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(54) Title: DOSAGE FORM FOR ADMINISTERING CALCIUM ANTAGONIST

(57) Abstract

A dosage form (10) is disclosed comprising a member selected from the group consisting of nicardipine and its pharmaceutically acceptable salts for administering to a patient in need of cardiovascular therapy.

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DOSAGE FORM FOR ADMINISTERING CALCIUM ANTAGONIST

TECHNICAL FIELD

This invention pertains to a dosage form comprising the beneficial drug nicardipine useful for treating cardiovascular conditions. The invention also concerns a method for treating cardiovascular conditions by administering a dosage form that delivers nicardipine at a therapeutically effective rate for the management of the cardiovascular conditions.

BACKGROUND OF THE INVENTION

The beneficial drug nicardipine, 1,4-dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylic acid methyl 2-[methyl(phenylmethyl)amino] ethyl ester and its pharmaceutically acceptable salts, is a calcium antagonist clinically useful for the treatment of cardiovascular conditions. Nicardipine is clinically useful for treating cardiovascular conditions such as ischemia, hypertension, congestive heart failure, cerebrovascular diseases and coronary artery disease. Nicardipine reduces myocardial oxygen demand through coronary vasodilation and it has cardioprotective and vascular antispastic effects. Nicardipine's chemical structure and synthesis are disclosed in The Merck Index, 10th Ed., p 931, (1983). Nicardipine's therapeutic properties are disclosed in a study reported in Clinical Therapeutics, Vol. 10, pp 316 to 325, (1988). The drug was administered in the study intravenously for its cardiovascular effects.

In the light of the above presentation, it will be appreciated by the pharmaceutical and medical professions that a considerable need exists for an oral dosage form useful for administering nicardipine and its salts for the management of cardiovascular diseases and for its clinical relevance. The need exists for a dosage form that can deliver the valuable drug nicardipine and its salts at a rate controlled by the dosage form to a patient in critical need of nicardipine cardiovascular therapy. The pressing demand exists also for an oral dosage form that can deliver nicardipine at a controlled rate and at a constant dose per unit time over a prolonged period of time for its beneficial hemodynamic

effects, which delivery occurs substantially independent of the variable environment of the gastrointestinal tract. It will be appreciated further by those versed in the dispensing art, that such a novel and unique form that can administer nicardipine in a rate controlled dose over time, and simultaneously provide cardiovascular therapy, would represent an advancement and a valuable contribution to the arts.

Accordingly, in view of the above presentation, it is an immediate object of this invention to provide a dosage form for delivering nicardipine and its salts in a rate controlled amount, and which dosage form substantially overcomes the deficiencies associated with the prior art.

Another object of the present invention is to provide a dosage form for administering nicardipine in a rate controlled dose over a prolonged period of time for cardiovascular therapy.

Another object of the invention is to provide a pharmaceutical dosage form that makes available sustained and controlled nicardipine therapeutic activity.

Another object of the invention is to provide a novel dosage form manufactured as an osmotic device that can administer nicardipine to a biological receptor to produce the desired pharmaceutical effects.

Another object of the present invention is to provide a dosage form manufactured as an osmotic dosage form that substantially reduced and/or substantially eliminates the unwanted influences of the gastrointestinal environment of use and still provide controlled administration of nicardipine over time.

Another object of the present invention is to provide a dosage form for administering a member selected from the group consisting of nicardipine and its pharmaceutically acceptable salts for calcium antagonist therapy.

Another object of the present invention is to provide a dosage form adapted for oral administration of nicardipine, which dosage form comprises a first composition and a contacting second composition that act in harmony for the rate controlled administration of nicardipine over time.

Another object of the present invention is to provide a complete pharmaceutical regimen comprising a composition comprising nicardipine that can be dispensed from a drug delivery device, the use of which device requires intervention only for initiation and possibly for termination of the regimen.

Another object of the invention is to provide a method of treating cardiovascular diseases by orally administering nicardipine in a rate controlled dosage per unit time to a warm-blooded animal in need of cardiovascular therapy.

Other objects, features and advantages of the invention will be more apparent to those versed in the dispensing arts from the following detailed specification, taken in conjunction with the drawings and the accompanying claims.

BRIEF DESCRIPTION OF THE DRAWINGS

In the drawing figures, which are not drawn to scale but are set forth to illustrate various embodiments of the invention, the drawing figures are as follows:

Figure 1 is a view of a dosage form designed and shaped for orally administering nicardipine or nicardipine and its salts to a gastrointestinal receptor of a warm-blooded animal;

Figure 2 is an opened view of the dosage form of Figure 1 for illustrating the structure of the dosage form;

Figure 3 is an opened view of the dosage form of Figure 1 depicting the dosage form manufactured comprising means for providing immediate drug delivery of nicardipine and means for providing controlled and prolonged drug delivery of nicardipine;

Figure 4 is an opened view of the dosage form of Figure 1 depicting a different structural embodiment of the dosage form provided by the invention; and,

Figures 5 through 12 depict release rates and cumulative amounts of nicardipine delivered over time by dosage forms provided by the invention.

DESCRIPTION OF THE INVENTION INCLUIDNG BEST MODE

Turning now to the drawing figures in detail, which drawing figures are an example of the dosage form provided by this invention, and which example is not to be construed as limiting, one example of

the dosage form is illustrated in Figure 1 and designated by the numeral 10. In Figure 1, dosage form 10 comprises a body member 11 comprising a wall 12 that surrounds and encloses an internal compartment, not seen in Figure 1. Dosage form 10 comprises at least one exit means 13 for connecting the interior of dosage form 10 with the exterior environment of use.

In Figure 2, dosage form 10, manufactured as an osmotic device, is seen in opened view. In Figure 2, dosage form 10 comprises body 11, wall 12, that is sectioned at 14, and which wall surrounds and defines as internal compartment 15. Wall 12 comprises at least one exit means 13 that connects compartment 15 with the exterior of dosage form 10.

Wall 12 of dosage form 10 comprises in at least a part a composition that is permeable to the passage of an exterior fluid present in the environment of use. Wall 12 is substantially impermeable to the passage of nicardipine and ingredients present in compartment 15. Wall 12 comprises a composition that is substantially inert, and it maintains its physical and chemical integrity during the dispensing life of nicardipine from dosage form 10. The phrase keeps its physical and chemical integrity means wall 12 does not lose its structure and it does not change during the dispensing life of dosage form 10.

