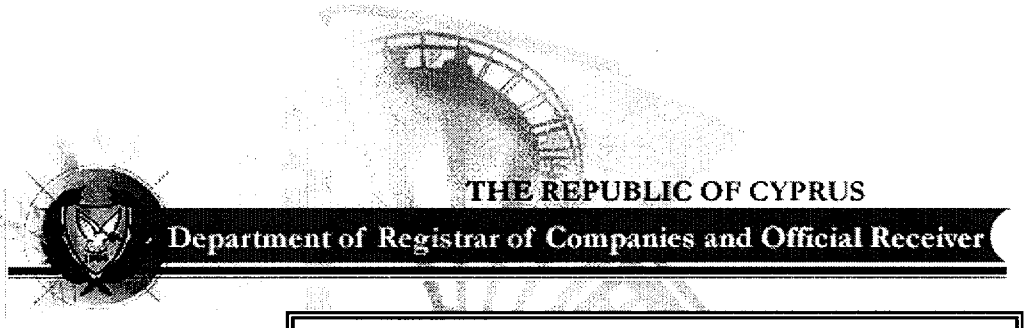

ΚΥΠΡΙΑΚΟ ΓΡΑΦΕΙΟ ΔΙΠΛΩΜΑΤΩΝ ΕΥΡΕΣΙΤΕΧΝΙΑΣ
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(54) **Controlled release formulation**

(57) The formulation contains an encapsulated active substance and a release controlling substance which is a carbohydrate, a carbohydrate-related compound or a mixture of such compounds. The release controller may be a saccharide, sucrose, fructose, glucose, sorbitol, polyethyleneglycol or dextran. Many suitable active substances and encapsulating materials are exemplified.

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SPECIFICATION

Pharmaceutical mixture

The present invention is concerned with an oral pharmaceutical preparation containing an encapsulated pharmaceutically active substance. More specifically the preparation is a dry powder for mixture or said dry powder dissolved in an aqueous solution.

The object of the invention is to provide a preparation wherein the dissolution of the active substance from the encapsulation is controlled.

Among alternative forms of orally administering pharmaceutically active substances the use of a solution or a suspension of the active principle in an aqueous solution is a form often seen in pediatric use. This preparation is called a mixture. The dry powder including the active principle and adjuvants which is to be dissolved or suspended is called dry powder for mixture.

The preparation is stored as a dry powder. Before administration the dry powder is dissolved or suspended in an aqueous solution giving rise to a liquid formulation for oral administration — a mixture. Alternatively the mixture can be prepared in the factory and stored at least for two years prior to administration. Pharmaceutically active substances for use in mixtures have been encapsulated either to mask bad taste or to control the release in the body.

Hitherto medicines have been coated with polymers or with polymers in combination with plasticizers to control drug release (microencapsulation). Applied on granulates of a drug it retards the rate of dissolution.

The main way to control drug dissolution from microcapsules is the amount of polymer applied, in order to obtain the expected plasma profile of the drug. This can also be obtained by adding water soluble substances to the coat during the coating process.

The present invention provides a mixture, wherein bad taste of the drug is masked and/or having retarded dissolution of the active substance to obtain slow release effect.

The present invention provides a pharmaceutical preparation containing an encapsulated active substance and having controlled release of the active substance, masking any unpleasant taste of the active substance and having increased stability of the active substance wherein the preparation contains 40-99% on a weight-weight basis of the ready to use preparation, of a release controlling substance which is a carbohydrate, a carbohydrate-related compound or a mixture of such compounds.

The mixture is obtained either by suspending the dry powder in an aqueous solution or by suspending the microcapsules in a solution of the release controlling substance.

The drug release from the microcapsules within the mixture, here called leakage, is very low, but in the body the drug is released from the microcapsules and available for absorption.

This invention also provides for increased drug stability in the mixture.

This result is obtained by adding to the encapsulated active substance and customary adjuvants a release-controlling substance (sink).

The sink can be a carbohydrate or a carbohydrate-related compound, for instance a poly- or a oligosaccharide such as dextrane; a disaccharide such as saccharose, maltose or lactose; a monosaccharide such as glucose, fructose, galactose, mannose or xylitol; a carbohydrate-related compound e.g. a polyhydroxy compound or a polyhydroxy polyether, such as mannitol, sorbitol, glycerol, glycol, a glycoside of a monosaccharide or a substance derived from ethyleneglycol for instance polyethyleneglycol (trade names Carbowaxes® and Carbopoles®).

The sink can be one or a mixture of two or more of the mentioned substances.

