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As. 2417/P

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES
E. S. D.

SUPERINDUSTRIA Y COMERCIO
Radicacion : 00397487 00000005 Folios: 2
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Tramite : 682 PATENTES D 1 REGISTRO/ 538 PETICION
Dependencia: 2028 DIVISION DE NUEVAS CREACIONES

Ref.: Expediente No. 00-097.407
Solicitud de Patente a nombre de
Johnson & Johnson Consumer Companies, Inc.

Yo, JIMENA ESCOBAR URIBE, identificada como aparece al pie de mi firma, domiciliada en Bogotá, en la Carrera 11 A No. 94-76 Of. 305, obrando como apoderada de la sociedad Johnson & Johnson Consumer Companies, Inc., domiciliada en Skillman, New Jersey, Estados Unidos de América, solicitante de la patente de la referencia, pido a usted que se proceda a examinar si la invención, cuya patente se tramita en el expediente de la referencia, es patentable.

Adjunto al presente memorial el recibo No. 03 - 52,300 de julio 25, 2003, por la suma de $335.000.oo, con lo cual queda cubierta la tasa oficial correspondiente a dicho estudio.

Señor Superintendente,

JIMENA ESCOBAR URIBE
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020/
Bogotá, D.C.,

Doctora
Jimena Escobar Uribe
Apoderada

Oficio Nº 06918

REFERENCIA	**Radicación**	**00 97407**
	Trámite	**002**
	Evento	**001**
	Actuación	**430**
	Folios	**012**

Como resultado del examen de patentabilidad de la solicitud de patente de invención Nº 00 97407, realizado según el artículo 45 de la decisión 486 de la comisión de la Comunidad Andina, se notifica:

Documentos estudiados:

. Descripción: folios 4-19
. Ejemplos: folios 19-29
. Capítulo reivindicatorio estudiado: folios 30-40
. Se reivindica prioridad presentada en Estados Unidos, el 23.12.99, bajo el número 09/471825

Objeto de la invención

Según las reivindicaciones 1 a 55 de la presente solicitud, se refiere a una composición que comprende una capa de liberación sostenida y una capa de liberación rápida; la capa de liberación sostenida comprende un polímero hidrosoluble y un primer farmacéuticamente activo; la capa de liberación rápida comprende un agente formador de matriz y un segundo agente farmacéuticamente activo. La composición se puede incorporar en forma unitaria de dosificación, tal como un inserto vaginal; también se proveen métodos para preparar la composición.

Clasificación internacional de patentes A 61 K 9/22

Claridad de las reivindicaciones

El art. 30 de la Decisión 486 contempla que "*Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción.*"

Las expresiones "capa de liberación sostenida" y "capa de liberación rápida" de la manera como son usadas en la reivindicación 1, no se consideran que definen una velocidad de liberación en términos absolutos, simplemente dicen que una capa libera más rápida que la otra.

Es claro, a partir de la lectura de la descripción, que el primer y el segundo componente farmacéutico pueden ser iguales, aspecto que no se encuentra dentro de las reivindicaciones.

El término "polímero hidrosoluble" no es exacto ni limita la materia que se desea proteger, debido a que puede significar cualquier polímero con un mínimo de solubilidad en agua.

De acuerdo con la reivindicación 8 el aceite vegetal hidrogenado es un ácido graso, sin embargo los aceites vegetales hidrogenados contiene ácidos grasos esterificados en su mayoría, por lo tanto dicha reivindicación es contradictoria y poco clara.

La descripción describe composiciones vaginales, aspecto que no se encuentra en la reivindicación 1

El listado de principios activos de la reivindicación 9 va desde minerales hasta fertilizantes, lo cual es muy amplio y poco coherente en una composición de uso vaginal

Favor hacer las aclaraciones y correcciones del caso.

Determinación del estado de la técnica:

Consultadas las fuentes de información con que cuenta este despacho, se encontraron los siguientes documentos, anteriores a la fecha de prioridad de la presente solicitud - 23.12.99-, relacionados con la materia de la presente solicitud:

Nº	Documento	Título	Fecha de publicación
1	WO 9302662	"Composiciones farmacéuticas antivirales para administración vaginal"	18.02.93
2	US 4915953	Forma farmacéutica para la entrega de acetaminofén o fenilpropanolamina	10.04.90

Evaluación de los requisitos de patentabilidad:

El artículo 14 de la decisión 486 de la comisión de la comunidad andina establece que: "*Los países miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial*"

En cumplimiento del artículo 14 de la decisión 486 de la comisión de la comunidad andina, se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

