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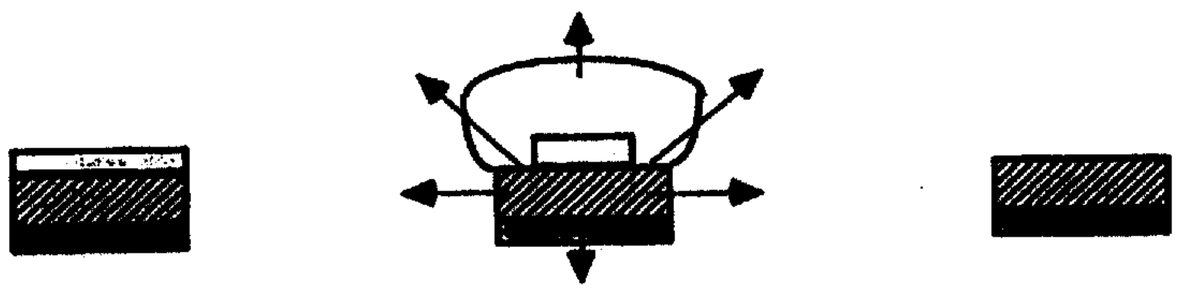
(54) **COMPRIME POUR LIBERATION REGULEE D'AGENTS ACTIFS**

(54) **TABLET FOR THE CONTROLLED RELEASE OF ACTIVE AGENTS**



(57) La présente invention porte sur un comprimé permettant une libération régulée d'un agent actif et comprenant (a) une couche centrale renfermant un agent actif encastré dans une matrice hydrophobe non gonflante, non érodable; (b) une première couche barrière appliquée sur la couche centrale et recouvrant une face unique de celle-ci; et (c) une seconde couche barrière éventuelle appliquée sur la couche centrale et recouvrant la face opposée de celle-ci et placée à l'opposé de la première. La partie centrale comprend jusqu'à environ 80 % d'agent actif et d'environ 5 % à environ 80 % en poids de cires non gonflantes ou d'une substance polymère insoluble dans un milieu aqueux, et les première et seconde couches barrière comprennent indépendamment (1) une substance polymère présentant un degré élevé de gonflement et de gélification en milieu aqueux ou (2) une cire non gonflante ou une substance polymère insoluble en milieu aqueux.

(57) The present invention provides a tablet for the controlled release of an active agent comprising (a) a core layer comprising an active agent embedded in a non-swelling, non-erodible hydrophobic matrix; (b) a first barrier layer applied to and coating a single face of the core layer; and (c) an optional second barrier layer applied to and coating the opposite face of the core layer and oppositely disposed to the first barrier layer; wherein the core comprises up to about 80 % active agent and from about 5 % to about 80 % by weight of nonswellable waxes or polymeric material insoluble in aqueous medium, and the first and second barrier layers independently comprise (1) polymeric material exhibiting a high degree of swelling and gelling in aqueous medium, or (2) nonswellable wax or polymeric material insoluble in aqueous medium.

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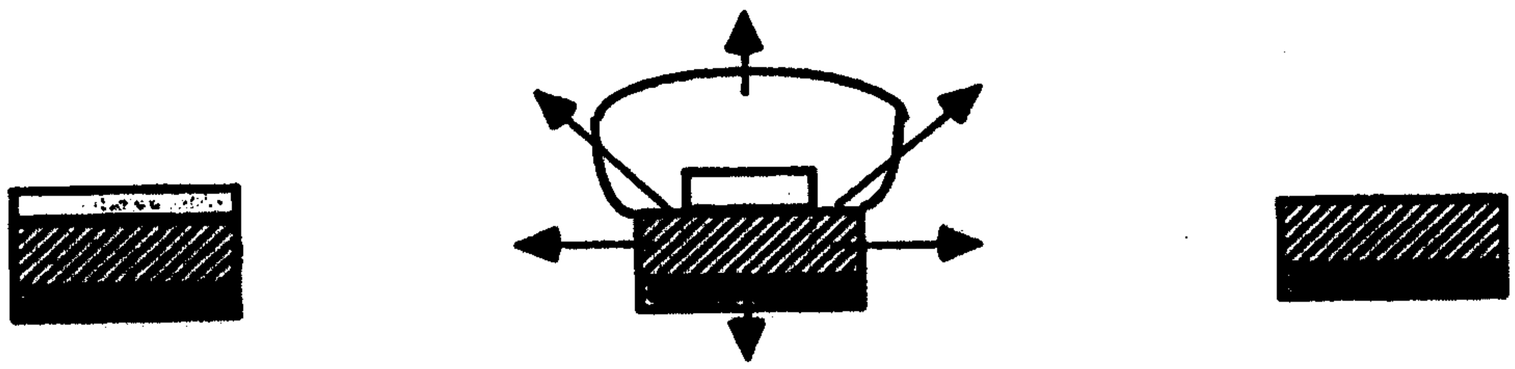
(54) Title: TABLET FOR THE CONTROLLED RELEASE OF ACTIVE AGENTS



(57) Abstract

The present invention provides a tablet for the controlled release of an active agent comprising (a) a core layer comprising an active agent embedded in a non–swelling, non–erodible hydrophobic matrix; (b) a first barrier layer applied to and coating a single face of the core layer; and (c) an optional second barrier layer applied to and coating the opposite face of the core layer and oppositely disposed to the first barrier layer; wherein the core comprises up to about 80 % active agent and from about 5 % to about 80 % by weight of nonswellable waxes or polymeric material insoluble in aqueous medium, and the first and second barrier layers independently comprise (1) polymeric material exhibiting a high degree of swelling and gelling in aqueous medium, or (2) nonswellable wax or polymeric material insoluble in aqueous medium.

Tablet for the Controlled Release of Active Agents

Technical Field

The present invention relates to a device for the controlled release of an active substance. More particularly, it relates to a layered tablet whose properties are such that it releases the active substance at a constant rate over a significant time period.

Background of the Invention

Many delivery systems for the delayed or controlled release of an active substance are currently available. Of these, the most popular is the matrix system containing uniformly dispersed drug because of its effectiveness as well as low cost and ease of manufacture. However, the release behavior of these systems is inherently nonlinear in nature as a result of the decreasing release rate with time due to an increase in diffusional resistance and/or a decrease in effective area at the diffusion front.

Numerous matrix systems have been devised in an effort to achieve linear release of the active substance. Several controlled release systems comprising an active substance dispersed in an insoluble matrix surrounded by an insoluble coating, in which the active agent is exposed through an aperture in the coating, have been described. For example, a ring shaped system in which the aperature is present in the center of the ring is described in EPA 259219. U.S. Pat. No. 3,851,648 discloses a cylindrical device in which the aperature runs along the length of the cylinder and defines a cavity. A truncated cone in which the small end of the cone is exposed to the dissolving fluid is disclosed in EPB-259113. The basis for these systems is that the surface area of exposed active agent continuously increases as dissolution proceeds, to compensate for the increased diffusion path between the aperature and the dissolving core.

A device comprising a shaped core containing the active substance surrounded by an impermeable coating which contains one or more apertures, in which the core geometry is used to control the surface area of the exposed surface is disclosed in EPA-542364.

A three-layered matrix system comprising a shaped core coated with erodible polymeric material is disclosed by Cremer *et al.*, *Proceed. Intern. Symp. Control. Rel. Bioact. Mater.*, **1995**, 22, 732-733. In this system, the release profile is controlled by erosion rate of the coating layers and the geometrical shape of the core.

A coated right cylinder having an exposed circumferential strip is disclosed in U.S. Pat. No. 4,972,448.

A matrix system for releasing insoluble drugs into the system in granular form comprising a generally cylindrical core which is coated on one or both faces with an inert or insoluble polymeric material is disclosed in U.S. Pat. No. 4,838,177. The core is obtained by compression

of the active substance and a swellable and gellable polymer or mixture of polymers. The release profile in this system is controlled by the high degree of swelling of the core.

Brief Description of the Drawing

FIG. **1** shows, respectively, the structure of a two-layered tablet of type MH when dry, after hydration, and when spent. In tablets of this type, a non-swelling, non-erodible hydrophobic core layer M containing an active agent is coated on a single face with a swellable and gellable hydrophilic barrier layer H. The arrows indicate the directions of drug diffusion. Diffusion occurrs through aqueous channels in uncoated surfaces of the core matrix formed by dissolution of the drug and any soluble excipients and through the hydrophilic barrier layer as it swells and erodes.

FIG. **2** shows, respectively, the structure of a three-layered tablet of type HMH when dry, after hydration, and when spent. In tablets of this type, a non-swelling, non-erodible hydrophobic core layer M containing an active agent is coated on opposing faces with swellable and gellable hydrophilic barrier layers H. The arrows indicate the directions of drug diffusion. Diffusion occurrs through the uncoated sides of the hydrophobic core and through the hydrophilic barrier layer as it swells and erodes.

FIG. **3** shows, respectively, the structure of a three-layered tablet of type HML when dry, after hydration, and when spent. In tablets of this type, a non-swelling, non-erodible hydrophobic core layer M containing an active agent is coated on a single face with a swellable and gellable hydrophilic barrier layer H and on the opposite face with a non-swelling, non-erodible barrier L. The arrows indicate the directions of drug diffusion. The routes of diffusion are through the uncoated side wall of the tablet and through the hydrophilic barrier layer as it swells and erodes. Drug diffusion also occurrs through the lipophilic barrier layer as soluble ingredients in the non-erodible coating dissolve and form pores. In systems of this type, the decreasing release rate due to increasing path length from the side wall is compensated by increasing the core surface area exposed to the dissolving fluid as the hydrophilic barrier layer swells and erodes.

