592618

COMMONWEALTH of AUSTRALIA

PATENTS ACT 1952

APPLICATION FOR A STANDARD PATENT

XXX
We ELAN CORPORATION, PLC.,
of Monksland Industrial Estate,
Athlone,
County Westmeath,
REPUBLIC OF IRELAND

hereby apply for the grant of a Standard Patent for an invention entitled:

"SUSTAINED RELEASE CAPSULE OR TABLET FORMULATION"

which is described in the accompanying ~~provisional~~ complete specification.

Details of basic application(s):—

Number	Convention Country	Date
64/87	REPUBLIC OF IRELAND	9th January 1987

APPLICATION ACCEPTED AND AMENDMENTS ALLOWED 1.11.89

The address for service is care of DAVIES & COLLISON, Patent Attorneys, of 1 Little Collins Street, Melbourne, in the State of Victoria, Commonwealth of Australia.

Dated this 2nd day of February 19 87

To: THE COMMISSIONER OF PATENTS

H. M. Rimington

(a member of the firm of DAVIES & COLLISON for and on behalf of the Applicant).

Davies & Collison, Melbourne and Canberra.

Form 8

AUSTRALIA

Patents Act 1952

DECLARATION IN SUPPORT OF A CONVENTION APPLICATION FOR A PATENT

In support of the Convention application made for a patent for an invention entitled:
"SUSTAINED RELEASE CAPSULE OR TABLE FORMULATION"

I, ANNE RYAN,

of 27 Clyde Road, Ballsbridge, Dublin 4, REPUBLIC OF IRELAND

do solemnly and sincerely declare as follows:-

1. ~~I am the applicant for the patent~~

(or, in the case of an application by a body corporate)

1. I am authorized by ELAN CORPORATION PLC, the applicant for the patent to make this declaration on its behalf.

2. The basic application as defined by section 141 of the Act was made in REPUBLIC OF IRELAND on the 9th day of January, 19 87, by ELAN CORPORATION, PLC.

3. ~~I am the actual inventor of the invention referred to in the basic application~~

(or, where a person other than the inventor is the applicant)

3. Seamus MULLIGAN and Randall T. SPARKS

of 4 Beech Lawn, Monksland, Athlone, County Westmeath, Republic of Ireland, and 2620 Pinebrook Drive, Gainesville, Georgia, United States of America, respectively, ~~are~~ the actual inventor of the invention and the facts upon which ~~I am entitled~~ the applicant is entitled to make the application are as follows:-

The actual inventors have assigned the invention to the said applicant.

4. The basic application referred to in paragraph 2 of this Declaration was the first application made in a Convention country in respect of the invention the subject of the application.

(or, where a request is made under section 142AA of the Patents Act 1952, for an earlier application made in a Convention country to be disregarded)

4.-(1.) The basic application referred to in paragraph 2 of this Declaration was not the first application made in a Convention country in respect of the invention the subject of the application.

(2.) An earlier application in respect of the invention the subject of the application was made in ..... on .....

(3.) A request has been made to you under section 142AA of the *Patents Act* 1952 to disregard that earlier application.

(Here set out in succeeding sub-paragraphs the facts that show that section 142AA is applicable)

Except as stated in this paragraph, the basic application referred to in paragraph 2 of this Declaration the first application made in a Convention country in respect of the invention the subject of the application.

Declared at Dublin this 12th day of January, 19 87

ELAN CORPORATION, PLC

By: Anne Ryan
(Signature of Declarant)
ANNE RYAN
Attorney

TO:
THE COMMISSIONER OF PATENTS.

(IMPORTANT Cross out inapplicable words in above Form.)

(12) PATENT ABRIDGMENT (11) Document No. AU-B-68207/87
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 592618

(54) Title
DIHYDROPYRIDINE/POLYVINYLPYRROLIDONE PHARMACEUTICAL ADSORBATE

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(56) Prior Art Documents
AU 68206/87 A61K 47/00 3/44 9/22

(57) The adsorbates according to the present invention result in improved drug delivery relative to known active drug adsorbates in a cross-linked polymer since the adsorbates in the formulations of the present invention yield a matrix system exhibiting both delayed or sustained release of active drug and improved absorption of said active drug in vivo.