Wall 12, in one presently preferred embodiment comprises a cellulose ethyl ether, or wall 12 comprises a composition comprising a cellulose ethyl ether, a cellulose ether, and other wall forming members. More specifically, wall 12 comprises from 45 weight percent to 80 weight percent of ethylcellulose, from 5 weight percent to 30 weight percent hydroxypropylcellulose and from 5 weight percent to 30 weight percent polyethylene glycol, with the total weight percent of all components comprising wall 12 equal to 100 weight percent. In another specific embodiment, wall 12 comprises 45 weight percent to 80 weight percent of ethylcellulose, from 5 weight percent to 30 weight percent hydroxypropylcellulose, from 5 weight percent to 30 weight percent polyethylene glycol, and from 2 weight percent to 20 weight percent of polyvinyl pyrrolidone, with the total amount of all components comprising wall 12 equal to 100 weight percent.

Wall 12, in another presently preferred embodiment comprises 100 weight percent of a cellulose polymer comprising a member selected from the group consisting of a cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate and cellulose triacetate. In another embodiment wall 12 comprises is a composition comprising from 60 weight percent to 95 weight percent of a member selected from the group consisting of a cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate and cellulose triacetate, from 0 weight percent to 35 weight percent of a member selected from the group consisting of a cellulose ether selected from the group consisting of hydroxypropylcellulose and hydroxypropylmethylcellulose, and from 0 weight percent to 30 weight percent of polyethylene glycol, with the total amount of all components comprising wall 12 equal to 100 weight percent.

Internal compartment 15, in drawing figure 2, comprises from 5 mg to 150 mg of the therapeutic drug nicardipine, represented by dots 16. The drug nicardipine 16 can be present in the form of its pharmaceutically acceptable salt, such as those formed by hydrochloric acid, hydrobromic acid, sulfonic acid, phosphoric acid, acetic acid, propionic acid, citric acid, oxalic acid, maleic acid, chlorotheophylline, gluconic acid, choline, or the like. Internal compartment 15 optionally comprises an osmagent 17, represented by dashes. The osmagents are known also as osmotically effective solutes. Osmagents 17 operable for the present purpose comprise sodium chloride, potassium chloride, sodium sulfate, potassium sulfate, magnesium chloride, lithium chloride, potassium acid phosphate, tartaric acid, raffinose, and the like. Generally compartment 15 optionally comprises from 1 mg to 75 mg of osmagent 17.

Figure 3 depicts another embodiment of dosage form 10, seen in opened section at 14. In drawing figure 3, dosage form 10 comprises body 11, wall 12, exit means 13, internal compartment 15, nicardipine 16 and osmotically effective compound 17. In Figure 3, dosage form 10 comprises additionally an overcoat 18 coated onto the exterior surface of wall 12. Overcoat 18 comprises a composition comprising

from 1 mg to 35 mg of nicardipine and its non-toxic salts, and an aqueous soluble carrier comprising hydroxypropylmethylcellulose. Overcoat 18 makes available instantly the drug nicardipine. In operation, when dosage form 10 is in a fluid environment of use, overcoat 18 dissolves or undergoes dissolution and concurrently delivers nicardipine 19 to the drug receptor.

In drawing Figure 4, another dosage form 10 provided by the invention is seen in opened section. In Figure 4, dosage form 10 comprises a body 11, wall 12, which wall 12 is sectioned at 14, with wall 12 surrounding and defining internal compartment 15. Wall 12 comprises at least one exit means 13 that connects compartment 15 with the exterior of dosage form 10. In dosage form 10, the internal compartment 15 comprises a first composition 19, which also can be defined optionally as a first lamina 19, and a second composition 20, which also can be defined optionally as a second lamina 20. First composition 19 and second composition 20 initially are in laminar arrangement and they cooperate with each other and with dosage form 10 for the effective delivery of nicardipine from dosage form 10.

In compartment 15, the first composition 19 comprises from 2 weight percent to 40 weight percent of nicardipine, or of nicardipine and its nontoxic salts, identified by dots 21; from 35 weight percent to 85 weight percent of a polyethylene oxide identified by curved lines 22, which polyethylene oxide 22 comprises a member selected from the group consisting of a polyethylene oxide comprising a molecular weight of about 100,000, a polyethylene oxide having a molecular weight of 200,000 a polyethylene oxide having a molecular weight of about 300,000, and a polyethylene oxide having a molecular weight of about 325,000; and from 0 weight percent to 20 weight percent of a hydroxypropylmethylcellulose having a number average molecular weight of 9,000 to 18,000, identified by dashes 23; which first composition 19 optionally comprises from zero weight percent to 3 weight percent of a lubricant, such as zero weight percent to 3 weight percent of magnesium stearate, with the total weight percent of all ingredients equal to 100 weight percent.

First composition 19, in more specified embodiments comprise, from 10 weight percent to 25 weight percent of nicardipine

hydrochloride, from 75 weight percent to 80 weight percent of polyethylene comprising a 100,000 molecular weight, from 4 weight percent to 7.5 of hydroxypropylmethylcellulose comprising a 11,300 molecular weight and from 0.3 weight percent to 0.75 weight percent magnesium stearate; and a first composition comprising from 35 weight percent to 45 weight percent nicardipine hydrochloride, from 40 weight percent to 50 weight percent of a polyethylene oxide comprising a 200,000 molecular weight, from 5 weight percent to 15 weight percent of a polyethylene oxide comprising a 300,000 molecular weight, from 3 weight percent to 8 weight percent of hydroxypropylmethyl cellulose comprising a 11,300 molecular weight, and from 0.3 weight percent to 0.75 weight percent of magnesium stearate.

The second composition 20 comprises form 50 weight percent to 75 weight percent of a polyethylene oxide comprising a 4,500,000 to 5,500,000 molecular weight identified by vertical lines 24; from 15 weight percent to 35 weight percent of an osmagent identified by dots 25; from 3 weight percent to 15 weight percent of a hydroxypropylmethylcellulose comprising a 9,000 to 18,000 molecular weight identified by slanted lines 26; from zero weight percent to 3 weight percent of a lubricant, such as stearic acid, magnesium stearate or the like, identified by short dashes 27; and from zero weight percent to 3 weight percent of a colorant, such as ferric oxide, with the total weight percent of all ingredients equal to 100 weight percent.

The second composition 20, in more specific embodiments comprises 60 weight percent to 70 weight percent of a polyethylene oxide comprising a 5,000,000 molecular weight, from 25 weight percent to 35 weight percent of osmagent sodium chloride, from 4 weight percent to 6 weight percent of a hydroxypropylmethylcellulose comprising a 11,300 molecular weight, from 0.75 weight percent to 1.25 weight percent ferric oxide, and from 0.4 weight percent to 0.7 weight percent magnesium stearate. The presence of the polyethylene oxide and the osmagent in the second composition increases the operating efficiency of dosage form 10. The operating efficiency occurs by the simultaneous hydration and swelling of the polyethylene

oxide coupled with the osmotic imbibition of exterior fluid through the semipermeable wall by the osmagent at a rate dependent on the concentration gradient across the wall. These combined physical actions are maintained at a high level over a prolonged period of time, thereby enabling the second compositions to push the first composition at a more constant and uniform rate over a corresponding prolonged period of time. The constant push against the first compartment assures a more uniform rate of release of nicardipine from the dosage form and concomitantly substantially prevents a declining and decreasing release rate over time. The polyethylene oxides used for manufacturing dosage form 10 is commercially available from the Union Carbide Corporation, South Charleston, West Virginia.

