AUSTRALIA

PATENTS ACT 1990

681236

PATENT REQUEST : STANDARD PATENT

I/We being the person(s) identified below as the Applicant(s), request the grant of a patent to the person(s) identified below as the Nominated Person(s), for an invention described in the accompanying standard complete specification.

Full application details follow:

[71/70] Applicant(s)/Nominated Person(s):

Synthelabo

of

22, avenue Galilee, 92350 Le Plessis-Robinson, France

[54] Invention Title:

Sustained-release dosage forms of alfuzosin hydrochloride

[72] Name(s) of actual inventor(s):

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Basic Convention Application(s) Details:

[31] Application Number	[33] Country	Code	[32] Date of Application
94.03257	France	FR	21 March 1994

DATED this TWENTIETH day of MARCH 1995

Keith Davies

a member of the firm of DAVIES COLLISON CAVE for and on behalf of the applicant(s)

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NOTICE OF ENTITLEMENT

We, **Synthelabo,** the applicant/Nominated Person named in the accompanying Patent Request state the following:-

The Nominated Person is entitled to the grant of the patent because the Nominated Person would, on the grant of a patent for the invention to the inventors, be entitled to have the patent assigned to the Nominated Person.

The Nominated Person is entitled to claim priority from the basic application listed on the patent request because the Nominated Person made the basic application.

DATED this TWENTIETY day of MARCH 1995

Keith Davies

a member of the firm of
DAVIES COLLISON
CAVE for and on behalf
of the applicant(s)

(DCC ref: 1729420)

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(12) PATENT ABRIDGMENT (11) Document No. AU-B-14955/95
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 681236

(54) Title
SUSTAINED-RELEASE DOSAGE FORMS OF ALFUZOSIN HYDROCHLORIDE

International Patent Classification(s)
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(74) Attorney or Agent
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(56) Prior Art Documents
EP 0204597
US 4315007

(57) Claim

1. Pharmaceutical composition which comprises a core comprising alfuzosin hydrochloride, which core is coated with a coating containing a polymer whose dissolution is pH-dependent.

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COMPLETE SPECIFICATION

NAME OF APPLICANT(S):

Synthelabo

ADDRESS FOR SERVICE:

DAVIES COLLISON CAVE
Patent Attorneys
1 Little Collins Street, Melbourne, 3000.

INVENTION TITLE:

Sustained-release dosage forms of alfuzosin hydrochloride

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

The present invention relates to targeted-release pharmaceutical forms of alfuzosin hydrochloride and to their application to the preparation of sustained-release dosage forms which are usable for a once-daily administration.

Alfuzosin hydrochloride, used orally in the symptomatic treatment of benign prostatic hypertrophy, displays an absorption whose intensity decreases along the digestive tract, absorption being low in the ileum and colon.

According to a traditional oral form, this compound must hence be administered several times daily.

For alfuzosin hydrochloride, a sustained-release oral form enabling a constant plasma concentration which is sufficient over 24 hours to be obtained must effect its release and its absorption mainly in the lower portions of the digestive tract.

The new dosage forms according to the present invention enable the release of alfuzosin hydrochloride in the digestive tract to be targeted, and are applicable to a once-daily oral administration while being very safe as regards any excessively rapid release.

The pharmaceutical forms (compositions) according to the invention contain a core, namely a tablet affording immediate release or sustained release or microparticles affording immediate release of

alfuzosin hydrochloride, coated with a membrane whose nature and thickness enable the release of the active principle to be controlled on the basis of pH and time.

The tablets affording immediate or sustained release of the active principle, all the dimensions of which are less than 10 mm, contain 3 to 10 % by weight of alfuzosin hydrochloride.

The first kind of tablet is prepared by aqueous granulation from the active principle and excipients such as lactose, microcrystalline cellulose, polyvinylpyrrolidone, sodium carboxymethylstarch and magnesium stearate, the second kind is prepared by aqueous granulation or melting, by combining the active principle with a lipid matrix composed, for example, of microcrystalline cellulose, dicalcium phosphate dihydrate, hydrogenated castor oil, polyvinylpyrrolidone and magnesium stearate.