CLAIM

1. A sustained release capsule or tablet formulation suitable for once daily administration comprising an adsorbate of a mixture of 1 part by weight of a pharmaceutically useful dihydropyridine and from 0.1 to 10 parts by weight of a polyvinylpyrrolidone having an average molecular weight greater than 55,000 adsorbed on a cross-linked polyvinylpyrrolidone in a ratio of 1 part by weight of ~~adsorbate~~ said mixture to 0.5 to 20 parts by weight of cross-linked polyvinylpyrrolidone, blended with a polymer or mixture of polymers which gel in the presence of water, the amount of said polymer or polymers being effective to produce the desired sustained release effect.

COMMONWEALTH OF AUSTRALIA

PATENT ACT 1952

592618

COMPLETE SPECIFICATION

(Original)

FOR OFFICE USE

Class Int. Class

Application Number: 68207/87
Lodged:

Complete Specification Lodged:
Accepted:
Published:

Priority:

Related Art:

This document contains the amendments made under Section 49 and is correct for printing.

Name of Applicant: ELAN CORPORATION, PLC

Address of Applicant: Monksland Industrial Estate,
Athlone, County Westmeath,
IRELAND

Actual Inventor(s): Seamus MULLIGAN
Randall T. SPARKS

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1 Little Collins Street, Melbourne, 3000.

Complete Specification for the invention entitled:

"SUSTAINED RELEASE CAPSULE OR TABLET FORM"

The following statement is a full description of this invention, including the best method of performing it known to us :-

This invention relates to a method for the manufacture of adsorbates for use in drug delivery systems and to the adsorbates and drug formulations thereby obtained.

It is frequently desirable to delay the release of an active substance from a pharmaceutical formulation *in vivo*. For example, it may be desirable to delay release of the active substance within the body so that the active substance is released at a particular target site. Various coated tablets are available which are resistant to gastric juices but which are readily soluble in the higher pH environment of the small intestine. Various controlled absorption pharmaceutical formulations are also available which have a particular dissolution pattern, resulting in a controlled absorption of the active substance and, therefore, more effective medication. For example, controlled absorption pellets of the latter type for oral administration are described in the Applicants' EP-A-0 122 077, EP-A-0 123 470, EP-A-0 156 077, EP-A-0 149 920 and European Patent Application No. 86 308 810.0.

The use of many active substances in therapy is complicated by solubility problems and this is especially the case with the dihydropyridine group of

drugs. Drugs of the latter type such as nifedipine are very poorly soluble in aqueous media and, whilst co-precipitates thereof with certain polymers are known to improve solubility, said co-precipitates normally require a polymer to active drug ratio exceeding 3:1 in order to be effective in producing products characterised by high bioavailability with prompt peak blood levels.

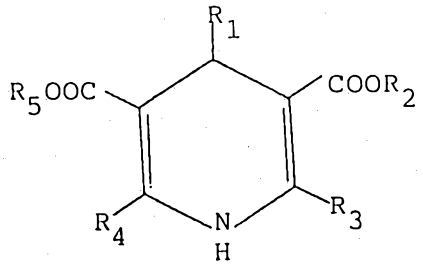
Pharmaceutical formulations based on an adsorbate of a drug within a cross-linked polymer, such as cross-povidone, are also known. Furthermore, solid, rapidly absorbable medicament formulations comprising a dihydropyridine, polyvinylpyrrolidone with an average molecular weight of 15,000 to 50,000 and cross-linked insoluble polyvinylpyrrolidone are known from Patent Application No. 1677/85 (EP-A-0 167 909). Such formulations are rapidly absorbable and as such must be administered three or four times daily to achieve effective therapeutic levels of the active ingredient.

It is an object of the present invention to provide a sustained release capsule or tablet formulation for once daily administration wherein the bioavailability of an otherwise poorly bioavailable active substance is enhanced and effective controlled release formulations thereof can be produced.