The expression, "exit means 13," as used herein, comprises means and methods suitable for the metered release of the beneficial drug nicardipine and/or its salts from dosage form 10. The means 13 includes at least one passageway, orifice, or the like, through wall 12 for communicating with nicardipine in dosage form 10. The expression, "at least one passageway," includes aperture, orifice, bore, pore, porous element through which the drug can migrate, hollow fiber, capillary tube, porous overlay, porous insert, and the like. The expression also includes a material that erodes or is leached from wall 12 in the fluid environment of use to produce at least one passageway in dosage form 10. Representative materials suitable for forming at least one passageway, or a multiplicity of passageways, include an erodible poly(glycolic) acid or poly(lactic) acid member in the wall; a gelatinous filament; poly(vinyl alcohol); leachable materials such as a removable pore forming polysaccharide, salt, oxide, or the like. A passageway, or a plurality of passageways can be formed by leaching a material such as sorbitol, lactose, maltose, or the like from the wall. The passageway can have any shape such as round, triangular, square, elliptical, or other irregular shapes, for assisting in the metered release of nicardipine from dosage form 10. Dosage form 10 can be constructed with one, or more passageways in spaced apart relations, or more than a single surface of a dosage form. Passageways are disclosed in United States Patents Nos.

3,845,770; 3,916,899; 4,063,064; and 4,088,864. Passageways formed by leaching are disclosed in United States Patent Nos. 4,200,098 and 4,285,987.

The osmagents used for the purpose of the present invention are also known as osmotically effective compounds and as osmotically effective solutes. The osmagents exhibit an osmotic pressure gradient across a semipermeable wall against an external fluid. The osmagent, along with the osmopolymer, imbibe fluid into the dosage form, thereby making available in situ fluid for imbibition and/or absorption by an osmopolymer to enhance its expansion for pushing the beneficial drug nicardipine from the dosage form. The osmagents can be inorganic or organic. Osmagents useful for the present purpose include magnesium sulfate, magnesium chloride, potassium sulfate, sodium sulfate, lithium sulfate, potassium acid phosphate, mannitol, sodium chloride, potassium chloride, urea, inositol, tartaric acid, raffinose, sucrose, glucose, sorbitol, and mixtures thereof. Osmagents are known to the prior art in U.S. Pat. No. 4,783,337.

The dosage form of the invention is manufactured by standard techniques. For example, in one embodiment the beneficial drug nicardipine is mixed with the compositional forming ingredients and pressed into a lamina possessing dimensions that correspond to the internal dimensions of the space adjacent to the passageway of the dosage form. In another manufacturing embodiment, the beneficial drug nicardipine and other first composition forming ingredients and a solvent are mixed into a solid, or a semisolid by conventional methods such as ballmilling, calendering, stirring, or rollmilling, and then pressed into a preselected lamina forming shape. Next, a lamina of a composition comprising an osmopolymer and an osmagent are place in contact with the lamina comprising the beneficial nicardipine, and the two lamina comprising the laminates are surrounded with a wall. The lamination of the first beneficial composition comprising the nicardipine and the second composition comprising the osmopolymer and the osmagent can be accomplished by using a conventional two-layered tablet press. The wall can be applied by molding, spraying, or dipping the pressed shapes into wall forming materials. Another and presently preferred technique that

can be used for applying the wall is the air suspension coating procedure. This procedure consists in suspending and trembling the two layered laminate in a current of air until the wall forming composition surrounds the laminate. The air suspension procedure is described in United States Patent No. 2,799,241; in J. Am. Pharm. Assoc., Vol. 48, pp 451-459 (1979); and, ibid, Vol. 49, pp 82-84 (1960). Other standard manufacturing procedures are described in Modern Plastic Encyclopedia, Vol. 46, pp 62-70 (1969); and in Pharmaceutical Sciences, by Remington, 14th Ed., pp 1626-1978, (1970), published by Mack Publishing Co., Easton, Penna.

Exemplary solvents suitable for manufacturing the wall, the laminates and laminae include inert inorganic and organic solvents that do not adversely harm the materials, and the final wall. The solvents broadly include a member selected from the group consisting of aqueous, alcohol, ketone, ester, ether, aliphatic hydrocarbon, halogenated, cycloaliphatic, aromatic, heterocyclic solvents, mixtures thereof, and the like. Typical solvents include acetone, diacetone, alcohol, methanol, ethanol, isopropyl alcohol, butyl alcohol, methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, methyl propyl ketone, n-hexane, n-heptane, ethylene glycol monoethyl ether, ethylene glycol nonethyl acetate, methylene dichloride, ethylene dichloride, propylene dichloride, carbon tetrachloride, chloroform, nitroethane, nitropropane, tetrachloroethane, ethyl ether, isopropyl ether, cyclohexane, cyclo-octane, benzene, toluene, naphtha, 1,4-dioxane, tetrahydrofuran, diglyme, aqueous and nonaqueous mixtures, acetone and water, acetone and methanol, acetone and ethyl alcohol, methylene dichloride and methanol, ethylene dichloride and methanol, ethyl alcohol and water, and the like.

DETAILED DESCRIPTION OF EXAMPLES

The following examples are merely illustrative of the present invention and they should not be considered as limiting the scope of the invention in any way, as these examples and other equivalents thereof will become more apparent to those versed in the art in the light of the present disclosure, the drawings and the accompanying claims.

EXAMPLE 1

A dosage form adapted, designed and shaped as an osmotic drug delivery system was manufactured as follows: first, 1.92 kg of nicardipine hydrochloride was dry blended with 7.54 kg of polyethylene oxide comprising a 100,000 molecular weight, 1.88 kg of polyethylene oxide comprising a 200,000 molecular weight and 0.60 kg of hydroxypropylmethylcellulose comprising a 11,200 molecular weight for 15 minutes in a Hobart® mixer. All the materials were pre-screened to 30 mesh. Next, 7.5 liters of anhydrous ethyl alcohol was added to the blended materials, followed by 15 minutes of additional blending in the blender. Then, the wet mass was passed through a stainless steel screen with 1/4 inch openings, about 6 mm, using a Fitzmill® comminutor, at low speed. Next, the screened blend was dried in an oven at 70°F, about 22°C, for 20 hours. The dried granules were passed through a 14 mesh screen, and then 56 g of magnesium stearate were added to yield 11,112 g of drug nicardipine granules.

