(CONVENTION. By one or more persons and/or a Com... 14 5

PATENT OFFICE LODGED AT SUB-OFFICE 13 NOV 1987 Melbourne ONE HUNDRED DOLLARS

PATENT OFFICE AUSTRALIA FIFTY DOLLARS

5985718

COMMONWEALTH OF A...

*Patents Act 1952-19...*

# CONVENTION APPLICATION FOR A PATENT

FEE STAMP TO VALUE OF $150 ATTACHED
MAIL OFFICER

(1) Here insert (in full) Name or Names of Applicant or Applicants, followed by Address (es).

~~I~~/We (1) CIBA-GEIGY AG

of Klybeckstrasse 141, 4002 Basle, Switzerland

(2) Here insert Title of Invention.

hereby apply for the grant of a Patent for an invention entitled: (2)

OSMOTIC CONTINUOUS DISPENSING ORAL DELIVERY SYSTEM CONTAINING A MODERATELY WATER-SOLUBLE METOPROLOL SALT HAVING IMPROVED CORE COMPOSITION AND USE THEREOF

(3) Here insert number(s) of basic application(s)

which is described in the accompanying complete specification. This application is a Convention application and is based on the application numbered (3)

930,828

(4) Here insert Name of basic Country or Countries, and basic date or dates

for a patent or similar protection made in (4) United States of America on 14th November 1986

AUSTRALIAN Reg 88(2) PATENT OFFICE

ADDRESS FOR SERVICE ALTERED

ARTHUR S. CAVE & CO, SYDNEY, N.S.W.

~~My~~ Our address for service is ~~Messrs. Edwd. Waters & Sons, Patent Attorneys, 50 Queen Street, Melbourne, Victoria, Australia.~~

DATED this 12th day of November 19 87

(5) Signature (s) of Applicant (s) or Seal of Company and Signatures of its Officers as prescribed by its Articles of Association.

LODGED AT SUB-OFFICE 13 NOV 1987 Melbourne

CIBA-GEIGY AG

by Louis C. Gebhardt

Registered Patent Attorney

To:

THE COMMISSIONER OF PATENTS.

AU Case ' 4-16168/=/CGC 1232 FORM 8

COMMONWEALTH OF AUSTRALIA

Patents Act 1952 - 1969

DECLARATION IN SUPPORT OF A CONVENTION APPLICATION FOR A PATENT

In support of the Convention Application made by CIBA-GEIGY AG for a patent for an invention entitled:

OSMOTIC CONTINUOUS DISPENSING ORAL DELIVERY SYSTEM CONTAINING A MODERATELY WATER-SOLUBLE METOPROLOL SALT HAVING IMPROVED CORE COMPOSITION AND USE THEREOF

We, Arnold Seiler and Ernst Altherr of CIBA-GEIGY AG, Klybeckstrasse 141, 4002 Basle, Switzerland
do solemnly and sincerely declare as follows:

1. We are authorised by the applicant for the patent to make this declaration on its behalf.

2. The basic application(s) as defined by Section 141 on the Act was(were) made in USA on November 14, 1986

by Shih-Wei Lee, Orangeburg, New York 10962, USA

3. Shih-Wei Lee, 278 Brandywine Drive, Orangeburg, New York 10962, USA

APPLICATION ACCEPTED AND AMENDMENTS ALLOWED 9-4-90

is the actual inventor(s) of the invention and the facts upon which the applicant is entitled to make the application are as follows: The said applicant is the assignee of the actual inventor(s).

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

DECLARED at Basle, Switzerland on October 2, 1987

CIBA-GEIGY AG

per

To: The Commissioner of Patents

(12) PATENT ABRIDGMENT (11) Document No. AU-B-81192/87
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 598318

(54) Title
**OSMOTIC CONTINUOUS DISPENSING ORAL DELIVERY SYSTEM CONTAINING A MODERATELY WATER-SOLUBLE METOPROLOL SALT HAVING IMPROVED CORE COMPOSITION AND USE THEREOF**

International Patent Classification(s)
(51)[4] **A61K 031/135**

(21) Application No. : **81192/87** (22) Application Date : **13.11.87**

(30) Priority Data

| (31) Number | (32) Date | (33) Country |
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| **930828** | **14.11.86** | **US UNITED STATES OF AMERICA** |