The microparticles affording immediate release of the active principle contain 3 to 15 % by weight of alfuzosin hydrochloride and are between 0.50 and 1.25 mm in size. They are generally prepared by aqueous granulation from the active principle, mannito and polyvinylpyrrolidone.

The tablets and the microparticles are then surrounded by a coating film by spraying with a coating solution in an air-fluidized bed apparatus or any other satisfactory device.

The coating contains a polymer whose dissolution is pH-dependent, for example Eduragit S® (methacrylic acid copolymer) which enables a coating film that dissolves at a pH above 7 to be obtained, thereby effecting a colonic release of the active principle.

The thickness of the coating film enables the latency time of release of the active principle at pH 7 to be modulated.

In the case of microparticles, the coating may further contain an impermeable polymer, and be composed, for example, of a combination of Eudragit S® and ethylcellulose, enabling the rate of release of the active principle to be modulated and effecting, as in the above case, a release of the active principle which is pH- and time-dependent as a result of the presence of the polymer which is soluble at a certain pH and of the thickness of the coating film.

The pharmaceutical forms according to the invention typically contains from 3 to 20 mg of alfuzosin hydrochloride.

They may be used for the preparation of sustained-release dosage forms of alfuzosin hydrochloride for a single daily administration.

These dosage forms can contain one or more pharmaceutical forms having coated cores as are defined above, and, possibly, one or more other pharmaceutical forms having coated or uncoated cores.

Mixing of these different forms enables the release of the active principle to be modulated over the whole length of the digestive tract.

The examples which follow illustrate the invention:

Example 1: tablets for colonic targeting.

tablets	% (by weight)
alfuzosin hydrochloride	3.3
lactose	69.4
microcrystalline cellulose	17.8
polyvinylpyrrolidone	5.0
sodium carboxymethylstarch	4.0
magnesium stearate	0.5
coating	
methacrylic acid copolymer	75.7
diacetylated monoglycerides	7.5
talc	16.8

Example 2: microparticles for colonic targeting.

microparticles	% (by weight)
alfuzosin hydrochloride	7.0
mannitol	32.0
microcrystalline cellulose	56.0
polyvinylpyrrolidone	5.0

coating	
methacrylic acid copolymer	65.0
ethylcellulose	35.0
diacetylated monoglycerides	9.0

Example 3: tablets in a hard gelatin capsule for a once-daily oral administration.

tablet no. 1	% (by weight)
alfuzosin hydrochloride	3.3
microcrystalline cellulose	30.0
dicalcium phosphate dihydrate	42.7
hydrogenated castor oil	18.0
polyvinylpyrrolidone	5.0
magnesium stearate	1.0

tablet no. 2	
alfuzosin hydrochloride	3.3
lactose	69.4
microcrystalline cellulose	17.8
polyvinylpyrrolidone	5.0
sodium carboxymethylstarch	4.0
magnesium stearate	0.5

coating of the tablet no. 2	
methacrylic acid copolymer	75.7
diacetylated monoglycerides	7.5
talc	16.8

Tests of dissolution of these different pharmaceutical forms were carried out at pH 2 and at pH 7. The following results were obtained:

Formulation according to Example 1, the coating representing 11 % of the weight of the tablet and having a thickness of 100 μm.

	% dissolved			
time (h)	0.5	1.0	2.0	3.0
pH 2	0	0	0	0
pH 7	0	0	30	100

This formulation, for which the release of alfuzosin hydrochloride is zero at acid pH and complete in the space of 3 hours at pH 7, with a latency time of 1 hour, enables release of the active principle to be effected in the colon.

By varying the thickness of the coating film, it is possible to modulate the latency time of release of the active principle at pH 7.

Formulation according to Example 2, the coating representing 14 % of the weight of the microparticles.

	% dissolved						
time (h)	0.5	1	2	3	4	6	8
pH 2	0.6	2	7	12	17	26	35
pH 7	1	5	23	47	64	83	91

This formulation, for which the release of alfuzosin hydrochloride varies with the pH, makes it possible to effect a rate of release of the active principle which varies over the whole length of the digestive tract.