FIG. **4** shows, respectively, the structure of the two-layered tablet of type ML when dry, after hydration, and when spent. In tablets of this type, a non-swelling, non-erodible hydrophobic core layer M containing an active agent is coated on a single face with a non-swelling, non-erodible barrier L. The arrows indicate the directions of drug diffusion. The arrows indicate the directions of drug diffusion. The release mechanism is diffusion through aqueous channels in uncoated surfaces of the core matrix formed by dissolution of the drug and any soluble excipients, and through the lipophilic barrier layer as soluble ingredients in the non-erodible coating dissolve and form pores.

FIG. **5** shows, respectively, the structure of the three-layered tablet of type LML when dry, after hydration, and when spent. In tablets of this type, a non-swelling, non-erodible

hydrophobic core layer M containing an active agent is coated on opposing faces with non-swelling, non-erodible barrier layers L. The arrows indicate the directions of drug diffusion. The arrows indicate the directions of drug diffusion. The primary route of diffusion is through the uncoated side wall of the tablet. Drug diffusion also occurrs through the lipophilic barrier layer as soluble ingredients in the non-erodible coating dissolve and form pores.

FIG. **6** is a plot of the fractional release *in vitro* of pseudoephedrine vs. time in hours for representative matrix formulations. The squares represent uncoated matrix tablet A. The circles represent a three-layed tablet of type HMH (formulation G). The triangles represent a three-layered tablet of type LML (formulation J). A three-layered tablet of type HML (formulation N) is represented by the symbol "+".

FIG. **7** is a plot of the fractional release *in vitro* of aminophylline or 2-methyl-3-(2-(S)-pyrroldinylmethoxy)pyridine vs. time in hours for from a three-layer tablet of type HML. The circles represent formulation O. The triangles represent formulation Q. Uncoated matrix formulation C is represented by the filled in triangles.

FIG. **8** is a plot of the plasma level in µg/mL vs. time in hours of aminophylline following oral administration to beagle dogs of the uncoated matrix formulation C and a three-layered matrix tablet of type HML (formulation Q). The upper curve represents formulation C and the lower curve represents formulation Q.

FIG. **9** is a plot of the plasma level in ng/mL vs. time in hours of 2-methyl-3-(2-(S)-pyrroldinylmethoxy)pyridine following oral administration to beagle dogs of a three-layered matrix table of type LML (formulation K).

Summary of the Invention

The matrix systems of the present invention utilize partial coating of a non-erodible core containg the active agent, in which delayed release from the coated surfaces compensates for the decreasing release rate from the core over time. No specialized matrix geometry of the tablet or nonuniform drug loading are necessary to achieve controlled release. Therefore, the matrix systems of the present invention are amenable to production using standard tableting equipment and procedures.

Accordingly, the present invention provides a tablet for the controlled release of an active agent comprising (a) a core layer comprising an active agent embedded in a non-swelling, non-erodible hydrophobic matrix; (b) a first barrier layer applied to and coating a single face of the core layer; and (c) an optional second barrier layer applied to and coating the opposite face of the core layer; wherein the core comprises up to about 80% active agent and from about 5% to about 80% by weight of nonswellable waxes or polymeric material insoluble in aqueous medium, and the first and second barrier layers independently comprise (1) polymeric material exhibiting a high degree

of swelling and gelling in aqueous medium or (2) nonswellable wax or polymeric material insoluble in aqueous medium.

Detailed Description of the Invention

In one embodiment, the present invention presents a tablet (MH) comprising a core layer comprising an active agent embedded in a non-swelling, non-erodible hydrophobic matrix and a hydrophilic barrier layer applied to and coating a single face of the core layer wherein the core comprises up to about 80% active agent and from about 5% toabout 80% by weight of nonswellable waxes or polymeric material insoluble in aqueous medium, and the hydrophilic barrier layer comprises polymeric material exhibiting a high degree of swelling and gelling in aqueous medium. The preferred method of applying the hydrophilic barrier layer is compression.

The core layer (M) is generally cylindrical in shape having flat, convex, or concave surfaces and comprises active agent uniformly distributed in polymeric material or wax which is non-swelling and non-erodible in aqueous medium and capable of maintaining these characteristics until the complete transfer of the active substance.

Non-swellable, non erodible hydrophobic polymers suitable for use either alone or in combination in the core layer are selected from acrylates, cellulose, ethylcellulose, cellulose acetate-propionate, polyethylenes, methacrylates, acrylic acid copolymers and high molecular weight polyvinylalcohols. Nonswellable waxes include at least one member selected from the fatty acids or glycerides. A preferred composition of the core layer is from about 20% to about 50% active agent, from about 25% to about 50% by weight of polymeric material or wax, and from about 25% to about 50% by weight of pharmaceutically acceptable excipients wherein the weight percentage is based on the total weight of the core layer. An especially preferred material for the core layer is carnauba wax. The core layer is generally prepared by compressing a mixture containing the active substance at a pressure of 4000 to 8000 lbs/cm^2 using concave or flat faced punches.

The hydrophilic barrier layer (H) comprises from about 5% to about 80% by weight of a polymeric material exhibiting a high degree of swelling in aqueous medium, and from about 90% to about 10% by weight of a polymeric material exhibiting a high degree of gelling in aqueous medium, or from about 40% to about 80% by weight of a single polymer which exhibits both swelling and gelling in aqueous medium, and from about 20% to about 60% by weight of pharmaceutically acceptable excipients wherein the weight percentage is based on the total weight of the barrier layer. Swellable polymers are materials that that exhibit the ability to swell in water and retain a significant fraction of water within its structure. See N.A. Peppas and A.R. Khare, "Preparation, Structure and Diffusional Behavior of Hydrogels in Controlled Release", *Advanced Drug Delivery Reviews*, **1993**, *11*, 1-35.

Polymers having a high degree of swelling suitable for use in the hydrophilic barrier layer are selected from cross-linked sodium carboxymethylcellulose, cross-linked

hydroxypropylcellulose, high-molecular weight hydroxypropylmethylcellulose, carboxymethylamide,potassium methacrylatedivinylbenzene copolymer, polymethylmethacrylate, poly(ethyleneoxide), CARBOPOL (high-molecular weight crosslinked acrylic acid homopolymers and copolymers), cross-linked polyvinylpyrrolidone, and high-molecular weight polyvinylalcohols. Other materials suitable for use in the hydrophilic barrier layer include xanthum gum and alginate.

Gellable polymers suitible for use in the hydrophilic barrier layer are selected from polyethylenedioxide, methylcellulose, carboxymethylcellulose, low molecular weight hydroxypropylmethylcellulose, low molecular weight polyvinyl alcohols, polyoxyethyleneglycols and non-crosslinked polyvinylpyrrolidone.

Polymers simultaneously exhibiting swelling and gelling properties sutiable for use in the hydrophilic barrier layer are selected from medium viscosity high-molecular weight hydroxypropylmethylcellulose and medium viscosity polyvinyl alcohols.

A preferred composition of the hydrophilic barrier layer is from about 40% to about 80% by weight of a single polymer which exhibits both swelling and gelling in aqueous medium, and from about 20% to about 60% by weight of pharmaceutically acceptable excipients. The most preferred polymer for use in the hydrophilic barrier layer is medium viscosity high-molecular weight hydroxypropylmethylcellulose.

Pharmaceutically acceptable excipients or carriers suitable for use in the core and barrier layer include sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof.

In another embodiment, the present invention provides a tablet (ML) comprising a core layer as described above and a lipophilic barrier layer applied to the core layer wherein the barrier layer comprises from about 10% to about 90% by weight of nonswellable waxes or polymeric material insoluble in aqueous medium and from about 90% to about 10% by weight of pharmaceutically acceptable excipients, wherein the polymeric material is selected from the group consisiting of acrylates, cellulose, ethylcellulose, cellulose acetate-propionate, polyethylenes, methacrylates, acrylic acid copolymers and high molecular weight polyvinylalcohols, and the waxes include at least one member selected from the fatty acids or glycerides.

Preferred material for the lipophilic barrier is a nonswellable wax selected from the fatty acids or glycerides. The most preferred wax for use in the lipophilic barrier layer is carnauba wax.

In another embodiment, the present invention provides a three-layered tablet (HMH) in which hydrophilic barrier layers, which may be the same or different, are applied to opposite faces of the core layer. Three-layer matrix tablets are preferably prepared by compression using concave or flat-faced punches. The ingredients for the bottom layer barrier layer are placed in the die and compressed at from about 200 to about 400 lbs/cm^2. The ingredients for the core layer are then added and recompressed at from about 200 to about 400 lbs/cm^2. The ingredients for the top layer are then added and the entire assemblage is compressed at from about 4000 to about 8000 lb/cm^2.

