238

ESCOBAR – URIBE ASOCIADOS

ABOGADOS

Carrera 11A No. 94-76 - Of.305 - P.O. Box 94948, Bogotá, D.C. - Colombia
Tels: (571) 6162051 - Fax (571) 6161889
www.escobaruribe.com - info@escobaruribe.com

As. 2840/P.

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

SUPERINDUSTRIA Y COMERCIO
Radicacion : 05054294 [illegible] Folios: 2
Fecha (AMD): 2006-02-09 14:44:28
Tramite : 002 PATENTES D 1 REGISTRO/ 538 PETICION
Dependencia: [illegible] DIVISION DE NUEVAS CREACIONES

Ref.: Expediente No. **05-054.294**
Solicitud de Patente a nombre de
McNeil-PPC, 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 **McNeil-PPC, 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. 06 - 3,391 de 17 de enero de 2006, por la suma de $388.000.oo, con lo cual queda cubierta la tasa oficial correspondiente a dicho estudio.

Señor Superintendente,

JIMENA ESCOBAR URIBE
C.C. 39.779.452 de Usaquén
T.P. 68.228
Cod. 5376
JEU/ra.

239

~~2870~~

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINDUSTRIA Y COMERCIO
Radicacion : 06054294 00000005 Folios: 2
Fecha (AMD): 2006-02-09 14:44:28
Tramite : 002 PATENTES D 1 REGISTRO/ 508 PETICION
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

RECIBO OFICIAL DE CAJA : 06 - 3,391
FECHA : ENERO 17 DE 2006

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
ESCOBAR URIBE ASOCIADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	49043493	17/01/2006	2,336,000.00

***** CONCEPTO *****

CANT.	RENTISTICO		CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	112 PTC CAP-I EXAMEN DE PATENTIBILIDA	388,000.00
			TOTAL : $	388,000.00

SON: TRESCIENTOS OCHENTA Y OCHO MIL PESOS

RESPONSABLE : ______________________________

RECIBO DE CAJA APLICADO AL EXPEDIENTE No.______________________

2020
Bogotá D C

Doctor(a):
JIMENA ESCOBAR URIBE.
Solicitante

REFERENCIA:	Radicación N°	05-54294
	Trámite	002
	Evento	001
	Actuación	416
	Oficio N°	1269
	Folios	001

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en los artículos 26 y 27 de la Decisión 486, de la Comisión de la Comunidad Andina, y en las demás disposiciones vigentes sobre la materia, se envía el extracto de la solicitud a la oficina de comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial, conforme lo establece el artículo 40 de la Decisión 486, **a partir del 03 de diciembre de 2005,** por indicación del solicitante.

Cúmplase
Dado en Bogotá D C, 31 OCT. 2005

ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe División de Nuevas Creaciones.

202051

241

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 05-054294

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCIÓN** FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **559** DE FECHA **30** DE **DICIEMBRE DE 2005** EL TÉRMINO HÁBIL SEÑALADO POR LA LEY EXPIRA EL **28** DE **MARZO** DEL **2006**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI ________ NO___ **X** _____

145

242

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
8 April 2004 (08.04.2004)

PCT

(10) International Publication Number
WO 2004/028513 A1

(51) International Patent Classification⁷: **A61K 9/28**, 9/20

(21) International Application Number: PCT/US2003/008897

(22) International Filing Date: 21 March 2003 (21.03.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

PCT/US02/31129	28 September 2002 (28.09.2002)	US
PCT/US02/31117	28 September 2002 (28.09.2002)	US
PCT/US02/31062	28 September 2002 (28.09.2002)	US
PCT/US02/31024	28 September 2002 (28.09.2002)	US
PCT/US02/31163	28 September 2002 (28.09.2002)	US

(71) Applicant: **MCNEIL-PPC, INC.** [US/US]; Grandview Road, Skillman, NJ 08558 (US).

(72) Inventors: **SOWDEN, Harry, S**; 209 Wood Road, Glenside, PA 19038 (US). **MCNALLY, Gerard, P.**; 177 Coldstream Drive, Berwyn, PA 19312 (US).