In a separate operation, 16.125 kg of polyethylene coagulant comprising a 5,000,000 molecular weight was mixed with 7.250 kg of sodium chloride, 1.25 kg of hydroxypropylmethylcellulose comprising a 11,200 molecular weight and 0.25 kg of red iron oxide. The sodium chloride and the iron oxide were pre-screened through a 20 mesh screen. Then, 18 l of anhydrous ethyl alcohol was added with mixing, followed by 15 minutes of additional mixing to produce a uniform blend. The wet mass was passed through a stainless steel screen with 6 mm opening using a Fluid Air® mill at 500 rpm. Then, the granules were dried in a steam-heated oven at 22°C for 70 hrs. The dried granules were passed through a 10 mesh screen using a fluid air mill operating at 1500 rpm. Next, 120 g of magnesium stearate was added with blending to yield 24.02 kg, of osmotic driving composition.

Next, the nicardipine drug granules and the osmotic driving composition were loaded into the hopper of a Kilian® tablet press comprising a bilayer mode. Then, 12,857 tablets were compressed at an average weight of 239.2 mg each. The compression speed was 21 rpm. The compressed, bilayer cores exhibited a hardness of 7-8 kp, and they were 11/32 inches, about 10 mm, in diameter. Then, 1000 of

the cores were place in a 6 inch truncated, about 15 cm, column and coated using a standard air suspension technique. The wall coating composition comprised 94% cellulose acetate comprising a 39.8% acetyl content and 6% polyethylene glycol 3350 dissolved in a 4% (weight/weight) solution in 90% methylene chloride/10% methanol (w/w). About 3,600 g of coating solution was applied to the cores. The wet weight gain for each core as 35.7 mg. A 25 mil passageway was laser drilled in each coated core. Then, the dosage forms were dried at 45°C at 45% relative humidity for 70 hours, followed by 3 hours at 45°C without humidity. The dry membrane weight about 30 mg. The final dosage forms comprised 21.10 mg of nicardipine hydrochloride. The release rate in mg/hr. and the cumulative amount of nicardipine release over a prolonged period of 28 hrs. is seen in accompanying Fig. 5 and Fig. 6.

EXAMPLE 2

The procedure set forth in Example 1 was followed in this example. The composition comprising the drug nicardipine used in this example was prepared according to Example 1. The osmotic driving composition was prepared as described, and in this example the osmotic driving composition comprises 64.5% polyethylene oxide Coagulant® possessing a 5,000,000 molecular weight, 29% of sodium chloride, 5% of hydroxypropylmethylcellulose possessing a 11,200 molecular weight, 1% of iron oxide, and 0.5 mg of magnesium stearate. The drug nicardipine composition and the osmotic driving composition were compressed under 2.25 tons of compression force into bilayer cores.

Next, 1000 g of the bilayer cores were coated in a Wurster® air suspension coater. The coating solution comprised 241.4 g of ethyl cellulose, 62.2 g of hydroxypropylcellulose and 62.2 g of polyethylene glycol all dissolved in 10,000 ml of anhydrous ethyl alcohol and 877.8 ml of sterile water. The bilayers were coated at a flow rate of 38-40 ml/min. until the bilayers were uniformly coated with the wall forming composition. The average coat applied to each bilayer was about 37.1 mg. The coated bilayers were laser drilled to effect a 24 mil passageway in each drug delivery system. The delivery systems were dried for 72 hrs. at 50°C and the average dry

wall weighed about 33.5 mg. Each drug delivery system comprised 22 mg of nicardipine hydrochloride. The release rate in mg/hr., and the cumulative amount released over an extended period of time are seen in accompanying Fig. 7 and Fig. 8.

EXAMPLE 3

The procedure of Examples 1 and 2 was followed in this example, with the conditions as previously set forth, except that in the present example the wall forming composition comprises 280.9 g of ethyl cellulose, 79 g of hydroxypropylcellulose, 79 g of polyethylene oxide, 12,000 ml of anhydrous ethyl alcohol and 1.053 l of sterile water. The dosage form comprised a dry wall of 44.8 mg and a passageway of 23.6 mil.

EXAMPLE 4

The procedure of Examples 1 and 2 were followed in this example, with all procedures as previously described, except that in this example the drug layer comprises 40 wt % nicardipine hydrochloride, 46.33 wt % polyethylene oxide with a 200,000 molecular weight, 8.18 wt % polyethylene oxide, having a 300,000 molecular weight, 5 wt % hydroxypropylmethylcellulose having a 11,200 molecular weight, and 0.50 wt % of magnesium stearate. The osmotic driving composition comprised 64.50 wt % polyethylene oxide coagulant possessing a 5,000,000 molecular weight, 29 wt % of sodium chloride, 5 wt % hydroxypropylmethylcellulose possessing a 11,200 molecular weight, 1 wt % ferric oxide, and 0.5 wt % magnesium stearate. The wall of the dosage form comprises 60 wt % ethyl cellulose, 20 wt % hydroxypropylcellulose and 20 wt % polyethylene glycol. The dosage form comprises a 0.76 mm orifice, and exhibited a rate of release and cumulative amount release as seen in Fig. 9 and Fig. 10.

EXAMPLE 5

The procedures set forth herein were followed in this example, wherein the drug layer comprises 110 mg of nicardipine hydrochloride, 127.4 mg of polyethylene oxide having a 200,000 molecular weight, 22.5 mg of polyethylene oxide having a 300,000 molecular weight, 13.7 mg of hydroxypropylmethylcellulose having a 11,200 molecular weight, and 1.4 mg of magnesium stearate. The osmotic driving composition comprises 118.7 of polyethylene oxide having a molecular weight of

5,000,000, 53.4 mg of sodium chloride, 9.2 mg of hydroxypropylmethylcellulose having a 11,200 molecular weight, 1.8 mg of ferric oxide, and 0.9 mg of magnesium stearate. The wall of the dosage form comprises 45.1 mg of cellulose acetate having a 39.8% acetyl content and 5 mg of polyethylene glycol. The dosage form comprises a 0.79 mm orifice and exhibits a release rate and a cumulative amount release over time curves as seen in Fig. 11 and Fig. 12.