In a preferred three-layer tablet of type HMH, the core layer comprises from about 20% to about 50% active agent, from about 25% to about 50% by weight of carnauba wax, and from about 25% to about 50% by weight of pharmaceutically acceptable excipients wherein the weight percentage is based on the total weight of the core layer, and the first and second barrier layers independently comprise from about 40% to about 80% by weight of medium-viscosity hydroxypropylmethylcellulose and from about 20% to about 60% by weight of pharmaceutically acceptable excipients wherein the weight percentage is based on the total weight of the barrier layer.

In another embodiment, the present invention provides a three-layered tablet (LML) in which lipophilic barrier layers, which may be the same or different, are applied to opposite faces of the core layer. In a preferred three-layer tablet of type LML, the core layer comprises from about 20% to about 50% active agent, from about 25% to about 50% by weight of carnauba wax, and from about 25% to about 50% by weight of pharmaceutically acceptable excipients wherein the weight percentage is based on the total weight of the core layer, and the first and second barrier layers independently comprise from about 10% to about 90% by weight of carnauba wax and from about 90% to about 10% by weight of pharmaceutically acceptable excipients.

In another embodiment, the present invention provides a three-layered tablet (HML) in which the core layer is coated on one face with hydrophilic barrier layer, and on the opposite face with a lipohilic barrier layer. In a preferred three-layer tablet of type HML, the core layer comprises from about 20% to about 50% active agent, from about 25% to about 50% by weight of carnauba wax, and from about 25% to about 50% by weight of pharmaceutically acceptable excipients wherein the weight percentage is based on the total weight of the core layer; the hydrophilic barrier layer comprises from about 5% to about 80% by weight of medium-viscosity hydroxypropylmethylcellulose and from about 20% to about 60% by weight of pharmaceutically acceptable excipients wherein the weight percentage is based on the total weight of the barrier layer; and the lipophilic barrier layer comprises from about 30% to about 90% by weight of carnauba wax and from about 70% to about 10% by weight of pharmaceutically acceptable excipients.

The active agents of the present invention may be any material suitable for release into aqueous medium including pharmaceutical agents, insecticides, pesticides, perfumes, and water-treatment agents such as germicides. Preferred active agents are pharmaceutical agents.

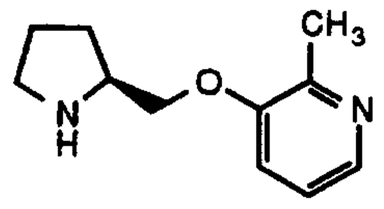
Representative pharmaceutical agents suitable for use in the tablets of the present invention include a variety of inorganic and organic pharmaceutical agents such as cognition enhancers, analgesics, anorexics, antihelmintics, antibacterials, anticonvulsants, antifungals, antidepressants, antibiotics, antihistamines, antiulcer drugs, antihypertensives, bronchodilators, immunosupressants, aldose reductase inhibitors, blood glucose lowering agents, adrenergics, muscle relaxants, anti-Parkinson agents, muscle contractants, hormonal agents, contraceptives, diuretics, electrolytes, bronchodilators, hypnotics, steroids, serotonin agonists or antagonists and H_2 antagonists.

Bronchodilators such as aminophylline are preferred pharmaceutical agents.

Also preferred are cough or cold agents such as brompheniramine dexbrompheniramine and chlorpheniramine maleates, phenylepherine and pseudoephedrine hydrochlorides and cetirizine.

Cognition enhancers, as described in U.S. Ser. No. 129,223, are a particularly preferred class of active agents.

The most preferred agent for use in the tablets of the present invention is



2-methyl-3-(2-(S)-pyrroldinylmethoxy)pyridine.

The matrix type (MH, ML, LML, HMH, or HML) suitable for delivery of a given drug is selected based on (1) the solubility of the drug and (2) drug loading in the core layer. For purposes of making this selection, drugs may be classified by solubility as follows:

(i) "very soluble" (>1g/mL);

(ii) "freely souble" (>0.1g/mL and <1g/mL);

(iii) "soluble" (>0.033g/mL and <0.1g/mL);

(iv) "sparingly soluble" (>0.01g/mL and <0.033g/mL);

(v) "slightly soluble" (>0.001g/mL and <0.01 g/mL); and

(vi) "very slightly soluble" (>0.0001g/mL and <0.001g/mL).

In general, two layered tablets of type MH and ML are preferred for drugs in solubility classes (v) and (vi) and drug loading of <30%.

All five matrix types (MH, ML, LML, HMH, or HML) are suitable to control the release of drugs in categories (i) to (v).

Three-layered tablets (HMH, LML and HML) are suitable for drugs in categories (i) to (v) with drug loading up to 60%. However, for drugs in categories (iv) and (v) with drug loading of greater than 30%, tablets of type HML or HMH are are preferred over tablets of type LML.

The release profile of an acitve agent from the matrix systems of the present invention is controlled by a number of variables including the thickness of the barrier layer(s), the concentration of soluble or insoluble material (polymer or wax) in the core and barrier layer(s), and the amount of any soluble or insoluble excipients.

For tablets of type MH and HMH, linearity of release can be improved by using a higher amount of barrier layer, or higher viscosity hydroxypropylmethylcellulose. Linearity of release is maintained by partial substitution with soluble excipients such as lactose or insoluble excipients such as Avicel PH101 (microcrystalline cellulose, swellable) or dicalcium phosphate (nonswellable), or mixtures thereof, does not result in nonlinearity.

For tablets of type ML and LML, the factor exerting the greatest influence on release kinetics is the wax concentration in the barrier layers. In general, increasing the wax concentration results in increased time dependency of release.

In three-layered tablets of type HML, linearity of release is generally increased by using a smaller lipophilic barrier layer relative to the hydrophilic barrier layer.

For all systems, the presence of high concentrations of diffusion-limiting materials (insoluble polymers and waxes) and insoluble excipients such as dicalcium phosphate and microcrystalline cellulose (Avicel, FMC Corp.) in either the barrier or core layer result in a slower release rate.

The foregoing may be better understood by reference to the following examples, which are presented for illustration and are not intended to limit the scope of the invention as defined in the appended claims.

Example 1

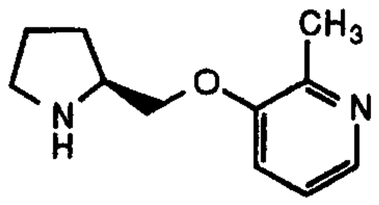
Preparation of Single Layer Hydrophobic Matrix (M)

Drug and exceipents were slowly added to molten wax and mixed well by stirring. The mixture was allowed to cool to ambeint temperature while maintaining mixing. The congealed solids were milled and passed through a 850 micron (20 mesh) screen to obtain granules. The tablets were prepared by compressing at 4000-8000 lbs/cm^2 using a flat-faced punch.

Using the foregoing procedure, 250 mg single layer hydrophobic matrix tablets having the following composition were prepared.

Table 1

Composition of Single Layer Hydrophobic Matrix Tablets

Formulation	A	B	C
Pseudoephidrine 	24% -	13.8%	
Aminophylline	-	-	41%
Carnauba wax	50%	60%	35%
Lactose (anhydrous)	26%	26.2%	24%
Total	250 mg	250 mg	250 mg

Example 2

Preparation of Layered Matrix MH

Tablets comprising a hydrophobic matrix (M) and a hydrophilic barrier layer (H) were prepared as follows. Drug and exceipents were slowly added to molten wax and mixed well by stirring. The mixture was allowed to cool to ambeint temperature while maintaining mixing. The congealed solids were milled and passed through a 850 micron (20 mesh) screen to obtain granules. Polymer and excipients were dry mixed and used as is. The barrier layer and core layer were compressed in succession using concave or flat-faced punches to form two-layered tablets. The initial compression force was 200-400 lbs/cm^2. The final compression force was 5400 lb/cm^2.

Using the foregoing procedure, a two-layered matrix tablet having the following composition was prepared.

Table 2

Composition of Two-Layer Matrix Tablet MH

Formulation	D	
	M	H
Psuedoephidrine	24%	-
Carnauba wax	50%	-
Methocell K100M	-	80%
Lactose (anhydrous)	26%	20%
Total	250 mg	100 mg

Example 3

Preparation of Layered Matrix HMH

Three-layer tablets comprising a hydrophilic barrier layer (H), a hydrophobic matrix core (M) and a hydrophilic barrier layer (H) were prepared as follows. Psuedoephedrine and lactose (anhydrous)were slowly added to molten carnauba wax and mixed well by stirring. The mixture was allowed to cool to ambeint temperature while maintaining mixing. The congealed solids were milled and passed through a 850 micron (20 mesh) screen to obtain granules. Polymer and excipients were dry mixed and used as is. Three-layer matrix tablets were prepared by compressing the bottom barrier layer at 200-400 lbs/cm^2 followed by the core layer 200-400 lbs/cm^2 and the top barrier layer at 4500 lb/cm^2.

Using the foregoing procedure, three-layered matrix tablets having the compositions described in Table 4 were prepared.

Table 3

Composition of Three-Layer Matrix Tablets HMH

Formulation	E		F	
	M	H	M	H
Psuedoephidrine	24%	-	24%	-
Carnauba wax	50%	-	50%	-
Methocell K100M	-	80%	26%	50%
Lactose (anhydrous)	26%	20%	-	30%
Avicell PH101	-	-	-	20%
dicalcium phosphate	-	-	-	-
Total	250 mg	100 mg	250 mg	100 mg

Table 3 (cont.)