(74) Agents: **JOHNSON, Philip, S.** et al.; Johnson & Johnson, One Johnson & Johnson Plaza, New Brunswick, NJ 08903 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

---

(54) Title: IMMEDIATE RELEASE DOSAGE FORM COMPRISING SHELL HAVING OPENINGS THEREIN

(57) Abstract: The invention provides an immediate release dosage form having a solid core and a shell readily soluble in gastrointestinal fluids. The dosage form also comprises one or more openings in the shell.

WO 2004/028513 A1

2H3
2~~4~~3

for example zinc salicylate, magnesium salicylate and calcium salicylate; quaternary ammonium salts; benzalkonium chloride; benzethonium chloride; trimethyl tetradecyl ammonium bromide (cetrimide); and cyclodextrins and their adducts, in an amount from about 1% to about 10% by weight of the shell.

Applicants have now discovered that an immediate release dosage form may be made from a solid core and a shell surrounding the core, wherein the core has a density of at least about 0.9 g/cc. The shell comprises one or more openings therein and is readily soluble in gastrointestinal fluids. The shell is preferably applied to the core by enrobing.

Summary of the Invention

The present invention provides a dosage form containing at least one active ingredient, which comprises a core and a shell surrounding the core, wherein the core has a density of at least about 0.9 g/cc, the shell comprises one or more openings, the shell is readily soluble in gastrointestinal fluids, and the dosage form provides for immediate release of at least one active ingredient upon contact of the dosage form with a liquid medium.

The invention also provides a dosage form comprising a core having an outer surface and a shell having outer and inner surfaces, wherein at least a portion of the shell surrounds the core such that the shell inner surface resides substantially conformally upon the core outer surface, at least a portion of the shell comprises one or more openings therein, one or more of the openings are from about 200 to about 2000 microns in diameter or width, at least a portion of the shell is readily soluble in gastrointestinal fluids, the average shell thickness is in the range from about 100 to about 400 microns, the shell comprises less than about 50% crystallizable sugar, and the dosage form is substantially free of charge control agents and the dosage form

~~244~~
244

We Claim:

1. A dosage form containing at least one active ingredient, which comprises a core and a shell surrounding at least a portion of the core, wherein the core has a density of at least about 0.9 g/cc, the shell comprises one or more openings, the shell is readily soluble in gastrointestinal fluids, and the dosage form provides for immediate release of at least one active ingredient upon contact of the dosage form with a liquid medium.

2. The dosage form of claim 1, wherein the shell comprises a plurality of openings.

3. The dosage form of claim 1, wherein one or more openings contact the core.

4. The dosage form of claim 2, wherein a plurality of openings contact the core.

5. The dosage form of claim 1, wherein the core comprises at least one active ingredient.

6. The dosage form of claim 1, wherein the shell comprises at least one active ingredient.

7. The dosage form of claim 5 or 6, wherein the dosage form provides for immediate release of at least one active ingredient contained in the core.