EXAMPLE 6

A series of dosage forms are prepared for delivery of nicardipine at a controlled rate orally to a warm-blooded animal in need of nicardipine therapy. The dosage forms are administered according to the method comprising the steps of: (A) admitting into a warm-blooded animal a dosage form comprising: (1) a wall surrounding a compartment, the wall selected from the group consisting of a composition comprising 20 mg to 30 mg of ethyl cellulose, 4 mg to 10 mg of hydroxypropylcellulose and 4 mg to 10 mg of polyethylene glycol; or, a composition comprising 30 mg to 40 mg of ethyl cellulose, 10 mg to 15 mg of hydroxypropylcellulose and 10 mg to 15 mg of polyethylene glycol; or, a composition comprising 15 mg to 25 mg of a cellulose acetate and 0.5 mg to 2 mg of polyethylene glycol; or, a composition comprising 40 mg to 50 mg of cellulose acetate and 3 mg to 8 mg of polyethylene glycol; (2) a compositional layer in the compartment comprising nicardipine present in an amount for performing a therapeutic program, said composition comprising 18 mg to 30 mg of nicardipine, from 80 mg to 90 mg of polyethylene oxide having a 200,000 molecular weight, from 15 mg to 25 mg of a polyethylene oxide having a 300,000 molecular weight, from 5 mg to 8 mg of hydroxypropylmethylcellulose, and from 0.5 mg to 1.5 mg of polyethylene glycol; or, a compositional layer in the compartment comprising nicardipine present in an amount for performing a therapeutic program, said composition comprising from 105 to 115 mg of nicardipine, from 120 mg to 130 mg of a polyethylene oxide having a 200,000 molecular weight, from 18 mg to 28 mg of a polyethylene oxide having a 300,000 molecular weight, from 10 mg to 15 mg of a hydroxypropylmethylcellulose having a 11,200 molecular weight, and

layer in the compartment for pushing the nicardipine composition from the dosage form, said pushing composition comprising from 60 mg to 70 mg of a polyethylene oxide Coagulant having a 5,000,000 molecular weight, from 25 mg to 35 mg of sodium chloride, from 3 mg to 8 mg of hydroxypropylmethylcellulose having a 11,200 molecular weight, from 0.5 mg to 1.5 mg of ferric oxide and from 0.2 mg to 0.75 of magnesium stearate; or a push composition comprising 110 mg to 125 mg of polyethylene oxide Coagulant having a 5,000,000 molecular weight, from 50 mg to 55 mg of sodium chloride, from 6 mg to 12 mg of hydroxypropylmethylcellulose having a 11,200 molecular weight, from 1 mg to 3 mg of ferric oxide and from 0.7 mg to 1.5 mg of magnesium stearate; and (4) or least one passageway in the wall for releasing the nicardipine; (B) imbibing fluid through the semipermeable part of the wall and the osmotic pressure gradient across the semipermeable wall causing the drug layer composition to hydrate and reduce viscosity and the osmotic push composition to expand and swell; and (C) deliver the beneficial nicardipine from the dosage form through the exit passageway to the warm blooded animal over a prolonged period of time.

In summary, it will be appreciated that the present invention contributes to the art an unobvious dosage form that possesses practical utility, and can administer nicardipine or a dose metered release rate per unit time. While the invention has been described and pointed out in detail with reference to operative embodiment thereof, it will be understood by those skilled in the art that various changes, modifications, substitutions and emissions can be made without departing from the spirit of the invention. It is intended therefore, that the invention embraces equivalents within the scope of the claims which follow.

The claims:

1. A dosage form for administering nicardipine to a patient, wherein the dosage form comprises:

(a) a wall comprising from 20 mg to 30 mg of ethyl cellulose, from 4 mg to 10 mg of hydroxypropylcellulose and 4 mg to 10 mg of polyethylene glycol, which wall surrounds;

(b) a compartment;

(c) a composition in the compartment comprising from 10 mg to 30 mg of a member selected from the group consisting of nicardipine and its pharmaceutically acceptable salts;

(d) a composition comprising a polyethylene oxide in the compartment for pushing the composition comprising nicardipine from the dosage form; and,

(e) at least one exit passageway in the wall for delivering nicardipine to the patient.

2. A dosage form for administering nicardipine to a patient, wherein the dosage form comprises:

(a) a wall comprising from 20 mg to 30 mg of ethyl cellulose, from 4 mg to 10 mg of hydroxypropylcellulose, and from 4 mg to 10 mg of polyethylene glycol, which wall surrounds;

(b) a compartment;

(c) a composition comprising from 105 mg to 115 mg of a member selected from the group consisting of nicardipine and its pharmaceutically acceptable salts in the compartment;

(d) a composition comprising a polyethylene oxide in the compartment for pushing the composition comprising nicardipine from the dosage form; and,

(e) at least one exit passageway in the wall for delivering the nicardipine from the dosage form.

3. A dosage form for administering nicardipine to a patient, wherein the dosage from comprises:

(a) a wall comprising from 30 mg to 40 mg of ethyl cellulose, from 10 mg to 15 mg of hydroxypropylcellulose and from 10 mg to 15 mg of polyethylene glycol, which wall surrounds;

(b) a compartment;

(c) a composition comprising from 10 mg to 120 mg of a member selected from the group consisting of nicardipine and its pharmaceutically acceptable salts in the compartment;

(d) a composition comprising a polyethylene oxide in the compartment for pushing the composition comprising nicardipine from the dosage form; and,

(e) at least one passageway in the wall for delivering the nicardipine from the dosage form.

4. A dosage form for administering nicardipine to a patient, wherein the dosage form comprises:

(a) a wall comprising from 15 mg to 50 mg of a cellulose acylate and from 0.5 mg to 8 mg of a polyethylene glycol, which wall surrounds a compartment;

(b) a composition comprising from 10 mg to 120 mg of a member selected from the group consisting of nicardipine and its pharmaceutically acceptable salts in the compartment;

(c) a composition comprising polyethylene oxide in the compartment for pushing the composition comprising nicardipine from the dosage form; and,

(d) at least one exit passageway in the wall for delivering the nicardipine from the dosage form.

AMENDED CLAIMS

[received by the International Bureau on 6 July 1990 (06.07.90); original claims 2 and 3 cancelled; original claim 1 amended; claim 4 amended and renumbered as claim 2 (1 page)]

1. A dosage form for administering nicardipine to a patient, wherein the dosage form comprises:

(a) a wall comprising from 20 mg to 40 mg of ethyl cellulose, from 4 mg to 15 mg of hydroxypropylcellulose and 4 mg to 15 mg of polyethylene glycol, which wall surrounds;

(b) a compartment;

(c) a composition in the compartment comprising from 15 mg to 150 mg of a member selected from the group consisting of nicardipine and its pharmaceutically acceptable salts, a polyethylene oxide having a 100,000 to 325,000 molecular weight, and a hydroxypropylmethylcellulose having a molecular weight of 9,000 to 18,000;

(d) a composition comprising a polyethylene oxide having a molecular weight greater than 4,500,000 and a hydroxypropylmethylcellulose possessing a 9,000 to 18,000 molecular weight in the compartment for pushing nicardipine from the dosage form; and,

(e) at least one exit passageway in the wall for delivering nicardipine to the patient.