Formulation	G		H	
	M	H	M	H
Psuedoephidrine	24%	-	24%	-
Carnauba wax	50%	-	50%	-
Methocell K100M	-	40%	-	50%
Lactose (anhydrous)	26%	60%	26%	30%
Avicell PH101	-	-	-	-
dicalcium phosphate	-	-	-	20%
Total	250 mg	100 mg	250 mg	100 mg

Table 3 (cont.)

Formulation	I			
	M	H	M	H
Psuedoephidrine	24%	-		
Carnauba wax	50%	-		
Methocell K100M	-	50%		
Lactose (anhydrous)	26%	30%		
Avicell PH101	-	10%		
dicalcium phosphate	-	10%		
Total	250 mg	100 mg		

Example 4

Preparation of Layered Matrix LML

Three-layer tablets comprising a hydrophobic barrier layer (L), a hydrophobic matrix core (M) and a hydrophobic barrier layer (L) were prepared as follows. Drug and excipients were slowly added to molten carnauba wax and mixed well by stirring. The mixture was allowed to cool to ambeint temperature while maintaining mixing. The congealed solids were milled and passed through a 850 micron (20 mesh) screen to obtain granules. The barrier layers were prepared by adding lactose to carnauba wax at 90 °C and mixing thoroughly. The mixture was allowed to cool to ambeint temperature while maintaining mixing. The resultant mass was milled and passed through a 850 micron (20 mesh) screen to obtain granules. Three-layer matrix tablets were prepared using concave or flat-faced punches by compressing the bottom barrier layer at 200-400 lbs/cm^2 followed by the core layer 200-400 lbs/cm^2 and the top barrier layer at 4500 lb/cm^2.

Using the foregoing procedure, three-layered matrix tablet having the following compositions were prepared.

Table 4

Composition of Three-Layer Matrix Tablets LML

Formulation	J		
	M	L1	L2
Psuedoephidrine	24%	-	-
Carnauba wax	50%	30%	10%
Lactose (anhydrous)	26%	70%	90%
dicalcium phosphate	-	-	-
Total	250 mg	150 mg	100 mg

Table 4 (cont.)

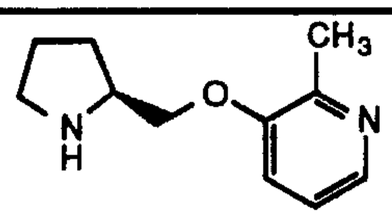
Formulation	K		
	M	L1	L2
	26.8%	-	-
Carnauba wax	33.7%	50%	50%
Lactose (anhydrous)	32.7%	50%	50%
dicalcium phosphate	6.8%	-	-
Total	148.4 mg	100 mg	100 mg

Table 4 (cont.)

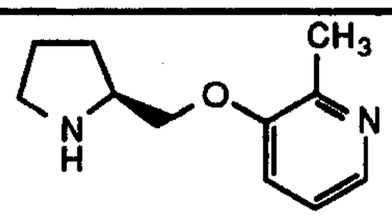
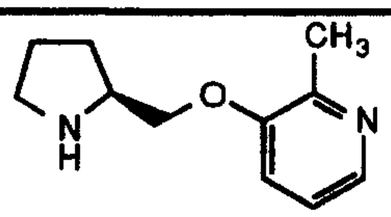
Formulation	L		
	M	L1	L2
	27.3%	-	-
Carnauba wax	33.3%	50%	50%
Lactose (anhydrous)	39.4%	50%	50%
dicalcium phosphate	-	-	-
Total	150 mg	100 mg	100 mg

Table 4 (cont.)

Formulation	M		
	M	L1	L2
	27.6%	-	-
Carnauba wax	40%	50%	50%
Lactose (anhydrous)	-	25%	25%
dicalcium phosphate	32.4%	25%	25%
Total	148.4 mg	100 mg	100 mg

Example 5

Preparation of Layered Matrix HML

Three-layer tablets comprising a hydrophilic barrier layer (H), a hydrophobic matrix core (M) and a hydrophobic barrier layer (L) were prepared as follows. Drug and excipients were slowly added to molten carnauba wax and mixed well by stirring. The mixture was allowed to cool to ambeint temperature while maintaining mixing. The congealed solids were milled and passed through a 850 micron (20 mesh) screen to obtain granules. The hydrophilic barrier layer H was prepared by dry-mixing the polymer and excipients. The hydrophobic barrier layer L was prepared by adding lactose to carnauba wax at 90 °C and mixing thoroughly. The mixture was allowed to cool to ambeint temperature while maintaining mixing. The resultant mass was milled and passed through a 850 micron (20 mesh) screen to obtain granules. Three-layer matrix tablets were prepared using concave or flat-faced punches by compressing the bottom barrier layer at 200-400 lbs/cm^2 followed by the core layer at 200-400 lbs/cm^2 and the top barrier layer at 4500 lb/cm^2.

Using the foregoing procedure, three-layered matrix tablet having the following compositions were prepared.

Table 5

Composition of Three-Layer Matrix Tablets HML

Formulation	N		
	M	H	L
Psuedoephidrine	24%	-	-
Carnauba wax	50%	-	30%
Methocell K15M	-	80%	-
Lactose (anhydrous)	26%	20%	70%
dicalcium phosphate	-	-	-
Total	250 mg	150 mg	200 mg

Table 5 (cont)

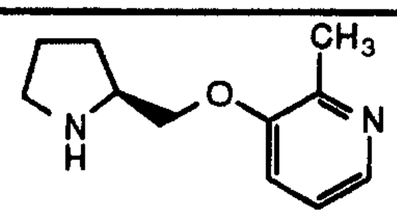
Formulation	O		
	M	H	L
	26.8%	-	-
Carnauba wax	33.7%	-	90%
Methocell K00MP CR	-	70%	10%
Lactose (anhydrous)	32.7%	15%	-
dicalcium phosphate	6.8	-	-
Avicel PH101	-	15%	-
Total	100 mg	100 mg	100 mg

Table 5 (cont)

Formulation	P		
	M	H	L
Aminophyline	41%	-	-
Carnauba wax	35%	-	30%
Methocell K15M	-	80%	-
Lactose (anhydrous)	24%	20%	70%
Total	250 mg	150 mg	200 mg

Table 5 (cont)

Formulation	Q		
	M	H	L
Aminophyline	41%	-	-
Carnauba wax	35%	-	30%
Methocell K15M	-	80%	-
Lactose (anhydrous)	24%	20%	70%
Total	250 mg	100mg	100 mg

Example 6

In Vitro Release Rates of Matrix Tablets

The in vitro release rates of matrix tablets were determined using USP apparatus II. The test conditions were as follows:

Method	Paddle
Medium	Distilled Water
Volume of medium	900 mL
Temperature	37 °C
Speed	100 rpm
Sampling volume	3 mL
Sampling Interval	0, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9 and 24 hours

At each sampling interval, 3 mL samples were taken and replaced with the same volume of distilled water to maintain a constant volume. Concentrations of the test compounds in the samples were assayed by UV spectrometry at 258 nm for pseudoephedrine, 290 nm for theophylline and 276 nm for 2-methyl-3-(2-(S)-pyrrolidinylmethyloxy)pyridine, respectively. Cumulative amounts of drug released from the tablets were calculated and plotted as a function of time. The release rates for matrix tablets G, J and M and single layer tables A are summarized in Figure 6. The results for matrix tablets O and Q and single layer tablet C are summarized in Figure 7. As indicated in Figures 6 and 7, substantial linearity of drug release can be obtained from all three tablet designs, i.e. HMH, LML and HML.

Example 7

In Vivo Performance of Layered Matrix HML

The *in vivo* performance of the three-layered matrix tablet Q was compared to the single layer matrix tablet C in beagle dogs.

Nine beagle dogs weighing 9.3-14.2 kg were used for the study. All dogs were fasted overnight before dosing. A single dose three-way crossover design with a 1 week dosing interval was used. The reference formulation was an aqueous solution on aminophylline (10.2 mg/mL). Drug was orally administered (102 mg) followed by 100 mL of water. Food was returned to the dogs after the 6-hour blood sample was obtained. Serial blood samples were collected at 0, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, and 32 hours after dosing. Plasma samples were immediately separated from the blood and frozen at -20 °C until assayed by TDX fluorescence polarization immunoassays. The results are summarized in Figure 8. As indicated in Figure 8, prolonged absorption was attained from both tablets. The more rapid early absorption rate observed for the

single-layer tablet can be attributed to higher initial release due to nonlinear release as well as the overall higher release rate when compared to the three-layered tablet.

Example 8

In Vivo Performance of Layered Matrix LML

The *in vivo* performance of the three-layered matrix tablet K in beagle dogs was measured as described in Example 7. The results are summarized in Figure 9. As indicated in Figure 9, prolonged release is also attained using matrix tablets of type LML.

WHAT IS CLAIMED IS:

1. A tablet for the controlled release of an active agent comprising

(a) a core layer comprising an active agent embedded in a non-swelling, non-erodible hydrophobic matrix;

(b) a first barrier layer applied to and coating a single face of the core layer; and

(c) an optional second barrier layer applied to and coating the opposite face of the core layer;

wherein the core comprises up to about 80% active agent and from about 5% to about 80% by weight of nonswellable waxes or polymeric material insoluble in aqueous medium, and the first and second barrier layers independently comprise

(1) polymeric material exhibiting a high degree of swelling and gelling in aqueous medium or

(2) nonswellable wax or polymeric material insoluble in aqueous medium.