(43) Publication Date : **19.05.88**

(44) Publication Date of Accepted Application : **21.06.90**

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**CIBA-GEIGY AG**

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**ARTHUR S. CAVE & CO.**

(56) Prior Art Documents
**AU 53269/86 A61K 31/135**
**AU 71626/87 A61K 31/135**

(57) Claim

1. An osmotic dispensing oral delivery system containing a pharmaceutically acceptable salt of metoprolol having a solubility in water between 0.1 and 0.6 gram per cubic centimeter in water at 37°C, capable of a total delivery of between 50 and 500 mg of metoprolol, wherein upon activation in the gastrointestinal tract of the host, from 60 up to 90 percent of said metoprolol salt is delivered at a substantially continuous rate of 5 to 12 percent by weight of the total weight of said salt, per hour, comprising:

a) a semipermeable shaped wall membrane substantially impermeable to said salt and permeable to gastrointestinal fluid;

b) a core compartment within and defined by said wall; said core being in the form of a solid osmotically active composition comprising 7.5 to 15 percent by weight poly-N-vinylpyrrolidone; up to 5 percent by weight of a tabletting lubricant; and 92.5 to 80 percent by weight of said metoprolol salt, all based upon the core composition weight; and

.../2

c) at least one passageway in the wall in communication with the core compartment and the external environment for dispensing the metoprolol salt into said gastrointestinal tract.

598318

Form 10

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952-69

# COMPLETE SPECIFICATION

(ORIGINAL)

Class Int. Class

Application Number:
Lodged:

Complete Specification Lodged:
Accepted:
Published:
Priority :

Related Art :

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

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Name of Applicant : CIBA-GEIGY AG

Address of Applicant : Klybeckstrasse 141, 4002 Basle, Switzerland

AUSTRALIAN PATENT OFFICE Reg 88(2)

Actual Inventor: SHIH-WEI LEE

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~~EDWD. WATERS & SONS, 50 QUEEN STREET, MELBOURNE, AUSTRALIA, 3000.~~

Complete Specification for the invention entitled:

OSMOTIC CONTINUOUS DISPENSING ORAL DELIVERY SYSTEM CONTAINING A MODERATELY WATER-SOLUBLE METOPROLOL SALT HAVING IMPROVED CORE COMPOSITION AND USE THEREOF

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

4-16168/=/CGC 1232

# OSMOTIC CONTINUOUS DISPENSING ORAL DELIVERY SYSTEM CONTAINING A MODERATELY WATER-SOLUBLE METOPROLOL SALT HAVING IMPROVED CORE COMPOSITION AND USE THEREOF

## BACKGROUND OF THE INVENTION

Osmotic delivery systems for the oral administration of drugs are well known in the art. These systems dispense the active agent in a controlled and continuous manner over a prolonged period of time to produce a desired beneficial effect. Such systems are typically represented by U.S. 3,845,770, U.S. 3,916,899, U.S. 4,016,880 and the like.

Experimental osmotic delivery systems employing metoprolol fumarate contained within a semipermeable cellulosic wall and their in vivo performance have been described in the literature, e.g. Theeuwes et al., Br.J.Clin.Pharm. (1985), Vol. 19, pp. 69S-76S; Godbillon et al., Br.J.Clin.Pharm. (1985), Vol. 19, pp. 213S-218S and Warrington et al., Br.J.Clin.Pharm. (1985), Vol. 19, pp. 219S-224S.

Unfortunately, while experimental oral osmotic devices employing a moderately water-soluble metoprolol salt such as metoprolol fumarate (1:1) as the core ingredient can be prepared on a unit basis in the laboratory by simple dip coating a compressed core of the salt with, for example, a cellulose acetate solution, to obtain a semi-permeable membrane coated core, such a technique is unsuitable for large scale production of uniform quality product. Due to the high friability of the metoprolol salt, a compressed core thereof, alone or with trace amounts of excipients such as poly-N-vinylpyrrolidone,

is characteristically too fragile to employ in conventional air suspension techniques, such as the Wurster Air suspension technique or the like.

Moreover, the addition of substantial amounts of excipients may be expected to interfere with the release rate characteristics of the active agent.