Accordingly, the invention provides a sustained release capsule or tablet formulation suitable for once daily administration comprising an adsorbate of a mixture of 1 part by weight of a pharmaceutically useful dihydropyridine and from 0.1 to 10 parts by weight of a polyvinylpyrrolidone having an average molecular weight greater than 55,000 adsorbed on a cross-linked polyvinylpyrrolidone in a ratio of 1 part by weight of ~~adsorbate~~ said mixture to 0.5 to 20 parts by weight of cross-linked

polyvinylpyrrolidone, blended with a polymer or mixture of polymers which gel in the presence of water, the amount of said polymer or polymers being effective to produce the desired sustained release effect.

The pharmaceutically useful dihydropyridines used in the present invention generally fall within the chemical formula



I

where R_1 is aryl or heteroaryl each of which may be substituted by various groups such as nitro and halogen whilst R_2, R_3, R_4 and R_5 which are the same or different, each represent alkyl groups which may be substituted by groups such as halogen, alkoxy, amino, alkylamino and arylalkylamino.

Preferred dihydropyridines covered by the general formula (I) are felodipine, nicardipine, nifedipine, nitrendipine, nimodipine, nisoldipine and 4-(2,1,3-benzoxadiazol-4-yl)-2,6-dimethyl-1,4-dihydro-3-isopropyloxycarbonyl-pyridine-5-carboxylic acid methyl ester.

The formation of the adsorbate may result in the dihydropyridine being in an amorphous state which can be verified by x-ray diffraction and, in addition, differential scanning calorimetery, which state is preferably retained in the sustained release formulations hereafter described.

The polyvinylpyrrolidone is preferably present in the adsorbate in an amount of 0.25 - 2 parts by weight relative to 1 part by weight of the dihydropyridine.

Furthermore, the formulation preferably contains 1 part by weight of ~~adsorbate~~ said mixture relative to 1 - 10 parts by weight of cross-linked polyvinylpyrrolidone.

The invention also provides a process for preparing a sustained release formulation as defined above, which comprises dissolving the dihydropyridine and the polyvinylpyrrolidone in a common solvent, mixing the solution thereby obtained with a given quantity of the cross-linked polyvinylpyrrolidone so as to permit adsorption of said dihydropyridine and said polyvinylpyrrolidone to said cross-linked polyvinylpyrrolidone, removing the solvent, and blending the resulting product with said polymer or mixture of polymers which gel in the presence of water and encapsulating or tabletting the resulting blend.

The solvent used is any pharmaceutically suitable co-solvent for the dihydropyridine and the polyvinylpyrrolidone.

The solvent is suitably selected from water, alcohols, ketones, halogenated aliphatic compounds, halogenated aromatic hydrocarbon compounds, aromatic hydrocarbon compounds and cyclic ethers or a mixture thereof.

Especially preferred solvents include water, hexane, heptane, methanol, ethanol, isopropyl alcohol, acetone, methylethyl ketone, methylisobutyl ketone, methylene chloride, chloroform, carbon tetrachloride, toluene, xylene and tetrahydrofuran.

The polyvinylpyrrolidone is chosen to modify the dissolution of the dihydropyridine from the cross-linked polyvinylpyrrolidone and also serves to prevent any crystallisation of the dihydropyridine in the polymer matrix structure of the adsorbate during dissolution. Principally, the polyvinylpyrrolidone serves to aid the

sustained release mechanism of the capsule or tablet dosage form according to the invention.

The polyvinylpyrrolidone preferably has an average molecular weight in the range 55,000 to 75,000. It is found that polyvinylpyrrolidones having a molecular weight greater than 55,000 have a viscosity which serves to sustain the release of active ingredient from the capsule or tablet formulation following administration. The greater the viscosity of the polyvinylpyrrolidone use, the slower the release of active ingredient.

An especially preferred cross-linked polyvinylpyrrolidone is cross-povidone (sold under the Trade Marks Polplasdone XL (GAF) and Kollidon CL (BASF)).