Evaluación de la NOVEDAD

El artículo 16 de la decisión 486 dispone *"Una invenciones considerará nueva cuando no está comprendida en el estado de la técnica"*

La publicación WO 9302662 revela formas de dosificación vaginales bicapa que tienen una capa de liberación sostenida que tiene un polímero hidrosoluble y una capa de liberación rápida

La patente US 4915953 revela dispositivos osmóticos de dos capas que comprenden una capa de liberación sostenida y una capa de liberación rápida en donde se describe que puede ser aplicado a formas vaginales que contienen activos y vitaminas

La presente solicitud reivindica composiciones que comprenden una capa de liberación sostenida que comprende un polímero hidrosoluble; y una capa de liberación rápida que comprende un agente formador de matriz

Comparando elemento por elemento, las composiciones que se reivindican son iguales a las del estado de la técnica y puede afectar la novedad de la presente solicitud.

En conclusión los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento	Reivindicaciones afectadas	Requisito que afecta
1	WO 9302662	1-55	Novedad
2	US 4915953	1-55	Novedad

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de la notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo 5 del título primero de la Circular Única Nº 10 de 2001

Álix Carmenza Céspedes de Vergel
Jefe de la División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 29 JUN. 2006

CONCEPTO TÉCNICO Número 0983	**EXAMINADOR TÉCNICO** Código 202024

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(81) Designated States: AU, BB, BG, BR, CA, CS, FI, HU, JP, KP, KR, LK, MG, MN, MW, NO, PL, RO, RU, SD, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG).

Published
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(54) Title: ANTIVIRAL PHARMACEUTICAL COMPOSITIONS FOR VAGINAL ADMINISTRATION

(57) Abstract

Biocompatible sustained-release vaginal antiviral compositions in form of effervescent tablets, bioadhesive tablets, bi-layered tablets, bioadhesive washes, are described.

drug solubility and as a function of the programmed drug release rate from the dosage form), but preferably this polymers are used in amounts varying from 15 to 60 w/w%.

A further preferred embodiment is provided by pharmaceutical forms devised for a pulsing release of the drug, i.e. able to release immediately a first portion of the drug and a second portion in a prolonged period of time. It is therefore possible a simpler posology and a better patient compliance. This kind of formulation may consist in bi-layered tablets as defined above. Still a further preferred embodiment is provided by vaginal tablets comprising bioadhesive polymers such as gelatine, xantanes, scleroglucane, collagene, pectine and amylopectine, dextranes, hyaluronic or polygalactouronic acid, alginic acid, alginates, polyvinylpyrrolidone, polyvinylalcohol, polyethylenglycols, polypropylenglycols and copolymers, polymethylvinylether maleic anhydride copolymer and derivatives, polyacrylic and methacrylic acid derivatives, carboxyvinylpolymers, cellulose derivatives: methylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, carboxymethylcellulose and its salts.

These bioadhesive properties of said polymers may be determined by the methods disclosed in S.T.P. Pharma 4 (8) 688-697, 1988.

The adhesive and bioadhesive properties of the formulations reported below were tested using a suitable apparatus described in a previous work (Maggi, L., Giunchedi, P., Conte, U., La Manna, A., Acta

United States Patent [19]

Jordan et al.

[11] **Patent Number: 4,915,953**

[45] **Date of Patent: * Apr. 10, 1990**

[54] **DOSAGE FORM FOR DELIVERING ACETAMINOPHEN OR PHENYLPROPANOLAMINE**

[75] Inventors: **Maureen L. Jordan**, Mt. View; **Atul D. Ayer**; **Paul R. Magruder**, both of Palo Alto; **David E. Edgren**, El Granada, all of Calif.

[73] Assignee: **ALZA Corporation**, Palo Alto, Calif.

[*] Notice: The portion of the term of this patent subsequent to Mar. 20, 2006 has been disclaimed.

[21] Appl. No.: **312,556**

[22] Filed: **Feb. 21, 1989**

Related U.S. Application Data

[63] Continuation of Ser. No. 92,857, Sep. 3, 1987, Pat. No. 4,814,181.