It has now been surprisingly discovered that the normal friability of such cores can be substantially eliminated by employing between about 7.5 and 15 percent by weight poly-N-vinylpyrrolidone in combination with the moderately soluble pharmaceutically acceptable salt of metoprolol.

## OBJECTS OF THE INVENTION

It is accordingly an object of the invention to provide an osmotic delivery system for a moderately water-soluble pharmaceutically acceptable metoprolol salt comprising a semipermeable membrane wall covering a core compartment containing an osmotically active solid core composition comprising about 7.5 to about 15 percent by weight poly-N-vinylpyrrolidone; up to about 5 percent by weight of a tabletting lubricant; and about 92.5 to about 80 percent by weight of said metoprolol salt, and at least one passageway in the wall, for dispensing the metoprolol salt, in communication with said core compartment and the external environment.

It is another object of the present invention to provide a method of treatment of conditions responsive to beta$_1$-adrenoreceptor blocking agents in man in need of the same by orally administering to man an effective unit dosage amount in the form of such a device.

These and other objects of the instant invention are more fully described in the following detailed disclosure.

## DETAILED DESCRIPTION OF THE INVENTION

One embodiment of the present invention relates to an osmotic dispensing oral delivery system containing a moderately water-soluble pharmaceutically acceptable salt of metoprolol for a total delivery of between about 50 and about 500 mg of metoprolol, capable of delivery, upon activation in the gastrointestinal tract, from about 60 up to about 90 percent of said metoprolol salt at a substantially continuous rate of about 5 to about 12 percent by weight of the total weight of said metoprolol salt per hour comprising

a) a semipermeable shaped wall membrane substantially impermeable to said salt and permeable to gastrointestinal fluid;

b) a core compartment within and defined by said wall, said core being in the form of a solid osmotically active composition comprising about 7.5 to about 15 percent by weight poly-N-vinylpyrrolidone; up to about 5 percent by weight of a tabletting lubricant; and about 92.5 to about 80 percent by weight of said metoprolol salt, all based on the core composition weight; and

c) at least one passageway in the wall in communication with the core compartment and the external environment for dispensing the metoprolol salt into said gastrointestinal tract.

The metoprolol salt containing device is suitable for treating those conditions in mammals, including man, responsive to beta$_1$-adrenoreceptor blocking agents. Preferred indications include the treatment of those indications for which metoprolol and its pharmaceutically acceptable salts are known to be useful, including hypertension, angina pectoris, cardiac arrhythmias, and in the treatment of hemodynamically stable patients with myocardial infarction to reduce cardiovascular mortality.

Conventional commercially available metoprolol tartrate has an immediate release profile and is not in a rate controlled continuous dispensing form. On multiple dosing, such non-continuous forms produce fluctuations between peaks and troughs in terms of blood plasma levels as well as the degree of beta-blockade. While more frequent administration of such conventional forms can reduce these fluctuations, it is burdensome to some patients and may lessen compliance. While single daily doses of the conventional metoprolol salt are adequate if the only aim is to reduce blood pressure, a three-times-a-day regimen is advisable for the maintenance phase for the respective indications of myocardial infarction and angina pectoris.

The instant device advantageously provides a once-a-day regimen for all of the above indications for the total release, per unit dose, of between about 60 and about 500 mg of metoprolol wherein from about 50 up to about 90 percent of metoprolol is released at a substantially continuous rate of about 5 to about 12 percent by weight per hour.

The pharmaceutically acceptable salt of metoprolol is advantageously moderately water-soluble, such that the salt dissolves in the aqueous environment upon activation in the environment of use, i.e. the gastrointestinal tract, by aqueous fluid being imbibed by diffusion through the semipermeable shaped wall into the core compartment to continuously form a concentrated osmotically active solution of dissolved metoprolol salt. The concentrated salt, or solute, solution exhibits an osmotic pressure gradient against the aqueous gastrointestinal fluid and is released through one or more passageways in the wall in communication with both the core compartment and the external environment, to dispense the metoprolol salt at a controlled, preferably generally constant rate [zero order]. The influx rate of aqueous fluid from the aqueous environment through the semipermeable wall is controlled by the continuous dissolution of the metoprolol salt containing composition in the

core of the device. Accordingly, the metoprolol salt chosen is advantageously one which processes only limited or moderate solubility in the imbibed aqueous fluid, such that the metoprolol salt is released in a slow and continuous manner a prolonged time by maintaining the rate of internal dissolution of the core composition.