The amount of sink should be between 40% and 99% (weight/weight), preferably 60-75% (weight/weight) of the entire preparation, that is of the ready to use suspension for oral administration (the mixture).

An alternative to adding the release-controlling substance to the encapsulated drug is to encapsulate the release-controlling substance together with the drug within the encapsulating shell.

Sugars that can be used according to the invention are among others sucrose, glucose, fructose and sorbitol.

As pharmaceutically active substance any drug can be used, for instance anyone of the following:

Chemoterapeutics: bacampicillin, ampicillin, flucloxacillin, tetracycline, dicloxacillin, chloramphenicol, gentamicin, erythromycin, lincomycin, rifampicin, sulphadiazine, sulphamethoxypyridazine, griseofulvine, nitrofurantoine.

Adrenergis and beta-receptor-stimulators: ephedrine, terbutaline, theophylline, enprophylline.

Expectorants and cough depressants: Ethylmorphine, dextromethorphan, noscapine, bromhexine.

Heartglucosides and antiarythmics: Digitoxine, digoxin, dispyramide, procainide, tocainide, alprenolol, atenolol, metoprolol, pindolol, propranolol.

Blood pressure depressants: betanidine, clonidine, guanetidine, methyldopa, reserpine trimetaphane, hydrolazine, bendropphlumetiazide, furosemide, chlorotiazide.

Antihistamines: brompheniramine, chlorcyclizine, chlorpheniramine, diphenhydramine, prometazine.

Peroral antidiabetes: carbutamide, chlorpropamide, tolazamide, tolbutamide.

Sedatives, Hypnotics, Antidepressants: hexobarbital, pentobarbital, phenobarbital, meprobamate, chlordiazepoxide, diazepam, flunitrazepam, nitrazepam, oxazepam, chlormethiazol, chlorpromazine, fluphenazine, perphenazine, prochlorperazin, haloperidol, lithium, alaproclate, zimeldine, amitryptiline, imipramine, nortriptyline.

Antiepileptics: phenytoine, ethotoin, ethosuximide, carbamazepine.

Analgesics, Anaesthetics: 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.

The preferred drug is bacampicillin hydrochloride (1'-ethoxycarbonyloxyethyl 6-[D(-)-2-amino-2-

phenylacetamido]-penicillanate hydrochloride), other epimeric forms and the racemic form of bacampicillin hydrochloride.

Other preferred drugs are theophylline, enprophylline and erythromycine.

The drugs mentioned above are used in neutral or salt form.

The following salts of the drugs mentioned above can be used:

Acetate, benzenesulfonate, benzoate, bicarbonate, bitartrate, bromide, calcium edetate, camsylate, carbonate, chloride, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, clycollylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isethionate, lactate, lactobionate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, pamoate (embonate), pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, sulphate, tannate, tartrate, teoclate, triethiodide.

Cationic salts can also 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.

The encapsulation of the drug can be achieved in the form of microcapsules, but the encapsulation is not restricted to the micro size.

Coating material

Polymers:

Synthetic polymers of polyvinyl type, e.g. polyvinylchloride, polyvinylacetate, polyvinylalcohol.

Polyethylene type, e.g. polyethylene, polystyrene.

Polymers of acrylic acid or acrylic acid ester type, e.g. methylmethacrylate or copolymers of acrylic monomers.

Biopolymers or modified biopolymers of cellulose, e.g. ethylcellulose, cellulose acetate phtalate.

The polymer can be water unsoluble, acid soluble or alkaline soluble and mixed with plastisizer or other filler and water soluble modified biopolymer, ex hydroxy propyl cellulose.

Also fats and oils, wax, higher fatty acids, higher alcohols or polyhydric alcohols can be used as such or in combination.

In one embodiment of the invention bacampicillin hydrochloride (BAPC) is encapsulated in an insoluble microporous polymer, such as ethyl cellulose and sucrose is used as sink to make a dry powder for mixture, which is then dissolved in water to make a mixture.

In another embodiment of the invention BAPC is encapsulated in a polymer soluble in acid, such as Eudragit® E 100 and sucrose is used as sink to make a dry powder for mixture, which is then dissolved in water to make a mixture.

In a further embodiment of the invention theophylline is microencapsulated in a shell of ethyl cellulose and sorbitol is used as sink to make a dry powder for mixture, which is then dissolved in water to make a mixture.

In a further embodiment of the invention acetylsalicylic acid is encapsulated in a shell of cellulose acetate phtalate and sucrose is used as sink to make a dry powder for mixture, which is then dissolved in water to make a mixture.