2. A dosage form for administering nicardipine to a patient, wherein the dosage form comprises:

(a) a wall comprising from 15 mg to 50 mg of a cellulose acylate and from 0.5 mg to 8 mg of a polyethylene glycol, which wall surrounds a compartment;

(b) a composition comprising from 5 mg to 150 mg of a member selected from the group consisting of nicardipine and its pharmaceutically acceptable salts in the compartment, a polyethylene oxide having a 100,000 to 325,000 molecular weight, and a hydroxypropylmethylcellulose having a molecular weight of 9,000 to 18,000;

(c) a composition comprising polyethylene oxide having a molecular weight greater than 4,500,000 and a hydroxypropylmethylcellulose possessing a 9,000 to 18,000 molecular weight in the compartment for pushing nicardipine from the dosage form; and,

(d) at least one exit passageway in the wall for delivering the nicardipine from the dosage form.

STATEMENT UNDER ARTICLE 19

The accompanying amendment amends claim 1 by incorporating claims 2 and 3 into amended claim 1. Newly amended claim 1 covers the preferred embodiment of claims 2 and 3 by grouping claims 1, 2 and 3 of the invention of applicants for a dosage form comprising nicardipine. Claims 2 and 3 are cancelled in the accompanying amendment. Claim 4 was amended by the amendment to more particularly point out dosage ranges and specific composition, and it was renumbered as claim 2. The claims as renumbered consecutively are now 1 and 2, under Section 205a.

FIG. 1

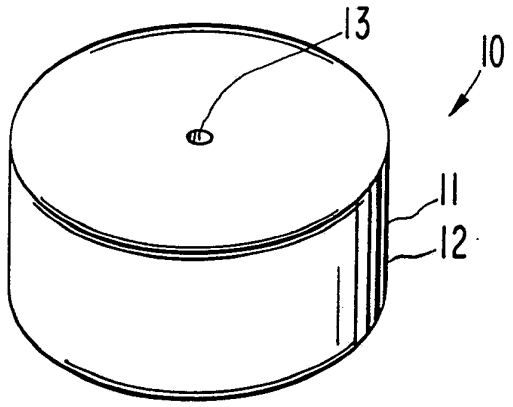


FIG. 2

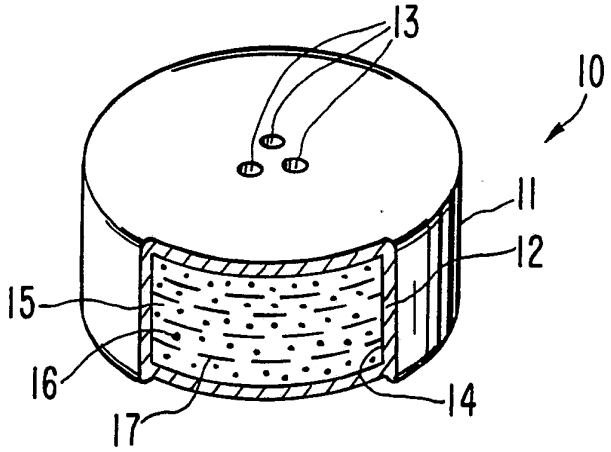


FIG. 3

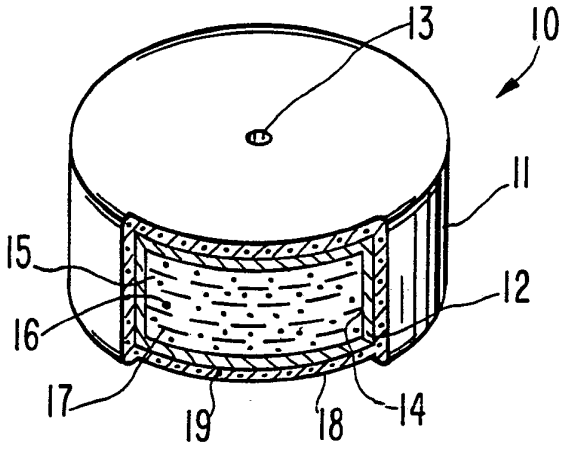


FIG. 4

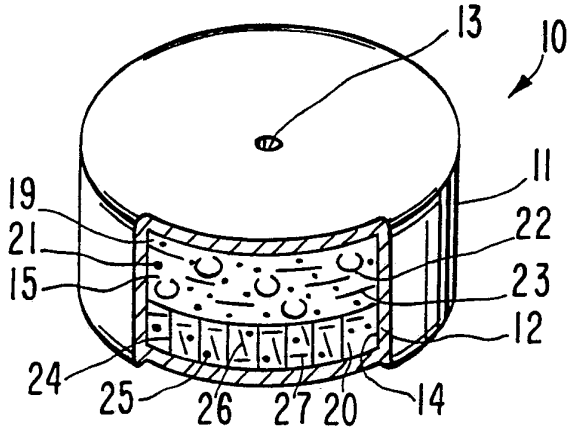


FIG.5

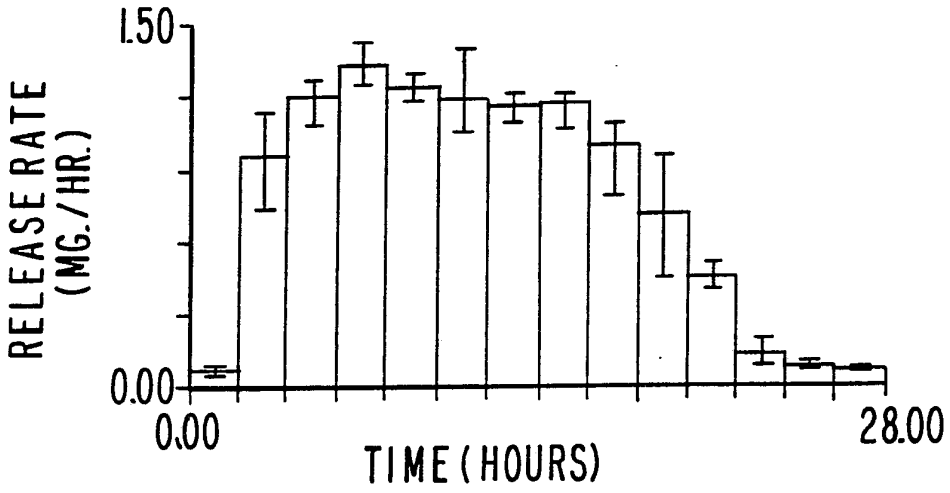

1.50
0.00
RELEASE RATE (MG./HR.)
0.00
28.00
TIME (HOURS)