[51] **Int. Cl.**[4] **A61K 9/24**

[52] **U.S. Cl.** **424/473**; 424/467; 424/472

[58] **Field of Search** 424/467–473

[56] **References Cited**

U.S. PATENT DOCUMENTS

4,320,759	3/1982	Theeuwes	424/473
4,449,983	5/1984	Cortese et al.	424/473
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4,573,405	6/1987	Guittard et al.	424/473
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4,814,181	3/1989	Jordan et al.	424/473

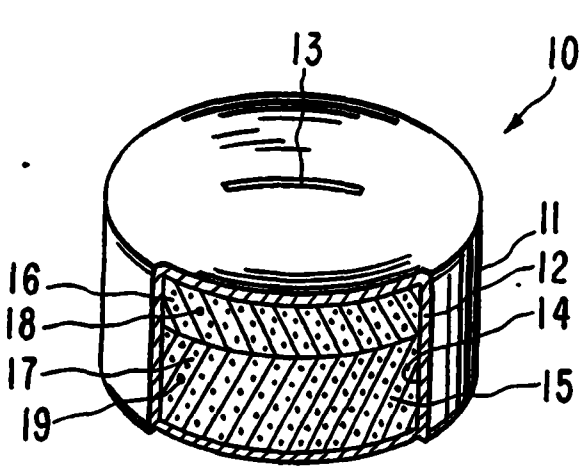
Primary Examiner—Nancy A. B. Swisher

Attorney, Agent, or Firm—Paul L. Sabatine; Edward L. Mandell; Steven F. Stone

[57] **ABSTRACT**

A dosage form is disclosed comprising a wall that surrounds a compartment with an exit means in the wall. The compartment comprises a first or fast releasing lamina and a second or short releasing lamina that are delivered through the exit means over two different periods of time.

2 Claims, 3 Drawing Sheets



DOSAGE FORM FOR DELIVERING ACETAMINOPHEN OR PHENYLPROPANOLAMINE

CROSS REFERENCE TO CO-PENDING APPLICATION(S)

This application is a continuation of U. S. patent application Ser. No. 07/092,857 filed Sept. 3, 1987, now U.S. Pat. No. 4,814,181 issued Mar. 21, 1989 and is co-pending with U. S. patent application Ser. No. 07/034,971 filed Apr. 6, 1987 now U.S. Pat. No. 4,786,503 issued Nov. 22, 1988, and co-pending U.S. patent application Ser. No. 07/313,006 filed Feb. 21, 1989. All the applications are assigned of record to ALZA Corporation of Palo Alto, Calif.

FIELD OF THE INVENTION

This invention pertains to both a novel and useful dosage form for delivering a beneficial agent to an environment of use. More particularly, the invention relates to a dosage form comprising a wall that surrounds a compartment. The compartment comprises a first lamina comprising a beneficial agent that is delivered in a short period of time, and a second lamina comprising a beneficial agent that is delivered in a prolonged period of time. At least one passageway thorough the wall permits delivery of the first lamina comprising its beneficial agent and delivery of the second lamina comprising its beneficial agent to an environment of use.

BACKGROUND OF THE INVENTION

Since the beginning of antiquity those engaged in pharmacy and medicine have sought a dosage form designed as a delivery system for the controlled administration of a beneficial agent to an environment of use. The first written reference to a delivery system, a dosage form, is in the Eber Papayrus written about 1552 B. C. The Eber Papayrus mentions dosage forms such as anal suppositories, vaginal pessaries, ointments, oral pill formulations and other dosage preparations. About 2500 years passed without any advance in dosage form development until the Arab physician Rhazes, 865–925 A. D., invented the coated pill. About a century later the Persian Avicenna, 980–1037 A. D., coated pills with gold or silver for increasing patient acceptability and for enhancing the effectiveness of the drug. Also around this time the first tablet was described in Arabian manuscripts written by Al-Zahrawi, 936–1009 A. D. The manuscripts described a tablet formed from the hollow impressions in two matched, facing tablet molds. Pharmacy and medicine waited about 800 years for the next innovation in dosage forms when in 1883 Mothes invented the capsule for administering a drug. The next quantum and profound leap in dosage forms came in 1972 with the invention of the osmotic delivery device invented by Theeuwes and Higuchi. This unique osmotic delivery device is manufactured in one embodiment for oral use. In this embodiment, it embraces the appearance of a tables comprising an internal drug core and a delivery portal. After a start-up period, it delivers drug at a controlled rate over a prolonged period of time. It is the first oral dosage form that delivers a drug throughout the entire gastrointestinal tract in a controlled dose per unit time.

While the above described osmotic system comprising a single drug core represents an outstanding and pioneering advancement in the osmotic delivery art,

and while the osmotic system is useful for dispensing innumerable drugs to the environment of use, it has now been

ARC 1393 discovered that these osmotic systems can be improved further to enhance the delivery kinetics and the usefulness of the osmotic systems. That is, it now has been unexpectedly discovered that a novel dosage form manufactured as an osmotic device can be provided to deliver a bio-affecting drug at a fast rate and deliver a bio-affecting drug at a slow rate in a substantially constant dose over a prolonged period of time. By providing a fast rate of delivery the dosage form makes drug available early in the delivery period and essentially eliminates the start-up time associated with the prior art osmotic dosage forms. The dosage form by providing a slow rate of delivery also makes available drug delivery at a controlled and constant rate over a prolonged period of time. The dosage form made available by this invention uniquely embodies delivery at two different rates, thereby functioning according to a pre-selected, built-in optimal program of drug presentation.