A release controlling substance is mixed with other constituents and microcapsules of the drug are added to this dry powder and mixed in a conventional blender. This dry powder is then added to bottles in a filling machine. Water is then added, by the customer or at the pharmacy, to dissolve the release controlling substance.

Alternatively, a solution of the release controlling substance and other constituents is prepared. The microcapsules of the drug can then be added either to this solution and then filled into bottles ready to use, or the microcapsules of the drug can be filled into a separate container and be added by the customer or the pharmacy to the solution prior to use.

Leakage studies

Leakage studies were carried out in order to show that the microcapsules will not release any significant amount of the drug into the sink causing bad taste in contact with water, causing degradation or losing its ability to work as controlled release formulation.

Microcapsules were added to sink solution according to the invention. The amount of drug which had been released from the microcapsules was analyzed. This is called leakage. The samples were in some instance stored up to 80 days in room temperature. The sink was analyzed spectrophotometrically. The result is given in percent leakage which is the amount of the drug which is in solution divided by the initial amount of microencapsulated drug.

In order to demonstrate the effect of the release controlling substance the release studies were also performed in water. Microcapsules were placed in a beaker and water was added. The stirring rate was 30 rpm and the amount of release was calculated as described above.

The following Examples are given to illustrate the invention.

Example 1

100 g of dry powder contains

Bacampicillin hydrochloride ethyl cellulose microcapsules (70% drug)	5.61 g
Sodium bicarbonate	0.83 g
Mannitol	9.35 g
Sucrose	83.1 g

Sodium bicarbonate, mannitol and sucrose were premixed before the microcapsules were added. The final mixing was carried out in a beaker. 4.81 g of the powder was added to 5 ml of water. The aqueous mixture contains 46% w/w of release controlling substances.

Time (days)	Leakage (%)
1	0.5
2	0.9
4	1.1
7	1.3
10	1.2

In this example the leakage of drug was analyzed with a mercurimetric titration method.

Time (days)	Release in water (%)
0.042	60
0.084	90

Example 2

25.8 g of pharmaceutical mixture contains

Bacampicillin hydrochloride	0.80 g
Eudragit® E 100 microcapsules (64% drug)	
Fructose	18.75 g
Water	6.25 g

Fructose was dissolved in water before the microcapsules were added.

The mixture contains 72.7% release controlling substances.

Time (hours)	Leakage (%)
2	<0.2

Time (hours)	Release in water (%)
0.008	50
0.05	90

Example 3

A pharmaceutical mixture contains:

Theophylline ethyl cellulose microcapsules (72% drug)		0.05 g
and either (a)	Fructose	23.44 g
	Water	7.82 g
or (b)	Sorbitol	20.94 g
	Water	7.82 g

The two mixtures were prepared according to Example 2.

The mixtures contain a) 75% b) 73% release controlling substance.

Time (days)	Leakage (%) a)	b)
1	<0.2	0.7
3	<0.2	-
5	<0.2	-
7	<0.2	-
10	<0.2	-

Time (days)	Release in water (%)
0.21	50
0.33	90

Example 4

31.3 g of pharmaceutical mixture contains:

Theophylline ethyl cellulose microcapsules (72% drug)	0.05 g
Sucrose	9.38 g
Sorbitol	9.38 g
Sucrose	9.38 g
Glycerol	9.38 g
Glucose	9.38 g
Fructose	9.38 g
Water	12.5 g

The three mixtures were prepared according to example 2.

The mixtures contain 60% of release controlling substances.

Time (days)	Leakage (%) a)	b)	c)
1	0.20	<0.2	0.26
2	0.31	0.35	0.28
5	0.65	0.82	0.49
9	1.15	1.77	0.90

Time (days)	Release in water (%)
0.21	50
0.33	90

Example 5

71.1 g of pharmaceutical mixture contains:

Acetyl salicylic acid cellulose acetate phtalate microcapsules (69% drug)	0.100 g
Sucrose	48.75 g
Phosphate buffer (pH 7.0)	26.25 g

Sucrose was dissolved in the phosphate buffer. The microcapsules were then added.

The mixture contains 65% release controlling substance.

Time (days)	Leakage (%)
1	3.5

Time (days)	Release in phosphate buffer pH 7.0 (%)
0.008	50
0.017	90

Example 6

	a	b	c
Bacampicillin hydrochloride	0.27 g	0.27 g	0.27 g
ethyl cellulose microcapsules (70% drug)			
Sodium bicarbonate	0.40 g	0.40 g	-
Mannitol	0.45 g	-	-
Sucrose	4.0 g	-	-
Water	5.0 g	5.0 g	5.0 g

The mixtures were prepared according to Example 1.