For forming capsules or tablets according to the invention, the adsorbate as defined above adsorbed on the cross-linked polyvinylpyrrolidone is granulated and blended with a polymer or mixture of polymers which gels in the presence of water, and optionally other ingredients. The blend thereby obtained can be tabletted or encapsulated according to conventional methods, thereby yielding a long acting matrix system which also exhibits improved drug absorption. Suitable polymers for blending with adsorbates for subsequent tabletting or encapsulation are inert polymers, which include both water soluble and water insoluble polymers such as, for example, polyvinyl alcohol, polyvinylpyrrolidone, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, alkyl-celluloses such as methyl- and ethylcellulose, shellac, polymers sold under the Trade Mark Eudragit, polyethylene glycol, sodium alginate, galactomannone or carboxypolymethylene or mixtures thereof.

Eudragit polymers are polymeric lacquer substances based on acrylates and/or methacrylates. Especially suitable Eudragits for use as the polymer which gels in water in the capsules or tablets according to the invention include co-polymers of acrylic and methacrylic acid esters which have varying permeability to water and active ingredient.

An especially suitable group of polymers is the polymers sold under the Trade Mark Methocel.

If one wishes to delay release of the active ingredient in vivo in capsule or tablet form, a combination of water soluble and a water insoluble polymer or a mixture of such polymers will be used, with the ratio of the water soluble to water insoluble polymer being varied to give the desired rate of release. Similarly, in the case of polymers/co-polymers of varying permeability, such as the Eudragits, the permeability characteristic of the polymers/co-polymers will be chosen to give the desired rate of release.

The adsorbates according to the present invention result in improved drug delivery relative to known active drug adsorbates in a cross-linked polymer since the adsorbates in the formulations of the present invention yield a matrix system exhibiting both delayed or sustained release of active drug and improved absorption of said active drug in vivo.

The invention will be further illustrated with reference to the following Examples.

EXAMPLE 1

Polyvinylpyrrolidone with an average molecular weight of 60,000 (0.75 kg) was dissolved in methylene chloride (8 kg). Nifedipine (1 kg) was then added to this solution and allowed to dissolve. The solution thereby obtained was then adsorbed onto cross-povidone (2.3 kg) and the solvent evaporated. The resulting powder was then passed through an oscillating granulator to obtain a finer particle size. X-ray diffraction and differential scanning calorimetry studies were performed on the powder and demonstrated that the nifedipine was in an amorphous form. The powder 50% was then tabletted with the following ingredients.

Methocel K100LV (Trade Mark)	8.0%
Avicel pH101 (Trade Mark)	41.5%
Magnesium stearate	0.5%

to obtain a tablet containing 20 mg of active ingredient. An x-ray diffraction pattern of the tablet was obtained which demonstrated the amorphous nature of the nifedipine had been retained.

In the above Example, the ratio of nifedipine, polyvinylpyrrolidone and cross-povidone may be altered within the limits which retain the amorphous nature of the drug. This also applies in the case of the subsequent Examples.

Furthermore, the Methocel used may be Methocel K4M, K15M, K100M, or E, J, F grades depending on the release characteristics desired.

The gel forming polymer may be used in an amount of 3 - 50% with proportional changes in the precentage of adsorbate used. This also applies in the case of the subsequent Examples.

EXAMPLE 2

Polyvinylpyrrolidone with an average molecular weight of 60,000 (0.65 kg) was dissolved in isopropyl alcohol (10 kg). Nicardipine (1 kg) was then added to the solution and allowed to dissolve. The solution thereby obtained was then adsorbed onto cross-povidone (3 kg) and the solvent evaporated. The resulting powder was passed through an oscillating granulator to obtain a finer particle size. The powder (60%) was then tabletted with the following ingredients:

Methocel K100M (Trade Mark)	8.0%
Avicel pH101 (Trade Mark)	31.5%
Magnesium stearate	0.5%

to obtain a tablet containing 60 mg of active ingredient.

EXAMPLE 3

The procedure of Example 1 was repeated except that the nifedipine was replaced by an equal amount (1 kg) of (4-(2,1,3-benzoxadiazol-4-yl)-2,6-dimethyl-1, 4-dihydro-3-isopropyloxycarbonyl-pyridine-5-carboxylic acid methyl ester (PN 200) and tablets containing 10 mg of active ingredient were produced.