FIG.6

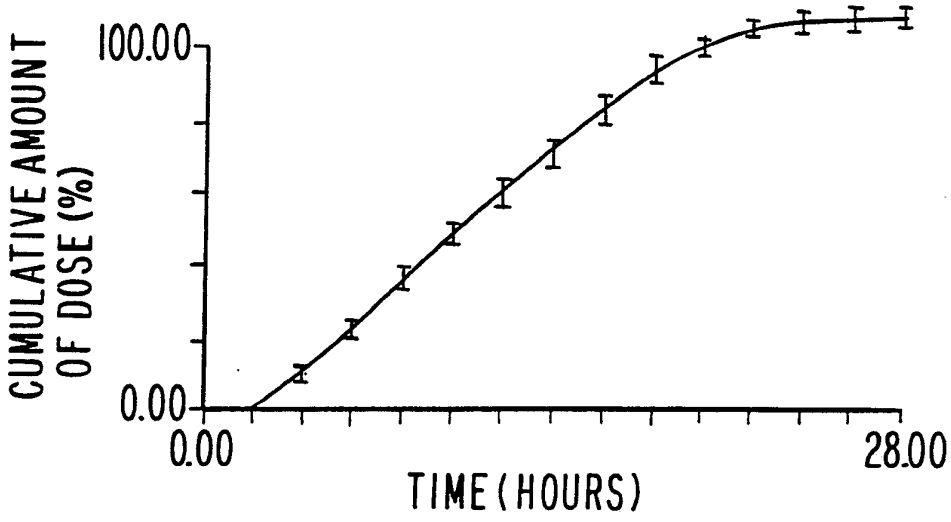

100.00
0.00
CUMULATIVE AMOUNT OF DOSE (%)
0.00
28.00
TIME (HOURS)

FIG.7

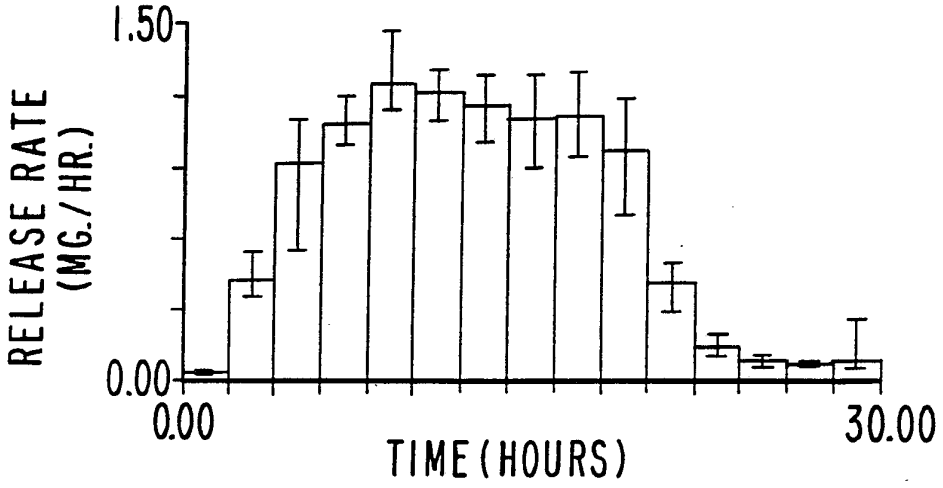

1.50
0.00
RELEASE RATE
(MG./HR.)
0.00
30.00
TIME (HOURS)

FIG.8

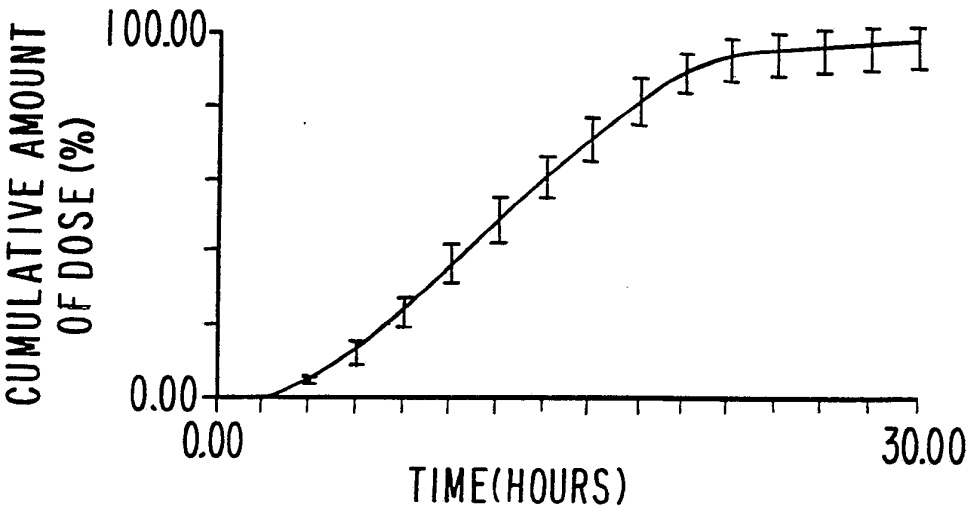

100.00
0.00
CUMULATIVE AMOUNT
OF DOSE (%)
0.00
30.00
TIME(HOURS)

FIG.9

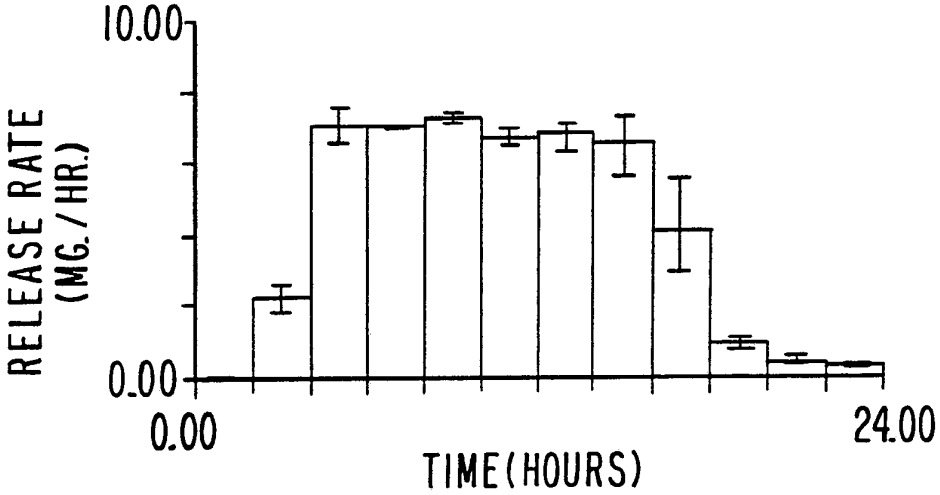

10.00
0.00
RELEASE RATE (MG./HR.)
0.00
24.00
TIME(HOURS)