Preferably, the pharmaceutically acceptable metoprolol salt exhibits useful properies for formulations in oral osmotic systems ad has a solubility in water between about 0.1 to about 0.6 grams per cubic centimeter in water at about 37°C and the solubility can be determined simply by placing the salt in water and diluting until complete solution. Suitable metoprolol salts include lower alkanoate salts of metoprolol salts and mono-or di-metoprolol salts of lower alkylene dicarboxylates, especially metoprolol fumarate (1:1) and metoprolol maleate (1:1). Most preferred is the metoprolol fumarate (1:1).

The semipermeable wall membrane is prepared from a material which can form films and is inert to the metoprolol salt drug or host, is pharmaceutically acceptable and is permeable to the external gastrointestinal fluid while essentially being impermeable to the metoprolol salt drug in the device. This selectively permeable membrane forming the wall is insoluble in the gastrointestinal tract and non-erodible or it can be bioerodible after a predetermined period with bioerosion corresponding to the end of the active drug release period. In each instance it is permeable to the gastrointestinal solvent but not to the metoprolol salt solute and is suitable for construction of the osmotic powered device. Typical materials for forming the wall include membranes known to the art as present in osmosis and reverse osmosis membranes, such as commercially available unplasticized cellulose acetate, plasticized cellulose triacetate, agar acetate, amylose triacetate, beta glucan acetate, beta glucan triacetate cellulose acetate ethyl carbamate, cellulose acetate phthalate, cellulose acetate methyl carbamate, cellulose acetate succinate, cellulose acetate dimethylaminoacetate,

cellulose acetate ethyl carbonate, cellulose acetate methyl sulfonate, cellulose acetate butyl sulfonate, cellulose ethers, cellulose acetate propionate, poly(vinyl methyl) ether polymers, cellulose acetate octate, cellulose acetate laurate, methyl cellulose, triacetate of locust bean gum, cellulose acetate with acetylated hydroxyethyl cellulose, hydroxylated ethylenevinylacetate, osmotic membranes made from polymeric epoxides, alkylene oxide-alkyl glycidyl ethers, polyurethanes, polyglolic acid, and polycation-polyanion membranes known in the art. Generally such membranes have a fluid permeability of between about 0.01 to 10 $cm^3/cm^2$ x hour or day or higher at atmospheric pressure against a saturated product solution at about 30°C, and simultaneously possess a high degree of impermeability to the metoprolol salt solution.

Preferred semipermeable membrane materials include polyurethanes, methyl cellulose, cellulose acetate, ethyl cellulose, and cellulose acetate butyrate. Most preferred is cellulose acetate.

In general, useful wall materials and device parameters are disclosed, for example, in U.S. Patent No. 3,916,899, the disclosure of which is incorporated by reference herein, in toto.

Suitable tabletting lubricants include, for example, those lubricants known in the art such as silica, talc, magnesium stearate and high molecular weight polyethylene glycol. Preferred is magnesium stearate. The preferred amount is between about 1 and about 5, most preferably between about 2 and about 4, percent by weight, based upon the total core weight.

The poly-N-vinylpyrrolidone (PVP, Povidone) constituent is well known in the art, water soluble and has an average molecular weight between about 10,000 and about 700,000, preferably between 10,000 and 100,000. Preferred is povidone USP, commercially available through GAF Corp. under the PLASDONE tradename. The amount of poly-N-vinylpyrrolidone, as stated above, is between about 7.5 and about 15 percent by weight, based upon the total core weight.

Preferably, the amount of poly-N-vinylpyrrolidone present in the core formulation is about 8.5 and about 13 percent by weight.

Preferably, PLASDONE K-30 (GAF Corp.) of a molecular weight of 40,000 is used.

The amount of the metoprolol salt, as metoprolol present in the core, can vary widely but is preferably between about 50 to about 500 mg per unit tablet device. Most preferably, the core contains between about 60 to about 200 mg of metoprolol salt.