EXAMPLE 4

Polyvinylpyrrolidone with an average molecular weight of 55,000 (0.75 kg) was dissolved in methylene chloride (12 kg) nifedipine (1 kg) was then added to this solution and allowed to dissolve. The solution thereby obtained was then adsorbed onto cross-povidone (3 kg) and the solvent evaporated. The resulting powder was then passed through an oscillating granulator to obtain a fine particle size. X-ray diffraction and differential scanning calorimetry studies showed that the drug was in amorphous form in this adsorbate. The powder (30%) was then tabletted with the following ingredients:

Methocel K100 LV (Trade Mark)	10%
Avicel pH101 (Trade Mark)	59.5%
Magnesium stearate	0.5%

to obtain a tablet containing 20 mg active ingredient.

Similarly x-ray diffraction and differential scanning calorimetry studies show this product to be amorphous.

EXAMPLE 5

A nifedipine adsorbate was prepared as in the case of Example 4. The powder thus prepared (50%) was then blended with the following ingredients:

Methocel K100 M (Trade Mark)	44.5%
Avicel pH101 (Trade Mark)	5.0%
Magnesium stearate	0.5%

and encapsulating to give capsules containing 20 mg of active ingredient.

EXAMPLE 6

Polyvinylpyrrolidone (1 kg) with an average molecular weight of 65,000 was dissolved in 10 kg methylene chloride. Felodipine (1.5 kg) was added and dissolved. The solution obtained was adsorbed onto cross-povidone (5 kg) and the solvent evaporated. The resulting powder was then passed through an oscillating granulator to obtain a fine particle size. X-ray diffraction and differential scanning calorimetry studies showed that the drug was in an amorphous form in this adsorbate. The powder (30%) was then tabletted with the following ingredients:

Methocel K15M (Trade Mark)	30.0%
Avicel pH101 (Trade Mark)	39.5%
Magnesium stearate	0.5%

to obtain a tablet containing 10 mg active ingredient.

EXAMPLE 7

Example 1 was repeated except that the adsorbate ~~adsorbed on the cross-povidone~~ (50%) was tabletted with

Sodium alginate	15.0%
Pregelatinised starch	33.5%
Talc	1.5%

to obtain tablets containing 50 mg of active ingredient.

EXAMPLE 8

Example 1 was repeated except that the adsorbate ~~adsorbed on the cross-povidone~~ contained nitrendipine and the final tablets contained 20 mg of the active ingredient.

EXAMPLE 9

Example 2 was repeated except that the adsorbate contained nimodipine and was tabletted with

Lactose V.S.P.	10.0%
Eudragit R.S.	10.0%
Eudragit R.L.	29.25%
Calcium stearate	0.75%

to form tablets containing 50 mg of nimodipine.

EXAMPLE 10

Example 1 was repeated except that the adsorbate ~~adsorbed on the cross-povidone~~ was tabletted with

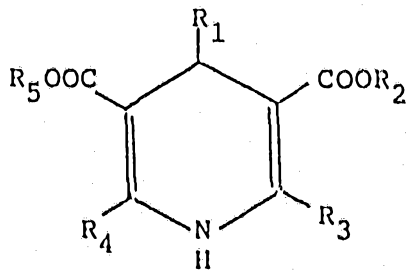
Dibasic calcium phosphate dihydrate N.F.	15.0%
Ethylcellulose 100 c.p.s.	15.0%
Polyethyleneglycol 6000	5.0%
Hydroxyethylcellulose	29.0%
Calcium stearate	1.0%

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A sustained release capsule or tablet formulation suitable for once daily administration comprising an adsorbate of a mixture of 1 part by weight of a pharmaceutically useful dihydropyridine and from 0.1 to 10 parts by weight of a polyvinylpyrrolidone having an average molecular weight greater than 55,000 adsorbed on a cross-linked polyvinylpyrrolidone in a ratio of 1 part by weight of ~~adsorbate~~ said mixture to 0.5 to 20 parts by weight of cross-linked polyvinylpyrrolidone, blended with a polymer or mixture of polymers which gel in the presence of water, the amount of said polymer or polymers being effective to produce the desired sustained release effect.