FIG.10

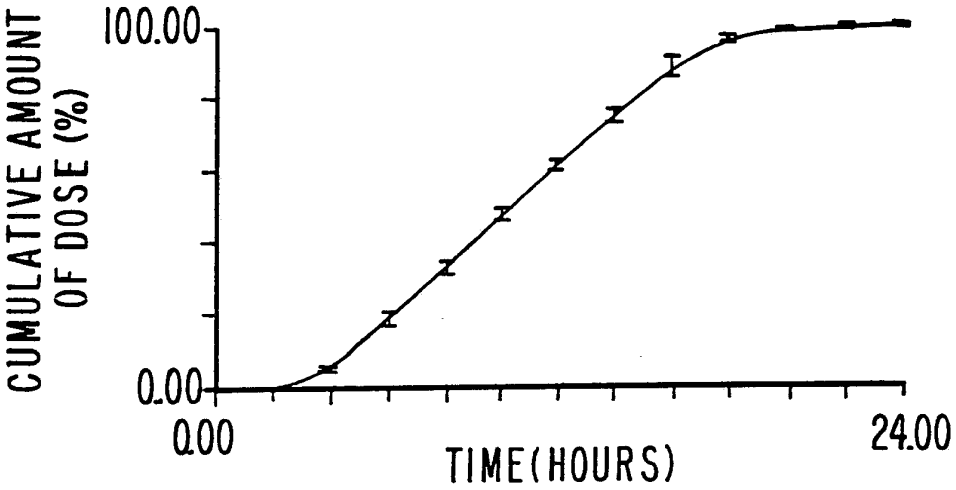

100.00
0.00
CUMULATIVE AMOUNT OF DOSE (%)
0.00
24.00
TIME(HOURS)

FIG. 11

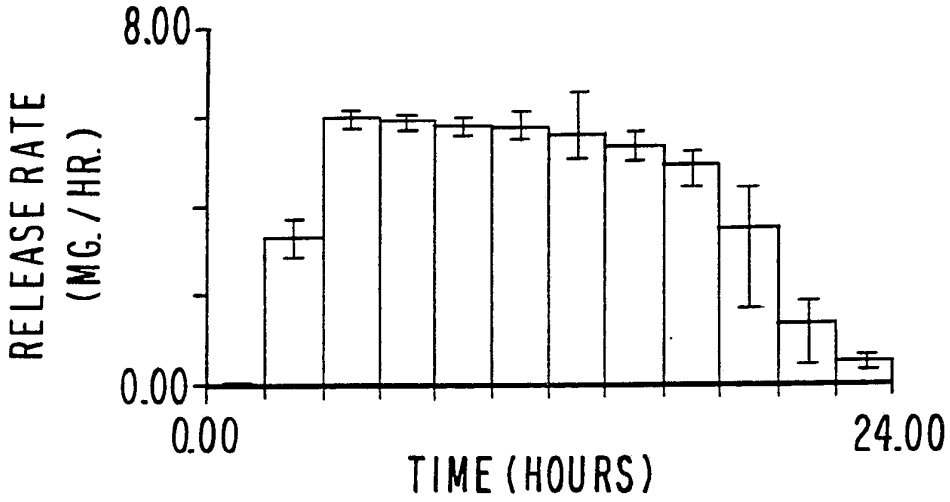
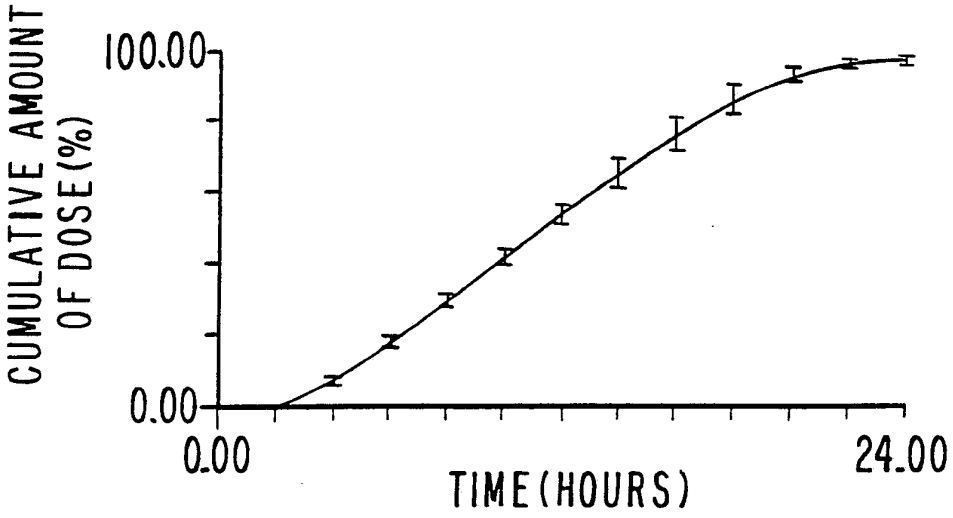

8.00
0.00
RELEASE RATE (MG./HR.)
0.00
24.00
TIME (HOURS)

FIG. 12


100.00
0.00
CUMULATIVE AMOUNT OF DOSE (%)
0.00
24.00
TIME (HOURS)

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 89/05670

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[5]: A 61 K 9/22, A 61 K 31/44

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[5]	A 61 K, A 61 M

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	US, A, 4783337 (WONG et al.) 8 November 1988 see the whole document, in particular column 24, example 3; claims 43,74,78 cited in the application	1-4
A	US, A, 4519801 (EDGREN) 28 May 1985 see the whole document, in particular examples	1-4
A	EP, A, 0238189 (ALZA CORP.) 23 September 1987 see page 15, lines 16-26; page 17, lines 5-9	1-4

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
25th April 1990	22.05.90
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	M. PE[illegible]

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 8905670 SA 33243

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 15/05/90
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 4783337	08-11-88	AU-B- 566110	08-10-87
		AU-A- 2251183	15-11-84
		BE-A- 898819	30-05-84
		CA-A- 1222950	16-06-87
		CH-A- 669329	15-03-89
		DE-A,C 3417113	15-11-84
		FR-A,B 2545721	16-11-84
		GB-A,B 2140687	05-12-84
		JP-A- 60041609	05-03-85
		NL-A- 8401470	03-12-84
		SE-B- 455918	22-08-88
		SE-A- 8402512	12-11-84
		US-A- 4612008	16-09-86
		US-A- 4765989	23-08-88
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