OBJECTS OF THE INVENTION

Accordingly, in view of the above presentation it is an immediate object of this invention to provide an improved dosage form, manufactured as an osmotic delivery device, for the controlled delivery of a drug at a fast rate and at a slow and constant, prolonged rate to a drug receptor for producing a therapeutic effect.

Another object of the invention is to provide an osmotic dosage form that comprises means for delivering a beneficial agent instantly, thereby overcoming the start-up time known to the prior art.

Another object of the invention is to provide an osmotic dosage form that comprises means for instantly delivering a beneficial agent followed by delivering a beneficial agent over a prolonged period of time.

Another object of the invention is to provide an osmotic dosage form comprising means for the concurrent and instant delivery of a beneficial agent and for delivery of a beneficial agent at a slow rate over a prolonged period of time.

Another object of the invention is to provide an osmotic dosage form comprising a wall that surrounds a compartment which compartment comprises means for providing a beneficial drug at a fast delivery rate and means for delivering a beneficial drug at a slow rate over time.

Another object of the invention is to provide an osmotic dosage form comprising a wall that surrounds a compartment, which compartment contains a drug that is available for immediate delivery for substantially eliminating the start-up time associated previously with osmotic dosage forms.

Another object of the invention is to provide an osmotic dosage form comprising a first lamina comprising a drug and a releasable binder, which lamina delivers drug immediately for increasing the period of time drug is available for performing its beneficial effects.

Another object of the invention is to provide an osmotic dosage form comprising a first delivery lamina that contains a drug and a releasable binder that delivers drug immediately, and a slow delivery second lamina that contains a drug and preferably a different releasable binder that delivers the drug at a slower rate over a prolonged period of time.

lates having a D.S. of 2.2 to 2.6 such as cellulose disuccinate, cellulose dipalmitate, cellulose dioctanoate, cellulose dipentate, and the like. Additional semipermeable polymers that can be used for manufacturing wall 12 include acetaldehyde dimethyl acetate, cellulose acetate ethylcarbamate, cellulose acetate phthalate for use in environments having a low pH, cellulose acetate methyl carbamate, cellulose acetate dimethylaminoacetate, semipermeable polyamides, semipermeable polyurethanes, semipermeable sulfonated polystyrenes, cross-linked selective semipermeable polymers formed by the coprecipitation of a polyanion and a polycation as disclosed in U. S. Pats. Nos. 3,173,876; 3,276,586; 3,541,005; 3,541,006; and 3,546,142; semipermeable polymers as disclosed by Loeb and Sourirajan in U. S. Pat. No. 3,133,132; lightly cross-linked plasticized polystyrene derivatives; cross-linked poly(sodium styrene sulfonate); crosslinked poly(vinylbenzyltrimethyl ammonium chloride); semipermeable 1 polymers exhibiting a fluid permeability of 10^{-5} to 10^{-1} (cc . mil/cm^{2}hr.atm) expressed as per atmosphere of hydrostatic or osmotic pressure difference across the semipermeable wall. The polymers are known to the art in U. S. Pat. Nos. 3,845,770; 3,916,889; and 4,160,020; and in *Handbook of Common Polymers* by Scott, J. R. and Roff, W. J., (1971) published by CC Press, Cleveland, Ohio.

Dosage form 10 comprises a beneficial agent 18 in fast releasing lamina 16 and a beneficial agent 19 in slow releasing lamina 17. The beneficial agent can be the same in both lamina, or the beneficial agent can be different in both lamina. The expression, "beneficial agent", as used herein, in a preferred embodiment, denotes a drug. In the present specification and claims the term, "drug" includes any physiologically or pharmacologically active substance that produces a local or systemic effect in animals, including warm-blooded mammals, humans and primates; avians; household, sport and farm animals; laboratory animals; fishes; reptiles; and zoo animals. The term, "physiologically", as used herein, denotes the administration of a drug to produce generally normal levels and functions in a warmblooded animal. The term, "pharmacologically" generally denotes variations in response to the amount of drug administered to the host. See *Stedman's Medical Dictionary*, (1966) published by Williams and Wilkins, Baltimore, Md.