8. The dosage form of claim 1, wherein the core comprises a compressed tablet.

9. The dosage form of claim 1, wherein the compressed tablet has a hardness from about 2 to about 30 kp/cm^{2}.

~~245~~
243

FIG. 1

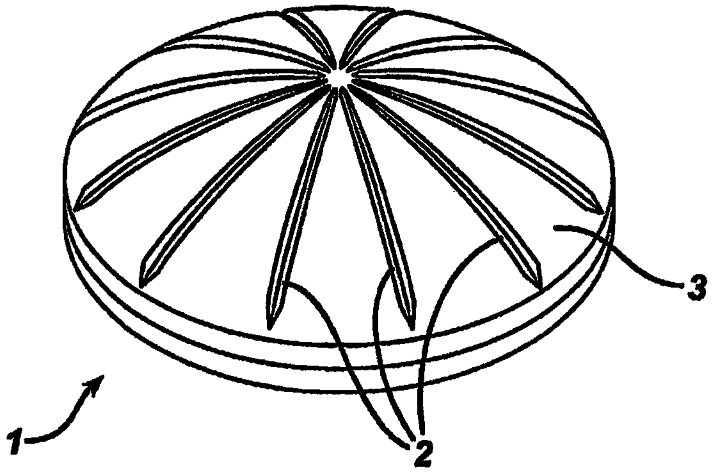
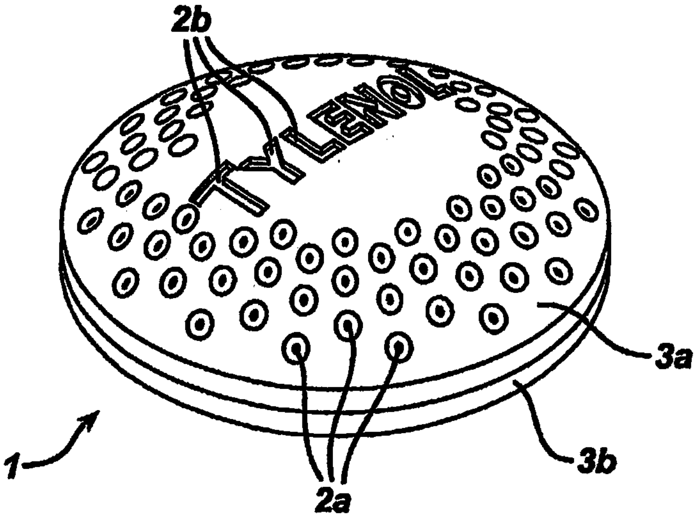


FIG. 2



245

FIG. 1

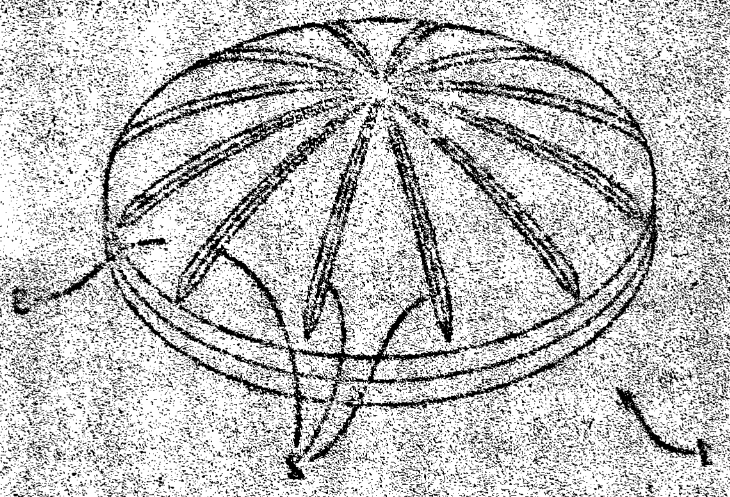
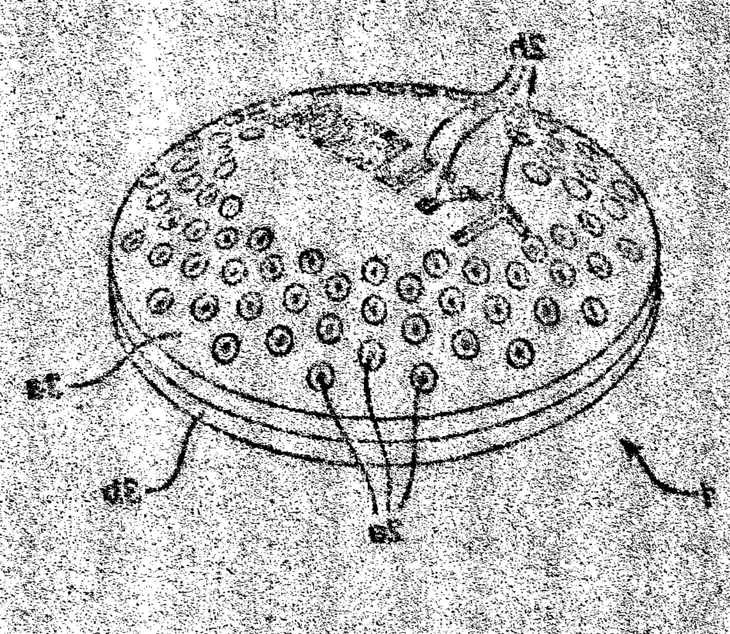


FIG. 2



~~246~~

246

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
19 July 2001 (19.07.2001)