The core compartment is advantageously in the form of a tablet which is film coated with the semipermeable membrane to form the wall. The core composition is advantageously prepared by combining the moderately water-soluble salt of metoprolol with the poly-N-vinyl-pyrrolidone, either by dry blending and granulating in the presence of a water-ethanol mixture or by mixing said salt with an aqueous ethanolic solution of poly-N-vinylpyrrolidone, and subsequently granulating the mixture, and then drying the granulation and milling the same and optionally blending the dried milled granules with a tabletting lubricant, and compressing the resulting granules into tablets to form the core. The cores have advantageous properties useful for formulation such as hardness between about 8-25 S.C.U. units (Strong Cobb Units) and fragibility being less than 1.5 %, especially less than 1 %.

The core tablet is then subsequently coated with a semipermeable film-forming solution by using conventional coating methods, e.g. air suspension techniques, such as the Wurster Air suspension technique, to obtain a core tablet coated with the semipermeable wall material. The resulting device is provided with at least one passageway to osmotically release the metoprolol salt, as a concentrated or saturated solution, from the core to the gastrointestinal tract at a controlled rate. The passageway(s) can be formed, in situ, by using a heterogeneous solution to coat the core tablet

containing the semipermeable membrane film-forming solution and a water or gastrointestinal fluid soluble material, whereby in the environment of use passageways are formed by erosion with aqueous solvent in situ, or the semipermeable shaped wall can be drilled, either mechanically or by use of a laser, to form the passageway or passageways.

The passageway orifice size will vary depending upon the size of the core, exact desired release profile, and the number of passageways. Where one passageway is present, the orifice size can vary, for example, between about 0.1 mm and about 0.8 mm.

Generally, the film-forming semipermeable wall material is applied to the tablet core in the form of an organic solvent containing solution. Suitable solvents include, for example, dioxane, diethyl ether, lower alkanols, such as methanol or ethanol, and halogenated lower alkanes, such as chloroform, methylchloride and methylene chloride, or mixtures thereof. The amount of semipermeable membrane material employed per unit dose will vary dependent upon, for example, the permeability characteristics of the membrane material. For example, using cellulose acetate as the film-forming material, between about 4 and about 20 percent by weight, preferably between about 10 and about 20 percent by weight based upon the total weight of the device, may be employed.

The following examples are merely illustrative of the present invention and should not be considered as limiting the scope of the present invention. All parts are by weight unless otherwise specified.

Example 1:

To 95.37 parts by weight metoprolol fumarate (1:1) there is added 8.10 parts by weight povidone USP and the mixture is milled to a powder and granulated with an ethanol/water mixture (70/30). The granulation mixture is then dried, sized and 1.53 parts by weight magnesium stearate NF mixed therewith. The resulting particulate

product is compressed into core tablets containing a total weight per tablet of 105 mg, containing 7.7 weight percent povidone, 1.5 weight percent magnesium stearate, and remainder metoprolol fumarate (1:1). The core tablets exhibited the following characteristics:

Hardness (SCU): 9-11
Friability (percentage of tablets broken): 0.2
Disintegration time (min): 9

Example 2:

To illustrate the fragility of core tablets containing insufficient amounts of poly-N-vinylpyrrolidone, the following composition was prepared in identical fashion with Example 1 but with a reduced amount of povidone USP:

| | Parts by Weight | Weight % |
|---|---|---|
| Metoprolol fumarate (1:1) | 95.37 | 93.5 |
| Povidone USP | 5.10 | 5 |
| Magnesium Stearate NF | 1.53 | 1.5 |

The core tablets exhibited the following comparative characteristcs:

| | | |
|---|---|---|
| Hardness (SCU) | : | 7-9 |
| Friability (%) | : | 7.2 |
| Disintegration (min) | : | 8 |

Example 3:

Employing the procedure of Example 1, the following core tablets were prepared (parts by weight):

| Example | 3 | 4 | 5 | 6 |
|---|---|---|---|---|
| Metoprolol Fumarate (1:1) | 95.37 | 95.37 | 95.37 | 95.37 |
| Povidone, USP | 10.10 | 13.10 | 8.10 | 11.10 |
| Magnesium Stearate NF | 1.53 | 1.53 | 2.53 | 2.53 |
| % Povidone | 9.4 | 12.0 | 7.6 | 10.2 |
| % Magnesium Stearate | 1.4 | 1.4 | 2.4 | 2.3 |
| Hardness (SCU) | 14-15 | 11-18 | 9-11 | 8-11 |
| Friability (%) | 0.3 | 0.2 | 0.2 | 0.2 |
| Disintegration (min) | 7 | 8 | 18 | 15 |