The beneficial drug that can be delivered by the dosage form includes inorganic and organic compounds without limitation, including drugs that act on the peripheral nerve, adrenergic receptors, cholinergic receptors, nervous system, skeletal muscles, cardiovascular system, smooth muscles, blood circulatory system, synaptic sites, neuroeffector junctional sites, endocrine system, hormone systems, immunological system, organ systems, reproductive system, skeletal system, autocoid systems, alimentary and excretory systems, inhibitors of autocoids, and histamine systems. The therapeutic drug that can be delivered for acting on these recipients include anticonvulsants, analgesics, anti-Parkinsons, anti-inflammatories, anesthetics, antimicrobials, anti-malarials, antiparasitic, antihypertensives, angiotensin converting enzyme inhibitor, antihistamines, antipyretics, alpha-adrenergic agnoist, alpha-blockers, biocides, bactericides, bronchial dilators, beta-adrenergic stimulators, beta-adrenergic blocking drugs, contraceptives, cardiovascular drugs, calcium channel inhibitors, depressants, diagnostics, diuretics, electrolytes, hypnotics, hormonals, hyperglycemics, muscle contractants, muscle relaxants, opthalmics, psychic energizers, parasympathomimetics, sedatives, sympathomimetics, tranquilizers, urinary tract drugs, vaginal drugs, vitamins, calcium channel blockers, and the like.

Exemplary drugs that can be delivered by fast drug releasing lamina 16, and by slow drug releasing lamina 17 of dosage form 10 are drugs that are very soluble in aqueous fluids such as prochlorperazine edisylate, ferrous sulfate, aminocaproic acid, potassium chloride, mecamylamine hydrochloride, procainamide hydrochloride, amphetamine sulfate, benzphetamine hydrochloride, isoproteronol sulfate, methamphetamine hydrochloride, phenmetrazine hydrochloride, bethanechol chloride, methacholine chloride, pilocarpine hydrochloride, atropine sulfate, scopolamine bromide, isopropamide iodine, tridihexethyl chloride, phenformin hydrochloride, methylphenidate hydrochloride, cimetidine hydrochloride theophylline cholinate, cephalexin hydrochloride, and the like.

Exemplary drugs that can be delivered by fast drug releasing lamina 16 and by slow drug releasing lamina 17 of dosage form 10 are drugs that are poorly soluble in aqueous fluids such as diphenidol, meclizine hydrochloride, prochlorperazinemaleate, phenoxybenzamine, thiethylperazine maleate, anisindone, diphenadione, erythrityl tetranitrate, digoxin, isoflurophate, acetazolamide, methazolamide, bendroflumethiazide, chlorpropamide, tolazamide, chlormadinone acetate, phenaglycodol, allopurinol, aluminum aspirin, methotrexate, acetyl sulfisoxazole, erythromycin, progestins, esterogenic, progestational, corticosteroids, hydrocortisone, hydrocorticosterone acetate, cortisone acetate, triamcinolone, methyltesterone, 17-beta-estradiol, ethinyl estradiol, prazosin hydrochloride, ethinyl estradiol 3-methyl ether, pednisolone, 17-alpha-hydrocyprogesterone acetae, 19-norprogesterone, norgestrel, norethindrone, progesterone, norgesterone, norethynodrel, and the like.

Examples of other drugs that can be delivered by lamina 16 and lamina 17 of dosage form 10 include aspirin, indomethacin, naproxen, fenoprofen, sulindac, indoprofen, nitroglycerin, propranolol, timolol, atenolol, alprenolol, cimetidine, clonidine, imipramine, levedopa, chloropromazine, methyldopa, dihydroxyphenylalnine, pivaloyloxyethyl ester of alpha-methyldopa, theophylline, calcium gluconate, ketoprofen, ibuprofen, cephalexin, erythromycin, haloperidol, zomepirac, ferrous lactate, vincamine, diazepam, captopril, phenoxybenzamine, nifedipine, diltiazem, verapamil, milrinone, madol, quanbenz, hydrochlorothiazide, and the like. The beneficial drugs are known to the art in *Pharmaceutical Sciences*, 14th Ed., edited by Remington, (1979) published by Mack Publishing Co., Easton, Pa.; *The Drug, The Nurse, The Patient, Including Current Drug Handbook*, by Falconer et al., (1974–1976) published by Sunder Co., Philadelphia, Pa.; *Medicinal Chemistry*, 3rd Ed., Vol. 1 and 2, by Burger, published by Wiley Interscience, New York and in *Physicians' Desk Reference*, 38th Ed., (1984) published by Medical Economics Co., Oradell, N.J.

