus der Gruppe bestehend aus Carnaubawachs, Ethylcellulose und einer Kombination aus Carnau-

bawachs und Bienenwachs, oder
(b) von einer Doppelwand kapselförmig umgeben ist, wobei die pharmazeutisch aktive Substanz in Ethylcellulose, Carnaubawachs und Bienenwachs eingekapselt ist.

Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verfahren zur Herstellung einer flüssigen Dosierungsform zur oralen Verabreichung einer pharmazeutisch aktiven Substanz umfassend eine in einem pharmazeutisch akzeptablen Öl suspendierte pharmazeutisch aktive Substanz, wobei die aktive Substanz
   (a) von einer einzigen Wand kapselförmig umgeben ist, wobei das Überzugsmaterial ausgewählt ist aus der Gruppe bestehend aus Carnaubawachs, Ethylcellulose und einer Kombination aus Carnaubawachs und Bienenwachs, oder
   (b) von einer Doppelwand kapselförmig umgeben ist, wobei die pharmazeutisch aktive Substanz in Ethylcellulose, Carnaubawachs und Bienenwachs eingekapselt ist, dadurch gekennzeichnet, daß gegebenenfalls feste Adjuvantien zu einem pharmazeutisch akzeptablen Öl zugegeben und mit diesem bis zum Erhalt einer homogenen Suspension gemischt werden, wonach die pharmazeutisch aktive Substanz in eingekapselter Form zugegeben und mit der Suspension vorsichtig gemischt wird.

2. Verfahren zur Herstellung einer flüssigen Dosierungsform nach Anspruch 1, dadurch gekennzeichnet, daß das pharmazeutisch akzeptable Öl hydriertes Kokosöl ist.

3. Verfahren zur Herstellung einer flüssigen Dosierungsform nach Anspruch 1, dadurch gekennzeichnet, daß die pharmazeutisch aktive Substanz in Carnaubawachs eingekapselt ist.

4. Verfahren zur Herstellung einer flüssigen Dosierungsform nach Anspruch 1, dadurch gekennzeichnet, daß die pharmazeutisch aktive Substanz in Carnaubawachs und Bienenwachs eingekapselt ist.

5. Verfahren zur Herstellung einer flüssigen Dosierungsform nach Anspruch 1, dadurch gekennzeichnet, daß die pharmazeutisch aktive Substanz in Ethylcellulose, Carnaubawachs und Bienenwachs eingekapselt ist.

6. Verfahren zur Herstellung einer flüssigen Dosierungsform nach Anspruch 1, dadurch gekennzeichnet, daß die aktive Substanz Remoxipride ist.

7. Verfahren zur Herstellung einer flüssigen Dosierungsform nach Anspruch 1, dadurch gekennzeichnet, daß die aktive Substanz ausgewählt ist aus der Gruppe bestehend aus Bacampicillin, Penicillin V, Benzylpenicillin und Flucloxacillin.

8. Verfahren zur Erreichung von Geschmacksmaskierung/gesteuerter Freisetzung/verbesserter Stabilität bei einer flüssigen oralen Formulierung einer pharmazeutisch aktiven Substanz, gekennzeichnet durch die Zugabe der pharmazeutisch aktiven Substanz in mikroverkapselter Form zu einem Träger bestehend aus einem pharmazeutisch akzeptablen Öl, worin die aktive Substanz
   (a) von einer einzigen Wand kapselförmig umgeben ist, wobei das Überzugsmaterial ausgewählt ist aus der Gruppe bestehend aus Carnaubawachs, Ethylcellulose und einer Kombination aus Carnaubawachs und Bienenwachs, oder
   (b) von einer Doppelwand kapselförmig umgeben ist, wobei die pharmazeutisch aktive Substanz in Ethylcellulose, Carnaubawachs und Bienenwachs eingekapselt ist.