Example 7:

Core tablets are prepared according to Example 1, containing per tablet 95 mg metoprolol fumarate (1:1), 2.90 mg magnesium stearate NF, and 11.10 mg povidone USP, having a hardness (SCU) of 8-11, a friability of 0.2 % and a disintegration time of about 15 minutes. The core tablets are film coated by air suspension with a methyl alcohol/methylene chloride solution of cellulose acetate containing about 16 mg cellulose acetate per tablet. The coated tablets are drilled to provide an exit passage orifice having a diameter of about 0.5 mm.

Example 8:

Coated tablets are prepared and drilled according to Example 7, but containing the following composition per tablet: metoprolol fumarate (1:1), 190.74 mg; povidone USP, 22.20 mg; magnesium stearate, 5.06 mg having a core composition hardness (SCU) of 11-16, a friability of 0.2 % and a disintegration time of 27 minutes, which is then coated with approximately 29 mg cellulose acetate and the dried coated tablet drilled to provide an exit passageway having a diameter of about 0.5 mm. Upon placement in simulated gastric fluid without enzymes at 37°C, in a U.S.P basket, wherein the fluid is stirred at 100 rpm, the following release characteristics are observed:

| Time Interval (Hours) | Average Hourly Release Rate (mg/h) | Average Cumulative Release (Percent) |
|---|---|---|
| 0 - 2 | 17.8 ± 2.7 | 18.7 |
| 2 - 4 | 21.4 ± 1.6 | 41.2 |
| 4 - 6 | 19.0 ± 0.9 | 61.2 |
| 6 - 8 | 17.0 ± 1.6 | 79.0 |
| 8 - 10 | 8.3 ± 1.4 | 87.7 |
| 10 - 12 | 4.5 ± 0.7 | 92.5 |

The claims defining the invention are as follows:

1. An osmotic dispensing oral delivery system containing a pharmaceutically acceptable salt of metoprolol having a solubility in water between 0.1 and 0.6 gram per cubic centimeter in water at 37°C, capable of a total delivery of between 50 and 500 mg of metoprolol, wherein upon activation in the gastrointestinal tract of the host, from 60 up to 90 percent of said metoprolol salt is delivered at a substantially continuous rate of 5 to 12 percent by weight of the total weight of said salt, per hour, comprising:

a) a semipermeable shaped wall membrane substantially impermeable to said salt and permeable to gastrointestinal fluid;

b) a core compartment within and defined by said wall, said core being in the form of a solid osmotically active composition comprising 7.5 to 15 percent by weight poly-N-vinylpyrrolidone; up to 5 percent by weight of a tabletting lubricant; and 92.5 to 80 percent by weight of said metoprolol salt, all based upon the core composition weight; and

c) at least one passageway in the wall in communication with the core compartment and the external environment for dispensing the metoprolol salt into said gastrointestinal tract.

2. A system according to claim 1, wherein the core compartment contains 8.5-13 % poly-N-vinylpyrrolidone.

3. A system according to claim 2, wherein the core compartment contains 8.5-13 % poly-N-vinylpyrrolidone of an average molecular weight of 40,000.

4. A sytem according to claim 1, wherein the salt is metoprolol fumarate (1:1).

5. A system according to claim 1, wherein the wall membrane consists essentially of cellulose acetate.

6. A system according to claim 1, wherein the core contains between 60 and 200 mg of metoprolol salt.

7. A system according to claim 1, wherein the lubricant is magnesium stearate.

8. A method of treating conditions responsive to $beta_1$-adrenoreceptor blocking agents in a mammal in need of the same, comprising administering orally to said mammal an effective amount of a device according to any one of claim 1-7.

9. An osmotic dispensing oral delivery system substantially as herein described with reference to any one of the Examples, excluding Example 2.

DATED this 26th day of March, 1990.

CIBA-GEIGY AG
By Its Patent Attorneys
ARTHUR S. CAVE & CO.

4015M/AC