PCT

(10) International Publication Number
WO 01/51040 A1

(51) International Patent Classification⁷: **A61K 9/22**, 9/24, 9/32, 9/36

(21) International Application Number: PCT/US01/00637

(22) International Filing Date: 9 January 2001 (09.01.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/175,827 13 January 2000 (13.01.2000) US

(71) Applicant *(for all designated States except US)*: **LABORATORIOS PHOENIX U.S.A., INC.** [US/US]; 1 Boca Place, 2255 Glades Rd., Suite 324A, Boca Raton, FL 33431 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **FAOUR, Joaquina** [AR/AR]; Olleros 2312, 8°B, 1426 Buenos Aires (AR). **VERGEZ, Juan, A.** [AR/AR]; Uriburu 1316, 1642 Becar, Buenos Aires 1642 (AR).

(74) Agent: MATOS, Rick; Innovar, L.L.C., P.O. Box 250647, Plano, TX 75025-0647 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: OSMOTIC DEVICE CONTAINING ALPRAZOLAM AND AN ANTIPSYCHOTIC AGENT

(57) Abstract: The present invention provides an osmotic device containing controlled release alprazolam in the core optionally in combination with an anti-psychotic agent, in a rapid release external coat. A wide range of anti-psychotic agents can be used in this device. Particular embodiments of the invention provide osmotic devices having predetermined release profiles. One preferred embodiment of the osmotic device includes an external coat that has been spray coated rather than compression coated onto the device. The device with spray coated external coat is smaller and easier to swallow than the similar device having a compression coated external coat. The device is useful for the treatment of depression, anxiety or psychosis related disorders.

WO 01/51040 A1

Materials suitable for preparing the finish coat are well known in the art and found in the disclosures of many of the references cited and incorporated by reference herein.

Generally, the terms “tablet” and “osmotic device” are used interchangeably herein in describing the invention. The osmotic device of the invention comprises at least one passageway (pore, hole, or aperture) that communicates the exterior of the semipermeable wall with the core of the device. The passageway can be formed according to any of the known methods of forming passageways in a semipermeable membrane. Such methods include, for example, 1) drilling a hole through the semipermeable membrane with a bit or laser; 2) including a water soluble material within the composition that forms the semipermeable membrane such that a pore forms when the osmotic device is in an aqueous environment of use; 3) punching a hole through the semipermeable membrane; or 4) employing a tablet punch having a pin to punch a hole through the semipermeable lamina. The passageway can pass through the semipermeable wall and one or more of any other lamina coated onto the semipermeable membrane or between the semipermeable membrane and the core. The passageway(s) can be shaped as desired. In some embodiments, the passageway is laser drilled and is shaped as an oval, ellipse, slot, slit, cross or circle.

Methods of forming passageways in semipermeable membranes of osmotic devices are disclosed in U.S. Patents No. 4,088,864 to Theeuwes et al., No. 4,016,880 to Theeuwes et al., No. 3,916,899 to Theeuwes et al., No. 4,285,987 to Ayer et al., No. 4,783,337 to Wong et al., No. 5,558,879 to Chen et al., No. 4,801,461 to Hamel et al., and No. 3,845,770 to Theeuwes et al., the disclosures of which are hereby incorporated by reference.

The preformed passageway, e.g., one made by mechanical means, is formed after the semipermeable membrane is applied to the core. It can be formed either before or after the inert water soluble coat and/or drug-containing external coat is applied to the semipermeable membrane.

The advantages of the present system over known systems for administering alprazolam in combination with an anti-psychotic agent include improved therapeutic benefit, simplified manufacturing, and/or increased patient compliance. Moreover, the

295.40; Schizoaffective Disorder 295.70; Schizoaffective Disorder of the Depressive Type; and Major Depressive Disorder with Psychotic Features 296.24, 296.34.

Psychoses are often associated with other diseases and conditions, or caused by such other conditions. For example, they are associated with neurological conditions, endocrine conditions, metabolic conditions, fluid or electrolyte imbalances, hepatic or renal diseases, and autoimmune disorders with central nervous system involvement. Psychoses may also be associated with use or abuse of certain substances. These substances include, but are not limited to cocaine, methylphenidate, dexmethasone, amphetamine and related substances, cannabis, hallucinogens, inhalants, opioids, phencyclidine, sedatives, hypnotics and anxiolytics. Psychotic disorders may also occur in association with withdrawal from certain substances. These substances include, but are not limited to, sedatives, hypnotics and anxiolytics. The embodiments of the present invention are useful for treatment of psychotic conditions associated with any of these conditions.