Formulation according to Example 3, the coating of the tablet no. 2 representing 11 % of the weight of this tablet.

	% dissolved						
time (h)	0.5	1	2	3	4	6	8
pH 2	4	8	13	17	19	22	24
pH 7	0.4	4	11	64	89	94	98

This formulation, which combines two types of tablet in the same hard gelatin capsule, effects a release of alfuzosin hydrochloride which is variable with the pH, and hence a rate of release of the active

principle which is variable over the whole length of the digestive tract.

By increasing the number of tablets affording colonic targeting in the hard gelatin capsule, the amount of active principle released in the colon is increased.

The plasma kinetics of pharmaceutical forms according to the invention were also studied.

The plasma kinetics of tablets affording colonic targeting according to the formulation of Example 1 were determined in twelve healthy volunteers after a single oral administration.

The results obtained showed that the tablet of alfuzosin hydrochloride arrives in the colon after 5 hours on average, and that the active principle is released in a maximum time of 11 hours. The apparent half-life of this formulation is 9 hours.

Moreover, the plasma kinetics of hard gelatin capsules containing tablets of alfuzosin hydrochloride according to the formulation of Example 3 were studied.

The results obtained with three types of capsule containing different proportions of the two types of tablet are shown in Figure 1.

The curve represented by -□- represents the plasma kinetics of a hard gelatin capsule containing 1 uncoated no. 1 tablet containing 3 mg of alfuzosin hydrochloride and 3 coated no. 2 tablets each containing 3 mg of alfuzosin hydrochloride.

The curve represented by -○- represents the plasma kinetics of a hard gelatin capsule containing 1 uncoated no. 1 tablet containing 5 mg of alfuzosin hydrochloride and 2 coated no. 2 tablets having a dosage identical to that of the no. 2 tablets of the preceding case.

The curve represented by -△- represents the plasma kinetics of a hard gelatin capsule containing 1 unc ed no. 1 tablet containing 3 mg of alfuzosin hydrochloride and 2 coated no. 2 tablets having a dosage identical to that of the no. 2 tablets of the preceding cases.

The results show that this formulation, which enables the release of alfuzosin hydrochloride to be modulated over the entire length of the digestive tract, and thus the plasma kinetics to be modified, is suitable for a once-daily administration while being, as a result of the combination of dependency on time and on pH, very safe for avoiding any more rapid release.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. Pharmaceutical composition which comprises a core comprising alfuzosin hydrochloride, which core is coated with a coating containing a polymer whose dissolution is pH-dependent.

2. Pharmaceutical composition according to Claim 1, in which the polymer is a methacrylic acid copolymer.

3. Pharmaceutical composition according to Claim 1 or 2, in which the core is a tablet comprising alfuzosin hydrochloride and excipients.

4. Pharmaceutical composition according to Claim 3, in which the core is a tablet consisting of a matrix comprising alfuzosin hydrochloride.

5. Pharmaceutical composition according to Claim 1 or 2, in which the core consists of microparticles.

6. Pharmaceutical composition according to Claim 5, in which the coating further comprises ethylcellulose.

7. Pharmaceutical composition according to any one of Claims 1 to 6, which comprises from 3 to 20 mg of alfuzosin hydrochloride.

8. Pharmaceutical composition according to Claim 1 substantially as hereinbefore described in Example 1 or 2.

9. Dosage composition which comprises one or more coated cores, as defined in any one of Claims 1 to 8, and possibly, one or more other coated or uncoated cores comprising alfuzosin hydrochloride.

10. Dosage composition according to Claim 9, in which the cores are contained in a hard gelatin capsule.

11. Dosage composition according to Claim 10 substantially as hereinbefore described in Example 3.

12. A method for the treatment of the human or animal body comprising administering a pharmaceutical composition as defined in any one of Claims 1 to 8 or a dosage composition as defined in Claim 9, 10 or 11.

13. The steps, features, compositions and compounds disclosed herein or 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 TWENTIETH day of MARCH 1995

Synthelabo

by DAVIES COLLISON CAVE
Patent Attorneys for the applicant(s)

Abstract

Sustained-release compositions of alfuzosin hydrochloride.