2. A tablet according to claim 1 comprising

(a) a core layer comprising an active agent embedded in a non-swelling, non-erodible hydrophobic matrix, and

(b) a barrier layer applied to and a single face of the core layer wherein the barrier layer comprises polymeric material exhibiting a high degree of swelling and gelling in aqueous medium.

3. A tablet according to claim 2 wherein the barrier layer is applied to the core layer by compression.

4. A tablet according to claim 3 wherein the core layer comprises from about 20% to about 50% active agent, from about 25% to about 50% by weight of nonswellable wax, and from about 25% to about 50% by weight of pharmaceutically acceptable excipients wherein the weight percentage is based on the total weight of the core layer.

5. A tablet according to claim 4 wherein the nonswellable wax is carnauba wax.

6. A tablet according to claim 5 wherein the barrier layer comprises from about 5% to about 80% by weight of a polymeric material exhibiting a high degree of swelling in aqueous medium, and from about 90% to about 10% by weight of a polymeric material exhibiting a high degree of gelling in aqueous medium and from about 20% to about 60% by weight of pharmaceutically acceptable excipients wherein the weight percentage is based on the total weight of the barrier layer.

7. A tablet according to claim 5 wherein the polymeric material having a high degree of swelling in aqueous medium is selected from the group consisting of cross-linked sodium carboxymethylcellulose, cross-linked hydroxypropylcellulose, high-molecular weight hydroxypropylmethylcellulose, carboxymethylamide,potassium methacrylatedivinylbenzene copolymer, polymethylmethacrylate, poly(ethyleneoxide), cross-linked polyvinylpyrrolidone, high-molecular weight polyvinylalcohols, high-molecular weight crosslinked acrylic acid homopolymers and copolymers xanthum gum and alginate; and
the polymeric material having a high degree of swelling is selected from the group consisting of polyethylenedioxide, methylcellulose, carboxymethylcellulose, low molecular weight hydroxypropylmethylcellulose, low molecular weight polyvinyl alcohols, polyoxyethyleneglycols and non-crosslinked polyvinylpyrrolidone.

8. A tablet according to claim 5 wherein the barrier layer comprises from about 40% to about 80% by weight of a single polymer which exhibits both swelling and gelling in aqueous medium, and from about 20% to about 60% by weight of pharmaceutically acceptable excipients wherein the weight percentages are based on the total weight of the barrier layer.

9. A tablet according to claim 6 wherein the polymer which exhibits both swelling and gelling in aqueous medium is selected from medium-viscosity polyvinylalcohols and medium-viscosity hydroxypropylmethylcellulose.

10. A tablet according to claim 9 wherein the polymer which exhibits both swelling and gelling in aqueous medium is medium-viscosity hydroxypropylmethylcellulose.

11. A tablet according to claim 5 wherein the barrier layer comprises from about 30% to about 90% by weight of nonswellable waxes or polymeric material insoluble in aqueous medium and from about 70% to about 10% by weight of pharmaceutically acceptable excipients, wherein include polymeric material is selected from the group consisiting of acrylates, cellulose, ethylcellulose, cellulose acetate-propionate, polyethylenes, methacrylates, acrylic acid copolymers and high molecular weight polyvinylalcohols, and the waxes include at least one member selected from the fatty acids or glycerides

12. A tablet according to claim 11 wherein the barrier layer comprises from about 30% to about 90% by weight of nonswellable wax selected from the fatty acids or glycerides.

13. A tablet according to claim 12 wherein the wax is carnauba wax.

14. A tablet according to claim 1 comprising

(a) a core layer comprising an active agent embedded in a non-swelling, non-erodible hydrophobic matrix;

(b) a first barrier layer applied to and coating a single face of the core layer; and

(c) a second barrier layer applied to and coating the opposite face of the core layer; wherein the core comprises up to about 80% active agent and from about 5% to about 80% by weight of nonswellable waxes or polymeric material insoluble in aqueous medium, and the first and second barrier layers independently comprise

(1) polymeric material exhibiting a high degree of swelling and gelling in aqueous medium or

(2) nonswellable wax or polymeric material insoluble in aqueous medium.

15. A tablet according to claim 14 wherein the barrier layers are applied by compression.

16. A tablet according to claim 15 wherein the core layer comprises from about 20% to about 50% active agent, from about 25% to about 50% by weight of nonswellable wax, and from about 25% to about 50% by weight of pharmaceutically acceptable excipients wherein the weight percentage is based on the total weight of the core layer.

17. A tablet according to claim 4 wherein the nonswellable wax is carnauba wax.

18. A tablet according to claim 17 wherein the first and second barrier layers independently comprise from about 5% to about 80% by weight of a polymeric material exhibiting a high degree of swelling in aqueous medium, and from about 90% to about 10% by weight of a polymeric material exhibiting a high degree of gelling in aqueous medium and from about 20% to about 60% by weight of pharmaceutically acceptable excipients wherein the weight percentage is based on the total weight of the barrier layer.

19. A tablet according to claim 18 wherein the polymeric material having a high degree of swelling in aqueous medium is selected from the group consisting of cross-linked sodium carboxymethylcellulose, cross-linked hydroxypropylcellulose, high-molecular weight hydroxypropylmethylcellulose, carboxymethylamide,potassium methacrylatedivinylbenzene copolymer, polymethylmethacrylate, poly(ethyleneoxide), cross-linked polyvinylpyrrolidone, high-molecular weight polyvinylalcohols, high-molecular weight crosslinked acrylic acid homopolymers and copolymers xanthum gum and alginate; and
the polymeric material having a high degree of swelling is selected from the group consisting of polyethylenedioxide, methylcellulose, carboxymethylcellulose, low molecular weight hydroxypropylmethylcellulose, low molecular weight polyvinyl alcohols, polyoxyethyleneglycols and non-crosslinked polyvinylpyrrolidone.

20. A tablet according to claim 18 wherein the barrier layers independently comprises from about 40% to about 80% by weight of a single polymer which exhibits both swelling and gelling in aqueous medium, and from about 20% to about 60% by weight of pharmaceutically acceptable excipients wherein the weight percentages are based on the total weight of the barrier layer.

21. A tablet according to claim 20 wherein the polymer which exhibits both swelling and gelling in aqueous medium is selected from medium-viscosity polyvinylalcohols and medium-viscosity hydroxypropylmethylcellulose.

22. A tablet according to claim 21 wherein the polymer which exhibits both swelling and gelling in aqueous medium is medium-viscosity hydroxypropylmethylcellulose.

23. A tablet according to claim 17 wherein the barrier layers independently comprise from about 10% to about 90% by weight of nonswellable waxes or polymeric material insoluble in aqueous medium and from about 90% to about 10% by weight of pharmaceutically acceptable excipients, wherein the polymeric material is selected from the group consisiting of acrylates, cellulose, ethylcellulose, cellulose acetate-propionate, polyethylenes, methacrylates, acrylic acid copolymers and high molecular weight polyvinylalcohols, and the waxes include at least one member selected from the fatty acids or glycerides.

24. A tablet according to claim 23 wherein the barrier layers comprise from about 10% to about 90% by weight of nonswellable wax selected from the fatty acids or glycerides and from about 90% to about 10% by weight of pharmaceutically acceptable excipients.

24. A tablet according to claim 23 wherein the barrier layers comprise from about 10% to about 90% by weight of caranuba wax and from about 90% to about 10% by weight of pharmaceutically acceptable excipients.

26. A tablet according to claim 17 wherein the first barrier layer comprises from about 5% to about 80% by weight of a polymeric material exhibiting a high degree of swelling in aqueous medium, and from about 90% to about 10% by weight of a polymeric material exhibiting a high degree of gelling in aqueous medium and from about 20% to about 60% by weight of pharmaceutically acceptable excipients wherein the weight percentage is based on the total weight of the barrier layer; and
the second barrier comprises from about 10% to about 90% by weight of nonswellable waxes or polymeric material insoluble in aqueous medium and from about 90% to about 10% by weight of pharmaceutically acceptable excipients.

27. A tablet according to claim 26 wherein the polymeric material exhibiting a high degree of swelling in aqueous medium is selected from the group consisting of cross-linked sodium carboxymethylcellulose, cross-linked hydroxypropylcellulose, high-molecular weight hydroxypropylmethylcellulose, carboxymethylamide,potassium methacrylatedivinylbenzene copolymer, polymethylmethacrylate, poly(ethyleneoxide), cross-linked polyvinylpyrrolidone, high-molecular weight polyvinylalcohols, high-molecular weight crosslinked acrylic acid homopolymers and copolymers xanthum gum and alginate; and
the polymeric material having a high degree of swelling is selected from the group consisting of polyethylenedioxide, methylcellulose, carboxymethylcellulose, low molecular weight hydroxypropylmethylcellulose, low molecular weight polyvinyl alcohols, polyoxyethyleneglycols and non-crosslinked polyvinylpyrrolidone.

28. A tablet according to claim 27 wherein the first barrier layer independently comprises from about 40% to about 80% by weight of a single polymer which exhibits both swelling and gelling in aqueous medium, and from about 20% to about 60% by weight of pharmaceutically acceptable excipients wherein the weight percentages are based on the total weight of the barrier layer.