2. A formulation according to claim 1, wherein said gel forming polymer is present in an effective amount between 3 to 50% by weight of the formulation.

3. A formulation according to claim 1 or 2, wherein the dihydropyridine falls within the general formula (I)



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wherein R_1 is aryl or heteroaryl each of which is optionally substituted and R_2, R_3, R_4 and R_5, which may be the same or different, each represents an optionally substituted alkyl group.

4. A sustained release formulation according to claim 3, wherein in the dihydropyridine of the general formula I, R_1 is aryl or heteroaryl each of which is optionally substituted by a halogen atom or a nitro group and R_2, R_3, R_4 and R_5, which may be the same or different, each represents an alkyl group optionally substituted by a halogen atom or by an alkoxy, amino, alkylamino or aralkylamino group.

5. A sustained release formulation according to claim 3 or 4, wherein the dihydropyridine is selected from felodipine, nicardipine, nifedipine, nitrendipine, nimodipine, nisoldipine and 4-(2,1,3-benzoxadiazol-4-yl)-2,6-dimethyl-1,4-dihydro-3-isopropyloxycarbonyl-pyridine-5-carboxylic acid methyl ester.

6. A sustained release formulation according to any one of claims 1 to 5, wherein the polyvinylpyrrolidone is present in the adsorbate in an amount of 0.25 - 2 parts by weight relative to 1 part by weight of the dihydropyridine.

7. A sustained release formulation according to any one of claims 1 to 6, which contains 1 part by weight of said mixture ~~adsorbate~~ relative to 1-10 parts by weight of cross-linked polyvinylpyrrolidone.

8. A sustained release formulation according to any one of claims 1 to 7, wherein the polyvinylpyrrolidone has an average molecular weight in the range 55,000 to 75,000.

9. A sustained release formulation according to any one of claims 1 to 8, wherein the polymer which gels in the presence of water is selected from polyvinyl alcohol, polyvinylpyrrolidone, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, alkylcelluloses, copolymers of acrylic and methacrylic acid esters, polyethylene glycol, sodium alginate, galactomannone and carboxypolymethylene or mixtures thereof.

10. A sustained release formulation according to claim 9, wherein the polymer is hydroxypropylmethylcellulose.

11. A sustained release formulation according to claim 1, substantially as hereinbefore described with particular reference to the accompanying Examples.

12. A process for preparing a sustained release formulation according to any one of claims 1 - 8, which comprises dissolving the dihydropyridine and the polyvinylpyrrolidone in a common solvent, mixing the solution thereby obtained with a given quantity of the cross-linked polyvinylpyrrolidone so as to permit adsorption of said dihydropyridine and said polyvinylpyrrolidone to said cross-linked polyvinylpyrrolidone, removing the solvent, and blending the resulting product with said polymer or mixture of polymers which gel in the presence of water and encapsulating or tabletting the resulting blend.

13. A process according to claim 12, wherein the solvent used is any pharmaceutically suitable co-solvent for the dihydropyridine and the polyvinylpyrrolidone.

14. A process according to claim 13, wherein the solvent is selected from water, alcohols, ketones, halogenated aliphatic compounds, halogenated aromatic hydrocarbon compounds, aromatic hydrocarbon compounds and cyclic ethers or a mixture thereof.

15. A process according to claim 12 or 13, wherein the solvent is selected from water, hexane, heptane, methanol, ethanol, isopropyl alcohol, acetone, methylethyl ketone, methylisobutyl ketone, methylene chloride, chloroform, carbon tetrachloride, toluene, xylene and tetrahydrofuran.

16. A process according to claim 12, substantially as hereinbefore described with particular reference to the accompanying Examples.

17. A sustained release formulation whenever prepared by a process claimed in any one of claims 12 - 15.

~~18. The steps or features, compositions and compounds~~ referred to or indicated in the specification and/or claims of this application, individually or collectively, and any and all combinations of any two ~~or more of said steps or features~~.

Dated this 2nd day of February 1987
ELAN CORPORATION, PLC
By its Patent Attorneys
Davies & Collison