Revendications
Revendications pour les Etats contractants suivants : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Forme posologique liquide pour administration orale d'un principe pharmaceutiquement actif, comprenant un principe pharmaceutiquement actif en suspension dans une huile acceptable d'un point de vue pharmaceutique, dans laquelle le principe actif est :
   (a) encapsulé en simple paroi, le matériau d'enrobage étant choisi parmi l'ensemble comprenant la cire de carnauba, l'éthylcellulose et une combinaison de cire de carnauba et de cire d'abeille, ou encore

(b) encapsulé en double paroi, le principe pharmaceutiquement actif étant encapsulé dans de l'éthylcellulose, de la cire de carnauba et de la cire d'abeille.

2. Forme posologique liquide selon la revendication 1, caractérisée en ce que l'huile acceptable d'un point de vue pharmaceutique est une huile de coprah hydrogénée.

3. Forme posologique liquide selon la revendication 1, caractérisée en ce que le principe pharmaceutiquement actif est encapsulé dans la cire de carnauba.

4. Forme posologique liquide selon la revendication 1, caractérisée en ce que le principe pharmaceutiquement actif est encapsulé dans de la cire de carnauba et de la cire d'abeille.

5. Forme posologique liquide selon la revendication 1, caractérisée en ce que le principe pharmaceutiquement actif est encapsulé dans de l'éthylcellulose, de la cire de carnauba et de la cire d'abeille.

6. Forme posologique liquide selon la revendication 1, caractérisée en ce que le principe actif est le rémoxipride.

7. Forme posologique liquide selon la revendication 1, caractérisée en ce que le principe actif est choisi parmi l'ensemble comprenant la bacampicilline, la pénicilline V, la bensylpénicilline et la flucloxacilline.

8. Procédé pour préparer une forme posologique liquide pour administration orale d'un principe pharmaceutiquement actif, comprenant un principe pharmaceutiquement actif en suspension dans une huile acceptable d'un point de vue pharmaceutique, dans laquelle le principe actif est :
(a) encapsulé en simple paroi, le matériau d'enrobage étant choisi parmi l'ensemble comprenant la cire de carnauba, l'éthylcellulose et une combinaison de cire de carnauba et de cire d'abeille, ou encore
(b) encapsulé en double paroi, le principe pharmaceutiquement actif étant encapsulé dans de l'éthylcellulose, de la cire de carnauba et de la cire d'abeille,
caractérisé en ce que des adjuvants éventuellement solides sont ajoutés à une huile acceptable d'un point de vue pharmaceutique et sont mélangés à cette dernière jusqu'à obtention d'une suspension homogène, ce après quoi le principe pharmaceutiquement actif sous forme encapsulée est ajouté et doucement mélangé à la suspension.

9. Procédé pour obtenir des propriétés de masquage du goût/libération retardée/meilleure stabilité dans une formulation orale liquide d'un principe pharmaceutiquement actif, caractérisé en ce qu'il consiste à ajouter le principe pharmaceutiquement actif sous forme microencapsulée à un véhicule constitué d'une huile acceptable d'un point de vue pharmaceutique, où le principe actif est
(a) encapsulé en simple paroi, le matériau d'enrobage étant choisi parmi l'ensemble comprenant la cire de carnauba, l'éthylcellulose et une combinaison de cire de carnauba et de cire d'abeille, ou encore
(b) encapsulé en double paroi, le principe pharmaceutiquement actif étant encapsulé dans de l'éthylcellulose, de la cire de carnauba et de la cire d'abeille.

Revendications pour les Etats contractants suivants : ES, GR

1. Procédé pour préparer une forme posologique liquide pour administration orale d'un principe pharmaceutiquement actif, comprenant un principe pharmaceutiquement actif en suspension dans une huile acceptable d'un point de vue pharmaceutique, dans laquelle le principe actif est :
(a) encapsulé en simple paroi, le matériau d'enrobage étant choisi parmi l'ensemble comprenant la cire de carnauba, l'éthylcellulose et une combinaison de cire de carnauba et de cire d'abeille, ou encore
(b) encapsulé en double paroi, le principe pharmaceutiquement actif étant encapsulé dans de l'éthylcellulose, de la cire de carnauba et de la cire d'abeille,
caractérisé en ce que des adjuvants éventuellement solides sont ajoutés à une huile acceptable d'un point de vue pharmaceutique et sont mélangés à cette dernière jusqu'à obtention d'une suspension homogène, ce après quoi le principe pharmaceutiquement actif sous forme encapsulée est ajouté et doucement mélangé à la suspension.