Pharmaceutical compositions which comprises a core comprising alfuzosin hydrochloride, which core is coated with a coating whose dissolution is pH-dependent and applications to the preparation of sustained-release dosage compositions which are usable for a once-daily oral administration.

14955/05

plasma conc.

(ng/ml)

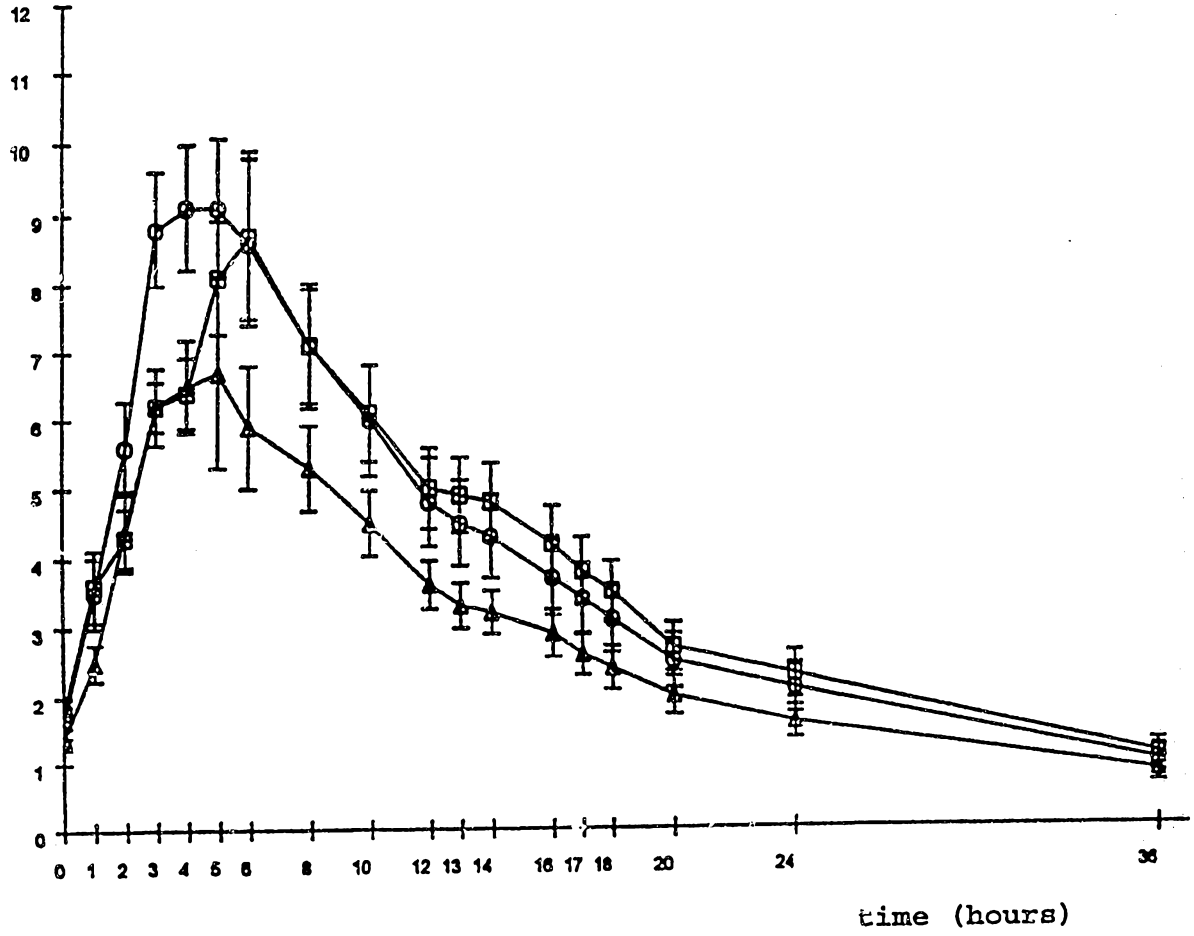


FIGURE 1