The drug in dosage form 10 in lamina 16 and in lamina 17 can be in various forms, such as uncharged molecules, molecular complexes, pharmacologically acceptable salts such as hydrochloride, hydrobromide sulfate, laurate, palmitate, phosphate, nitrite, borate, acetate, maleate, tartrate, oleate, and salicylate. For acidic drugs, salts of metals, amines or organic cations; for example, quaternary ammonium can be used. Deriva-

passed through a sizing mill to regrind the composition. The composition is ground to a small size, typically 20 mesh or smaller. Finally, a dry lubricant is added and the ingredients blended to produce the final lamina forming composition. The second lamina is made in a similar manner. Then, each composition is fed independently to the compaction press and compressed into the dosage form comprising parallel laminae.

Other standard manufacturing procedures can be used to form the laminae and the laminated dosage form. For example, the various ingredients can be mixed with a solvent by ballmilling, calendering, stirring or rollmilling, and then pressed into a preselected sized and shaped lamina. A second lamina made in a like process comprising a shape and size corresponding to the first lamina is then laminated with pressure to the first lamina to yield this structure of the dosage form.

Wall 12 can be applied around the slow releasing lamina and the fast releasing lamina by molding, spraying, or dipping the pressed laminae into the wall forming composition. Another and presently preferred technique that can be used for applying the wall is the air suspension procedure. This procedure consists in suspending and tumbling the pressed compositions in a current of air and a wall forming composition until the wall surrounds and coats the two pressed together laminae. The air suspension procedure is well suited for independently forming the wall. The air suspension procedure is described in U. S. Pat. No. 2,799,241; in *J. Am. Pharm. Assoc.*, Vol. 48, pp 451–459 (1959) and *ibid*, Vol. 49, pp 82–84, (1960). A dosage forming system can be coated also with a wall forming composition with a Wurster ® air suspension coater using organic solvents such a methylene dichloride/ methanol cosolvent, 80/20 wt/wt, using 2.5% to 4% solids. The Aeromatic ® air suspension coater using a methylene dichloride/methanol cosolvent, 87/13 wt/wt, also can be used for applying the wall of the lamina. Other wall forming techniques such as pan coating can be used for applying the wall. In the pan coating system a wall forming composition is deposited by successive spraying of the compositions on the drug accompanied by tumbling the compressed fast and slow releasing laminate in a rotating pan. A pan coater is used, in one manufacture, to produce a thicker wall. A larger volume of methanol can be used in a cosolvent to produce a thinner wall. Finally, the wall or lamina coated laminae are dried in a forced air oven at 50° C. for one to seven days to free the dosage form of solvent. Generally, the wall formed by these techniques will have a thickness of 2 to 20 mils, with a presently preferred thickness of 4 to 10 mils.

Exemplary solvents suitable for anufacturing the lamina include inorganic and organic solvents that do not adversely harm the lamina, the lamina forming ingredients and the final dosage form. The solvents broadly include a member selected from the group consisting of alcohols, ketones, esters, ethers, aliphatic hydrocarbons, halogenated solvents, cycloaliphatic solvents, aromatic, heterocyclic solvents, and mixtures thereof. Typical solvents include acetone, diacetone, methanol, ethanol, isopropyl alcohol, butyl alcohol, methyl acetate, ethyl acetate, isopropyl acetate, n-butylacetate, methyl isobutyl ketone, methyl propyl ketone, n-hexane, n-heptane, methylene dichloride, ethylene dichloride, propylene dichloride, ethyl ether, mixtures such as acetone and ethanol, acetone and water, acetone and methanol, methylene dichloride and methanol, ethylene dichloride and methanol, and the like.

The following examples illustrate means and methods for carrying out the present invention. The examples are merely illustrative and they should not be considered as limiting the scope of the invention, as these examples and other equivalents thereof will be come more apparent to those versed in the pharmaceutical dispensing art in the light of the present disclosure, the drawings and the accompanying claims.

EXAMPLE 1

A dosage form for the controlled delivery of the beneficial drug acetaminophen is made as follows: First, a slow acetaminophen releasing lamina is prepared by blending 19.375 g of acetaminophen, 1.625 g of hydroxypropylmethylcellulose having a molecular weight of 9,200, 2.875 g of lightly cross-linked sodium carboxymethylcellulose, and 1 g of polyvinylpyrrolidone in a V-blender for 20 to 25 minutes. Then, the homogeneous blend is transferred to a beaker and 10 ml of absolute ethanol is added to the blend and the mixing continued for an additional ten minutes. The wet blend is passed through a number 20 mesh screen to produce wet granules. The granules are dried at room temperature for 16 hours, and then passed through a 20 mesh screen. Next, the granules are lubricated with 0.125 g of magnesium stearate in a Vblender for 3 minutes.