29. A tablet according to claim 28 wherein the polymer which exhibits both swelling and gelling in aqueous medium is selected from medium-viscosity polyvinylalcohols and medium-viscosity hydroxypropylmethylcellulose.

30. A tablet according to claim 29 wherein the polymer which exhibits both swelling and gelling in aqueous medium is medium-viscosity hydroxypropylmethylcellulose.

31. A tablet according to claim 26 wherein the polymeric material insoluble in aqueous medium is selected from the group consisiting of acrylates, cellulose, ethylcellulose, cellulose acetate-propionate, polyethylenes, methacrylates, acrylic acid copolymers and high molecular weight polyvinylalcohols, and the nonswellable waxes include at least one member selected from the fatty acids or glycerides.

32. A tablet according to claim 31 wherein the barrier layers comprise from about 10% to about 90% by weight of nonswellable wax selected from the fatty acids or glycerides and from about 90% to about 10% by weight of pharmaceutically acceptable excipients.

23. A tablet according to claim 32 wherein the barrier layers comprise from about 10% to about 90% by weight of caranuba wax and from about 90% to about 10% by weight of pharmaceutically acceptable excipients.

34. A tablet according to claim 15 wherein the core layer comprises from about 20% to about 50% active agent, from about 25% to about 50% by weight of carnauba wax, and from about 25% to about 50% by weight of pharmaceutically acceptable excipients wherein the weight percentage is based on the total weight of the core layer, and the first and second barrier layers independently comprise from about 40% to about 80% by weight of medium-viscosity hydroxypropylmethylcellulose and from about 20% to about 60% by weight of pharmaceutically acceptable excipients wherein the weight percentage is based on the total weight of the barrier layer.

35. A tablet according to claim 34 wherein the active agent is selected from the group consisting of bronchodilators, cough and cold agents, cognition enhancers.

36. A tablet according to claim 34 wherein the active agent is 2-methyl-3-(2-(S)-pyrroldinylmethoxy)pyridine.

37. A tablet according to claim 15 wherein the core layer comprises from about 20% to about 50% active agent, from about 25% to about 50% by weight of carnauba wax, and from about 25% to about 50% by weight of pharmaceutically acceptable excipients wherein the weight percentage is based on the total weight of the core layer, and the first and second barrier layers independently comprise from about 10% to about 90% by weight of carnauba wax and from about 90% to about 10% by weight of pharmaceutically acceptable excipients.

38. A tablet according to claim 37 wherein the active agent is selected from the group consisting of bronchodilators, cough and cold agents, cognition enhancers.

39. A tablet according to claim 38 wherein the active agent is 2-methyl-3-(2-(S)-pyrroldinylmethoxy)pyridine.

40. A tablet according to claim 15 wherein the core layer comprises from about 20% to about 50% active agent, from about 25% to about 50% by weight of carnauba wax, and from about 25% to about 50% by weight of pharmaceutically acceptable excipients wherein the weight percentage is based on the total weight of the core layer;

the first barrier layer comprises from about 40% to about 80% by weight of medium-viscosity hydroxypropylmethylcellulose and from about 20% to about 60% by weight of pharmaceutically acceptable excipients wherein the weight percentage is based on the total weight of the barrier layer; and

the second barrier layer independently comprises from about 30% to about 90% by weight of carnauba wax and from about 70% to about 30% by weight of pharmaceutically acceptable excipients.

41. A tablet according to claim 37 wherein the active agent is selected from the group consisting of bronchodilators, cough and cold agents and cognition enhancers.