The mixture (a) contains 44% of release controlling substance.

The release in water of the microcapsules were the same as in Example 1.

Time (days)	Leakage (%) a	b	c
1	0.5	85	100
2	0.9		
4	1.1		
7	1.3		
10	1.2		

Example 7

Four different microcapsules coated with ethylcellulose were suspended in sorbitol dissolved in water according to following composition.

Microcapsules	50 mg
Sorbitol	45.1 g
Water	19.3 g

The mixtures contain 70% release controlling substance.

Microcapsules		Leakage in sorbitol sink (%)	(days)	Release in water (%)	(h)
KCl	(86)*	16	21	56	3
Paracetaminophene	(91)*	19	21	35	1
Flucloxacillin	(89)*	20	1	90	0.5
Fenoxymethyl penicillin potassium	(83)*	10	1	80	1

* content of active drug in the microcapsule

Example 8

0.2 g theophyllin microcapsules according to Example 3 were suspended in different sugar solutions

Release controlling substance % (w/w)		Leakage (%)	Time (days)
Xylitol	55	13	80
Glucose	50	17	40
Sorbitol	70	3	80
Fructose	75	3	80
Fructose-xylitol	19-41	10	80
Fructose-xylitol	38-28	6	80
Fructose-xylitol	56-14	4	80

It is thus possible to restrict the leakage in the mixture to only a few percent after almost three months storage in room temperature.

Example 9

65.4 g of pharmaceutical mixture contains:

Theophyllin wax coated microcapsules (52% drug)	1 g
Sorbitol	45.1 g
Water	19.3 g

The mixture was prepared according to Example 3.

The mixture contains 69% release controlling substance.

Time (days)	Leakage (%)
22	0.7

Time (days)	Release in water (%)
0.5	19

Example 10

26.31 g of pharmaceutical mixture contains

Prochloroperazin wax coated microcapsules (3.4% drug)	10 mg
Sorbitol	18 g
Water	8.3

The mixture was prepared according to Example 3.

The mixture contains 68% release controlling substance.

Time (days)	Leakage (%)
12	2.7

Time (days)	Release in water (%)
0.25	28

Example 11

27.15 g of pharmaceutical mixture contains:

Theophylline ethyl cellulose coated microcapsules (72%)	0.15 g
Polyethyleneglycol (Carbowax® 400)	20.25 g
Water	6.75 g

Polyethyleneglycol was mixed with water and the microcapsules were added.

The mixture contains 75% release controlling substance.

Time (days)	Leakage (%)
15	2.4

The release in water, see Example 3.

Example 12

13.877 g of pharmaceutical mixture contains:

Erythromycin	0.877 mg
cellulose acetate phtalate coated microcapsules (57% drug)	
Fructose	9.75
Water	3.25

The microcapsules were added to a solution of fructose in water.

The mixture contains 70% release controlling substance.

Time (days)	Leakage (%)
10	<1

Time (days)	Release in water (%)
0.25	46

Release studies

Microcapsules were suspended in 75% release controlling substance solution and after two or three days storage the microcapsules were filtered off and the release of the drug was measured. The microcapsules were placed in a beaker containing either simulated gastric fluid or simulated intestinal fluid at 37°C in order to simulate the in vivo situation. The stirring rate was 30 rpm. Samples were withdrawn after certain time points and those were analyzed for drug content spectrophotometrically.

The results show time to obtain 50, 70 and 90 percent release of the total amount of microencapsulated drug.

Theophylline microcapsules

Release (%)	Simulated gastric fluid (hours)		Simulated intestinal fluid (hours)	
	Original	Stored 3 days	Original	Stored 2 days
50	4.2	4.4	3.7	4.4
70	5.7	5.8	5.5	6.6
90	6.2	6.4	7.5	8.3

Acetyl salicylic acid

Release (%)	Simulated gastric fluid (%)		Simulated intestinal fluid (hours)	
	Original	Stored 2 days	Original	Stored 2 days
50			0.14	0.21
70			0.22	0.31
90			0.3	0.5
1 h	12%	8%		
2 h	25%	15%		

Bacampicillin hydrochloride Eudragit® E 100 microcapsules

Release (%)	Simulated gastric fluid (min)		Simulated intestinal fluid (min)	
	Original	Stored 2 days	Original	Stored 2 days
50	0.4	0.8	1.5	3
70	0.5	0.9	1.8	3.7
90	0.7	1.0	2.5	5

Microcapsule compositions as in Examples 7, 9 and 11.