Next, a fast releasing acetaminophen lamina is made by intimately blending 18.125 g of acetaminophen, 6.25 g of hydroxypropylcellulose exhibiting a hydroxypropoxy content of 10% to 13%, and 0.5 g of polyvinylpyrrolidone are blended for 20 minutes and then transferred to a beaker. Then, 10 ml of absolute alcohol is added to the blend and the blending continued for about 10 minutes. The wet blend then is passed through a 20 mesh screen and allowed to dry for 16 hours at room temperature. The dry blend is again screened through a 20 mesh screen. The dry granules are placed in a V-blender and blended with 0.125 g of magnesium stearate for 3 minutes.

Next, 451.6 mg of the slow drug releasing formulation is pressed into a 7/10" oval shape on a Manesty ® layer press and 206.9 mg of the fast releasing drug layer is pressed on top of the slow releasing layer to provide a bilayer drug core.

Next, the bilamina is surrounded with a semipermeable wall. The semipermeable wall forming composition comprises 80% cellulose acetate having an acetyl content of 39.8%, 10% hydroxypropylmethylcellulose having a molecular weight of 11,300 (HPMC E-5), and 10% polyethylene glycol. The semipermeable wall is applied in an Aeromatic ® air suspension coater. A coating solution comprising the cellulose acetate, hydroxypropylmethylcellulose and the polyethylene glycol dissolved in methylene chloride-methanol, 90:10 wt %, to give 4% solids, is sprayed around the bilamina to provide the wall. Next, the semipermeable wall coated dosage forms are dried in a forced air oven for 16 hours at 50° C. to evaporate the solvents.

Next, the dried dosage forms are divided into two groups. One group is drilled with a 50 mm orifice on two faces of the dosage form. The other group is drilled with a 20 mil wide by 197 mil long slit on each face. Then, both groups of dosage forms are placed in artificial gastric fluid and artificial intestinal fluid at 37° C. and the release rate ascertained in a USP release rate tester. The release rates for the dosage forms with the two

orifices is seen in FIG. 3. In FIG. 3 dosage form 10 comprises two 50 mil passageways. The release rate curve with the connecting squares denotes measurements made in artificial intestinal fluid and the release rate curve connected with plus marks denotes measurement made in artificial gastric fluid. In FIG. 4, the dosage form comprises two 0.5 cm slits. In FIG. 4 the release rate curve with the connecting squares denotes measurements made in artificial intestinal fluid, and the release rate curve connected by plus signs denotes the release rate measured in artificial gastric fluid.

EXAMPLE 2

A dosage form for delivering a beneficial drug to an environment of use is prepared as follows: A slow drug releasing lamina is fluid bed granulated in a Vector Freund Flo-Coater. The slow drug releasing lamina is prepared as follows: First, 22.25 kg of acetaminophen and 6.0 kg of polyethylene oxide having a molecular weight of 200,000 are placed in the bowl of the fluid bed granulator. Then, while the powders are mixing, 30 kg of a solution of of 5% hydroxypropylmethylcellulose exhibiting a molecular weight of 11,300 in distilled water is sprayed onto the ingredients to form a granulation. Then, 150 g of magnesium stearate is added to the granulation in a Rotocone ® blender and mixing continued for 5 minutes. The granulation's final composition comprises 74.5% acetaminophen, 20% polyethylene oxide, 5% hydroxypropylmethylcellulose and 0.5% magnesium stearate.

Next, a fast drug releasing layer is prepared as follows. 23.25 kg of acetaminophen, 2.1 kg of hydroxypropylcellulose exhibiting a hydroxypropoxy content of 10% to 13%, 3 kg of sodium bicarbonate and 0.09 kg of ferric oxide are placed in a granulator bowl of a VectorFreund Flocoater. While the ingredients are mixing in the granulator, 30 kg of a 5% hydroxypropylmethyl cellulose, having an average molecular weight of 11,300-E5, in water is sprayed onto the powder to form granules. The granules then are lubricated with 154.7 g of magnesium stearate for 5 minutes in a Rotocone blender. The final composition prepared by the granulation comprises 77.3% acetaminophen, 10% sodium bicarbonate, 7% hydroxypropylcellulose, 5% hydroxypropylmethylcellulose. 0.5% magnesium stearate and 0.3% ferric oxide.

The two lamina forming compositions were compressed into a bilaminate using a Manesty ® press. First, 469.8 mg of the slow formulation is added to the Manesty press and pressed to form a lamina. Then, 194.1 mg of the fast formulation is added to the Manesty press and pressed to form a fast releasing lamina in contact with the slow releasing lamina.