42. A tablet according to claim 38 wherein the active agent is 2-methyl-3-(2-(S)-pyrroldinylmethoxy)pyridine.

FIGURE 1

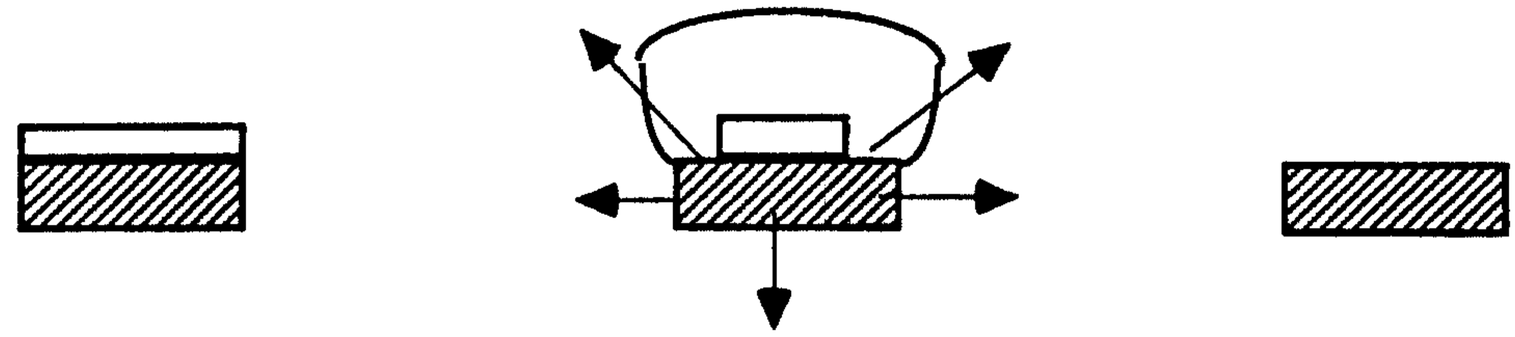


FIGURE 2

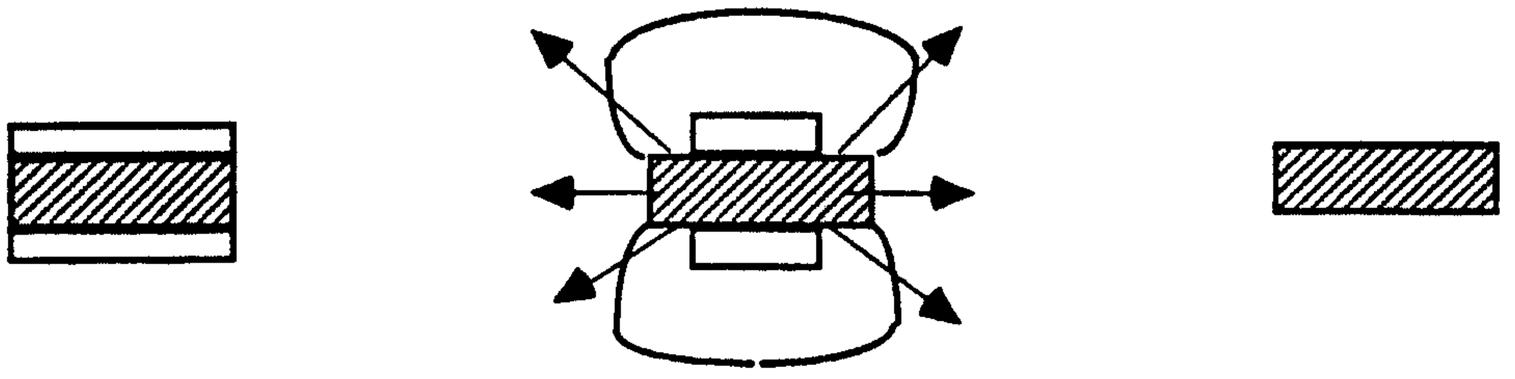


FIGURE 3

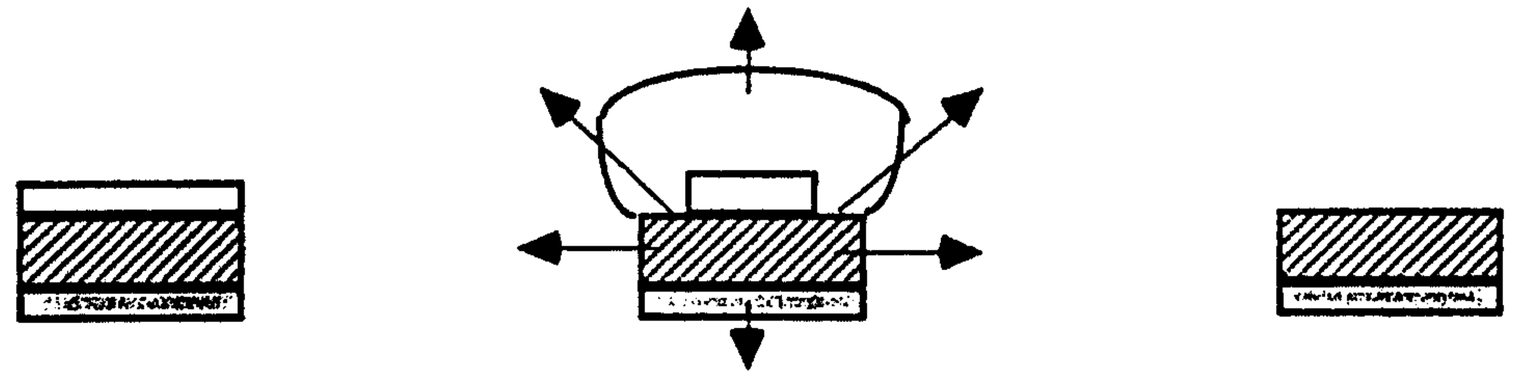


FIGURE 4

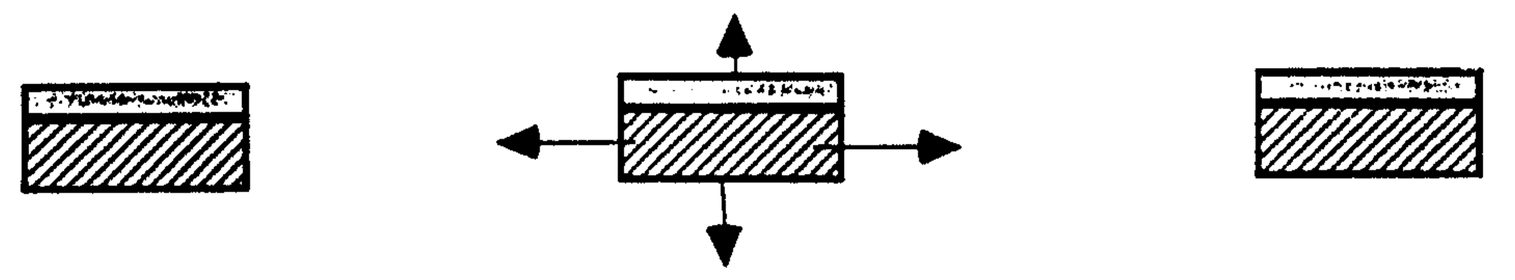


FIGURE 5

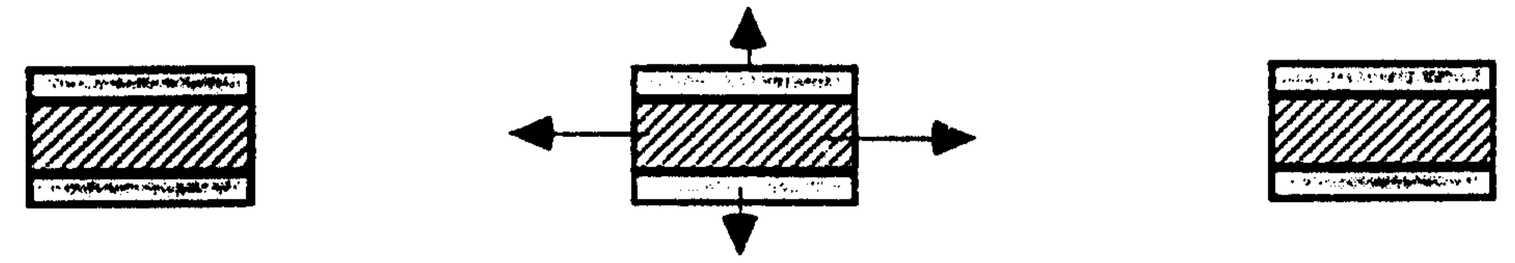


FIGURE 6

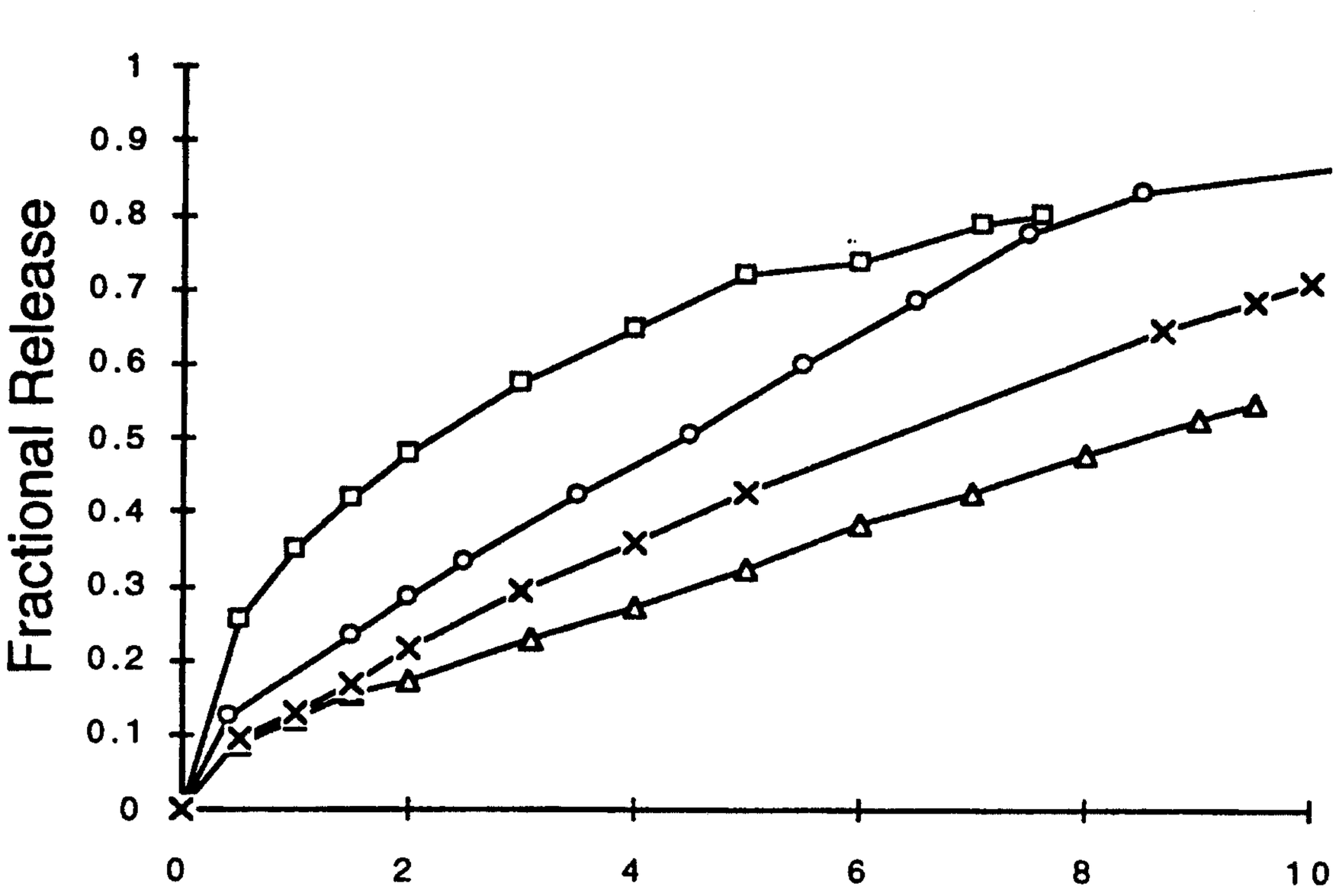

Fractional Release
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0
2
4
6
8
10
Time (hr)

FIGURE 7

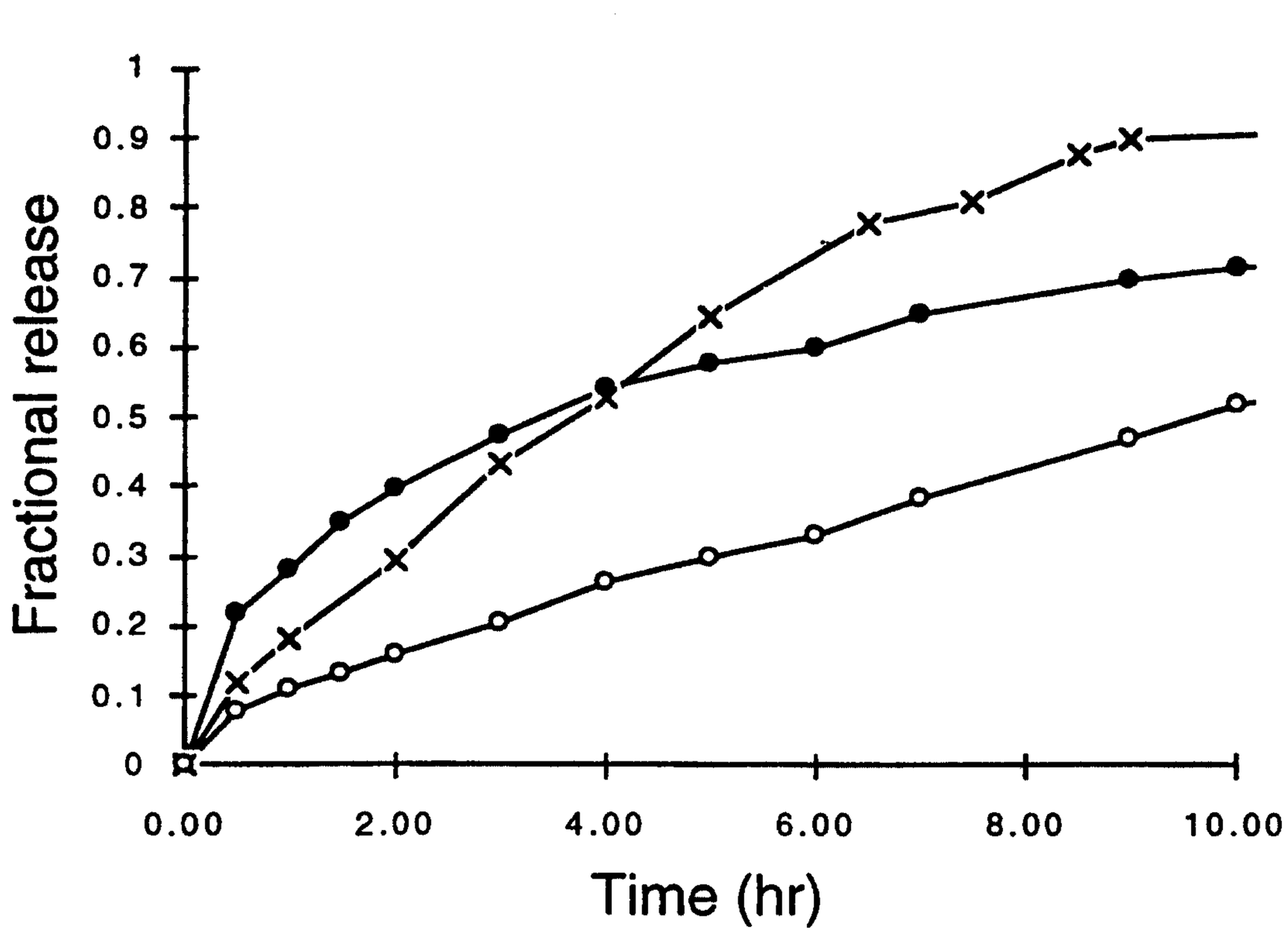

Fractional release
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.00
2.00
4.00
6.00
8.00
10.00
Time (hr)