2. Procédé pour préparer une forme posologique liquide selon la revendication 1, caractérisé en ce que l'huile acceptable d'un point de vue pharmaceutique est une huile de coprah hydrogénée.

3. Procédé pour préparer une forme posologique liquide selon la revendication 1, caractérisé en ce que le principe pharmaceutiquement actif est encapsulé dans la cire de carnauba.

4. Procédé pour préparer une forme posologique liquide selon la revendication 1, caractérisé en ce que le principe pharmaceutiquement actif est encapsulé dans de la cire de carnauba et de la cire d'abeille.

5. Procédé pour préparer une forme posologique liquide selon la revendication 1, caractérisé en ce que le principe pharmaceutiquement actif est encapsulé dans de l'éthylcellulose, de la cire de carnauba et de la cire d'abeille.

6. Procédé pour préparer une forme posologique liquide selon la revendication 1, caractérisé en ce que le principe actif est le rémoxipride.

7. Procédé pour préparer une forme posologique liquide selon la revendication 1, caractérisé en ce que le principe actif est choisi parmi l'ensemble comprenant la bacampicilline, la pénicilline V, la bensylpénicilline et la flucloxacilline.

8. Procédé pour obtenir des propriétés de masquage du goût/libération retardée/meilleure stabilité dans une formulation orale liquide d'un principe pharmaceutiquement actif, caractérisé en ce qu'il consiste à ajouter le principe pharmaceutiquement actif sous forme microencapsulée à un véhicule constitué d'une huile acceptable d'un point de vue pharmaceutique, où le principe actif est
   (a) encapsulé en simple paroi, le matériau d'enrobage étant choisi parmi l'ensemble comprenant la cire de carnauba, l'éthylcellulose et une combinaison de cire de carnauba et de cire d'abeille, ou encore
   (b) encapsulé en double paroi, le principe pharmaceutiquement actif étant encapsulé dans de l'éthylcellulose, de la cire de carnauba et de la cire d'abeille.

REGISTER ENTRY FOR EP0273890

European Application No EP87850382.0 filing date 07.12.1987

Priority claimed:
22.12.1986 in Sweden - doc: 8605515

Designated States BE CH DE ES FR GB GR IT LI LU NL SE AT

Title A LIQUID DOSAGE FORM FOR ORAL ADMINISTRATION OF A PHARMACEUTICALLY ACTIVE SUBSTANCE

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Classified to
A5B
A61K

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Publication No EP0273890 dated 06.07.1988
Publication in English

Examination requested 07.12.1987

Patent Granted with effect from 31.03.1993 (Section 25(1)) with title A LIQUID DOSAGE FORM FOR ORAL ADMINISTRATION OF A PHARMACEUTICALLY ACTIVE SUBSTANCE.

04.03.1993 J A KEMP & CO, 14 South Square, Gray's Inn, LONDON, WC1R 5LX, United Kingdom [ADP No. 00000026001]
registered as address for service
Entry Type 8.11 Staff ID. SS1 Auth ID. AA

**** END OF REGISTER ENTRY ****

RENEWAL DETAILS

PUBLICATION NUMBER EP0273890

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DATE FILED 07.12.1987

DATE GRANTED 31.03.1993

DATE NEXT RENEWAL DUE 07.12.1996

DATE NOT IN FORCE

DATE OF LAST RENEWAL 28.11.1995

YEAR OF LAST RENEWAL 09

STATUS PATENT IN FORCE

**** END OF REPORT ****