Microcapsules	Realease in water				
	Initially		Storage time		
	(%)	(h)	(days)	(%)	(h)
KCl	56	3	14	53	3
Paracetaminophene a)	35	1	14	48	1
Fenoxymethyl penicillin potassium a)	80	1	3	81	1
Theophyllin wax coated b)	19	12	25	17	12
Theophyllin ethyl cellulose coated c)	46	6	6	50	6

a) according to Example 7
b) according to Example 9
c) according to Example 11

Release studies have also been carried out on the compositions in Example 8. The release rate was performed according to USP XX (method II paddle) 100 rpm in 900 ml 37° water.

The release rate is expressed as percent released per hour. The initial release rate was 12%/h.

Release controlling substance	Release rate (%/h)	Time (days)
Xylitol	9.9	80
Glucose	9.7	40
Sorbitol	11.7	80
Fructose	11.8	80
Fructose-xylitol (19-41)	10.5	80
Fructose-xylitol (38-28)	11.9	80
Fructose-xylitol (56-14)	11.9	80

The influence on storage time of the microcapsules in the different sink solution is negligible.

Stability studies

Microcapsule suspensions were prepared with sink solutions according to the invention. The suspensions were stored and the drug content was measured with HPLC analysis as an selective and precise method.

Mixtures

Mixtures not according to the invention

a) According to Example 6 b

b) According to Example 6 c

c) According to Example 6 a

d)	Bacampicillin HCl microcaps. (72% drug) ethylcellulose coated	0.36
	Sucrose	8.32
	Water	4.48
e)	Bacampicillin HCl microcaps. (72% drug) ethyl cellulose coated	0.36
	Fructose	9.6
	Water	3.2
f)	Acetyl salicylic acid microcaps. (69% drug) cellulose acetate phtalate coated	0.72
	Sucrose	8.32
	Citrate buffer pH 3	4.48
g)	Erythromycin microcaps. (87% drug)	0.44 g
	cellulose acetate phtalate coated	8.32 g
	Phosphate buffer pH 7.0	4.48 g

Mixture	Storage condition time (days)	temp (°C)	Intact drug* (%)
a	1	25	2
b	1	25	60
c	10	25	91
d	7	25	83
e	7	25	89
f	30	50	70
g	30	50	82

*initially the amount of intact drug was 100%

The results imply that mixtures according to the invention has an improving effect on the stability of drugs.

CLAIMS

1. A pharmaceutical preparation containing an encapsulated active substance and having controlled release of the active substance, masking any unpleasant taste of the active substance and having increased stability of the active substance wherein the preparation contains 40-99% on a weight-weight basis of the ready to use preparation, of a release controlling substance which is a carbohydrate, a carbohydrate-related compound or a mixture of such compounds.

2. A preparation according to claim 1 containing 60-70% of the release controlling substance.

3. A preparation according to claim 1 or 2, wherein the carbohydrate is a monosaccharide or disaccharide.

4. A preparation according to claim 3 wherein the carbohydrate is sucrose, glucose or fructose.

5. A preparation according to any one of the preceding claims wherein the carbohydrate related compound is a polyhydroxy compound or a polyhydroxypolyether.

6. A preparation according to claim 5 wherein the carbohydrate related compound is Sorbitol.

7. A preparation according to any one of the preceding claims, wherein the active substance is a chemotherapeutic, an adrenergic or beta-receptor stimulator; an expectorant or cough depressant; a heart glucoside or antiarythmic; a blood pressure depressant; an antihistamine; a peroral antidiabetes; a sedative, hypnotic or antidepressant; an antiepileptic; or an analgesic or anaesthetic.

8. A preparation according to claim 7 wherein the active substance is bacampicillin or theophylline.

9. A preparation according to any one of the preceding claims in the form of a dry powder.

10. A preparation according to any one of claims 1 to 8 in the form of an aqueous solution ready for use.

11. A preparation according to claim 1 substantially as hereinbefore described with reference to any one of the Examples.

12. A method for producing a preparation as defined in claim 1 which comprises mixing an encapsulated active substance with an adjuvant and with the release controlling substance in an amount to provide 40-99% by weight release controlling substance in the ready to use mixture to provide a dry mix to which water can be added to provide the ready to use mixture.

13. A method for producing a preparation as defined in claim 1 which comprises mixing an encapsulated active substance with a solution of an adjuvant and with the release controlling substance in an amount to provide 40-99% by weight release controlling substance in the ready to use mixture.

14. A preparation as defined in any one of claims 1 to 11 for use in a method of treatment of the human or animal body by surgery or therapy or of diagnosis practised on the human or animal body.

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