FIGURE 8

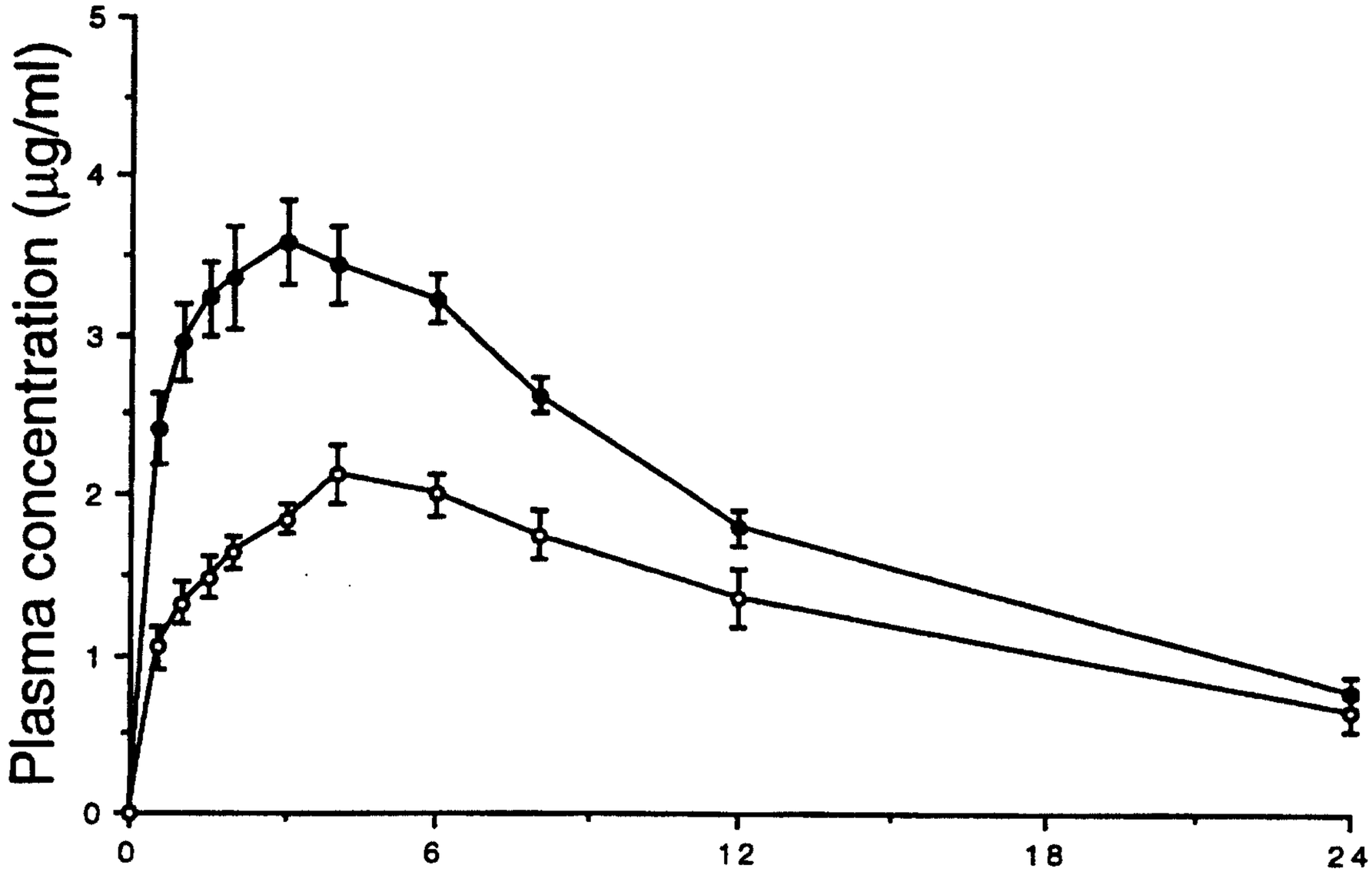
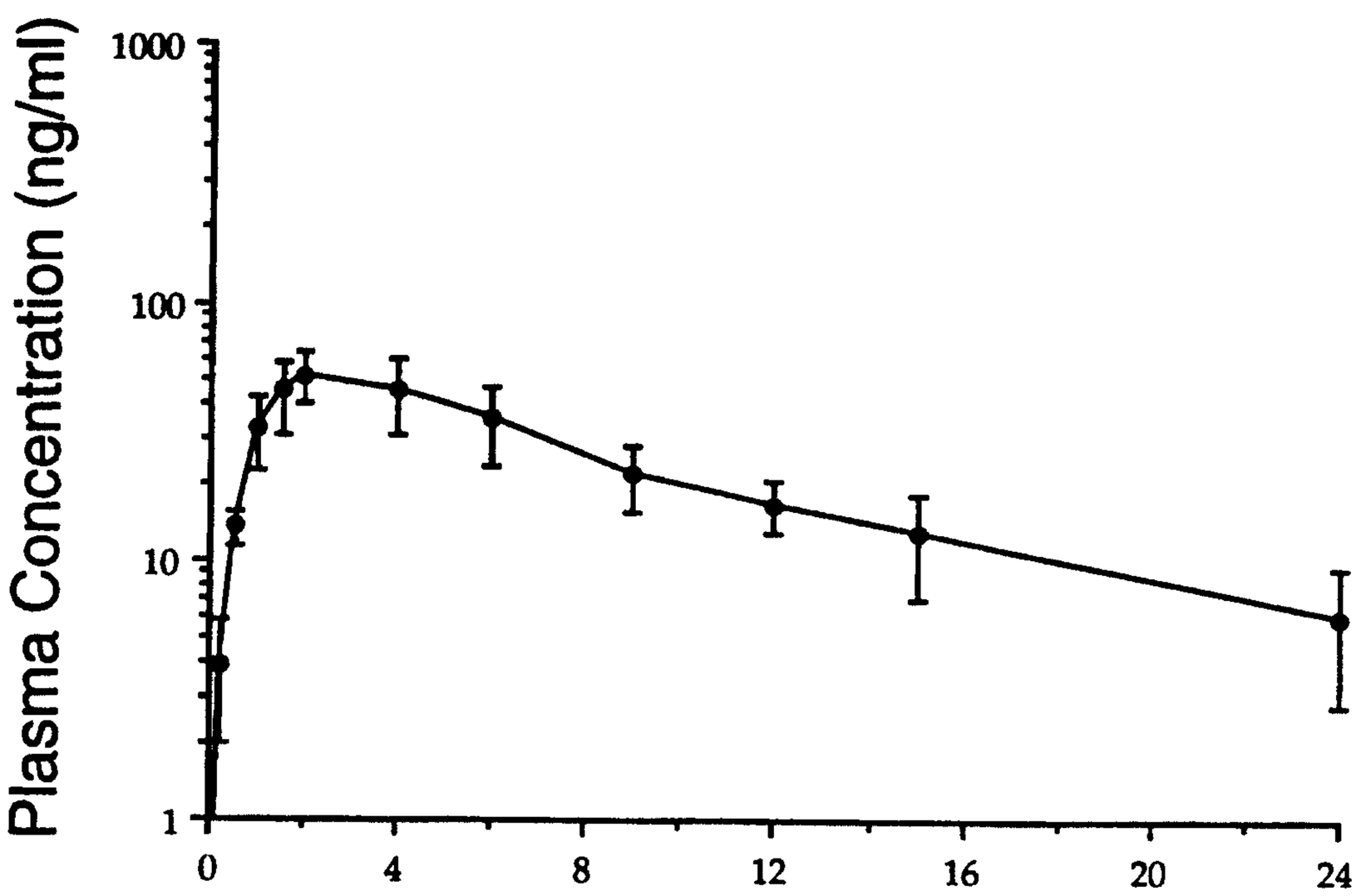


FIGURE 9


Plasma Concentration (ng/ml)
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100
10
1
0
4
8
12
16
20
24
Time (hr)