Next, the bilaminate is coated with a semipermeable wall. The semipermeable wall weighs 35.2 mg and comprises 70% cellulose acetae having an acetyl content of 39.8%, 15% polyethylene glycol 3350, and 15% hydroxypropylmethylcellulose having a number average molecular weight of 11,300. The semipermeable wall is applied in an AccelaCota ® rotating open coater. The coating solution consists of the cellulose acetate, the polyethylene glycol and the hydroxypropylmethylcellulose dissolved in methylene chloride:methanol, (90:10 wt %) to give a 4% solution.

After drying a slit passageway is formed in the wall using a laser generator. First a slit is laser drilled through the wall to connect the fast releasing lamina with the exterior of the dosage form. Then the dosage form is turned over and a laser slit passageway is drilled through the wall to the slow releasing lamina.

The release of drug from the dosage form is measured in artificial gastric fluid. The cumulative release rate is depicted in FIG. 5.

EXAMPLE 3

The procedure of example 2 is followed in preparing this example. The dosage form prepared in this example comprises (1) a fast dissolving lamina comprising 77.5% acetaminophen, 10% sodium bicarbonate, 7% hydroxypropylcellulose, 5% hydroxypropylmethylcellulose having a molecular weight of 11,300, and 0.5% magnesium stearate, (2) a slow releasing lamina comprising 74.5% acetaminophen, 20% polyethylene oxide having a molecular weight of 200,000 and 5% hydroxypropylmethylcellulose having a molecular weight of 11,300 and 0.5% magnesium stearate, and (3) a wall comprising 70% cellulose acetate having an acetyl content of 39.8%, 15% hydroxypropylmethylcellulose having a molecular weight of 11,300 and 15% polyethylene glycol 3350. In this example cumulative release rates are measured for dosage forms with different slit passageways are plotted in FIG. 6, the line connected through squares indicates the cumulative amount released for a dosage form comprising two slit passageways measuring 1.25 cm ×0.0007 cm; the line connected by plus signs denotes a dosage form comprising two slits of 1.25 cm×0.03 cm; the line connected by diamonds indicates a dosage form with one slit 1 cm ×0.07 cm, and the line connected through triangles denotes a dosage form with a single slit passageway 1.5 cm ×0.04 cm. In one preferred embodiment the passageway exhibits an area of 0.20 to 0.40 cm^2.

EXAMPLE 4

This example illustrates the effect of the weight of the wall on the cumulative amount released from a dosage form. In accompanying FIG. 7, the cumulative amount of acetaminophen released from a dosage form comprising a single passageway, a slow releasing lamina and a fast releasing lamina are illustrated as follows: the line connected with squares indicates the amount released from a dosage form with a wall weighing 13.1 mg, the lines connected by plus signs indicate the amount released when the wall weighs 77 mg, the line with triangles indicates the amount released when the wall weighs 25 mg, and line with X's indicates the cumulative amount released when the wall weighs 31 mg.

EXAMPLE 5

This example illustrates the release rate of dosage forms wherein the slow releasing lamina comprises different components. The fast releasing lamina of the dosage form comprises 80.0% phenylpropanolhydrochloride (PPA +Cl), 10% hydroxypropylcellulose, 5% sodium bicarbonate and 4.75% hydroxypropylmethylcellulose having a molecular weight of 11,300 and 0.25% magnesium stearate. The fast releasing lamina is used in two dosage forms comprising different slow releasing lamina. The slow releasing laminae are (a) a slow releasing lamina comprising 10% hydroxypropylmethylcellulose having a molecular weight of 9,200, 4% hydroxypropylmethylcellulose having a molecular weight of 241,900, 3% hydroxypropylcellulose, 2% hydroxypropylmethylcellulose having a molecular weight of 11,300, 80.5% PPAHCl and 0.5% magnesium stearate; and (b) a slow releasing lamina comprising 4%

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Re: Expediente No. **00-097.407**
Solicitud de patente a nombre de
Johnson & Johnson Consumer Companies, Inc.

Yo, JIMENA ESCOBAR URIBE, identificada como aparece al pie de mi firma, domiciliada en la carrera 11 A No. 94-76 Of. 305, obrando como apoderada en este negocio, atentamente solicito a usted se sirva conceder una prórroga de 30 días para dar respuesta a su oficio No. 06918 notificado por fijación en lista el 29 de junio de 2006, relacionado con la solicitud de patente que se está tramitando bajo el expediente de la referencia.

Acompaño el recibo No. 06 - 69,532 de 8 de septiembre de 2006, correspondiente a la tasa de la prórroga del término.

Señor Superintendente,

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