The above-mentioned diseases and disorders are treated in a mammal by administering one or more of the osmotic devices described herein. Each osmotic device is designed for once-daily administration. A patient receiving the osmotic devices will generally be administered one osmotic-device daily for a period of days, week, months or years to be determine by the prescribing physician. Generally, the period is at least one week.

The following examples should not be considered exhaustive, but merely illustrative of only a few of the many embodiments contemplated by the present invention. The methods described herein can be followed to prepare osmotic devices according to the invention.

EXAMPLE 1

A large scale batch of alprazolam (1 mg strength) tablets was prepared by mixing 0.950 g of Alprazolam, 7.00 g of hydroxypropyl methylcellulose 2208, 114.00 g of sodium chloride, 58,45 g of microcrystalline cellulose, 30.0 g of povidone, 80.00 g of polyethylene oxide (molecular weight of about 300,000). The mixture was wet with a blend of 110.00 ml of alcohol 96° and 1.40 g of Polysorbate 20. The blend was granulated and dried at 40 – 50°C for 3 hours; then, it was screened and mixed with 3.80 g of colloidal silicon dioxide. The blend was mixed to homogeneity and 4.40 g of magnesium stearate was added as

248

295.40; Schizoaffective Disorder 295.70; Schizoaffective Disorder of the Depressive Type; and Major Depressive Disorder with Psychotic Features 296.24, 296.34.

Psychoses are often associated with other diseases and conditions, or caused by such other conditions. For example, they are associated with neurological conditions, endocrine conditions, metabolic conditions, fluid or electrolyte imbalances, hepatic or renal diseases, and autoimmune disorders with central nervous system involvement. Psychoses may also be associated with use or abuse of certain substances. These substances include, but are not limited to cocaine, methylphenidate, dexmethasone, amphetamine and related substances, cannabis, hallucinogens, inhalants, opioids, phencyclidine, sedatives, hypnotics and anxiolytics. Psychotic disorders may also occur in association with withdrawal from certain substances. These substances include, but are not limited to, sedatives, hypnotics and anxiolytics. The embodiments of the present invention are useful for treatment of psychotic conditions associated with any of these conditions.

The above-mentioned diseases and disorders are treated in a mammal by administering one or more of the osmotic devices described herein. Each osmotic device is designed for once-daily administration. A patient receiving the osmotic devices will generally be administered one osmotic-device daily for a period of days, week, months or years to be determine by the prescribing physician. Generally, the period is at least one week.

The following examples should not be considered exhaustive, but merely illustrative of only a few of the many embodiments contemplated by the present invention. The methods described herein can be followed to prepare osmotic devices according to the invention.

EXAMPLE 1

A large scale batch of alprazolam (1 mg strength) tablets was prepared by mixing 0.951 g of Alprazolam, 7.00 g of hydroxypropyl methylcellulose 2208, 114.00 g of sodium chloride, 58.45 g of microcrystalline cellulose, 30.0 g of povidone, 80.00 g of polyethylene oxide (molecular weight of about 300,000). The mixture was wet with a blend of 110.00 ml of alcohol 96° and 1.40 g of Polysorbate 20. The blend was granulated and dried at 40 – 50°C for 3 hours; then, it was screened and mixed with 3.80 g of colloidal silicon dioxide. The blend was mixed to homogeneity and 4.40 g of magnesium stearate was added as

~~249~~

249

lubricant. The final blend was tabletted using biconcaves, 9.00-mm diameter punches. Cores weight: 300.0 mg. Hardness from 8 to 12 kp.

A first composition to cover the cores was prepared as follows: 36.90 g of cellulose acetate and 1.95 g of polyethylene glycol 400 in a mixture of 493 ml of methylene chloride and 122 ml of methyl alcohol. This polymer mixture was sprayed onto the tablets in a conventional pan coater to obtain film-coated tablets which membrane coating weighed 38.9 mg approximately. A 0.75-mm hole was drilled through the coating in one face of the tablet.

The third composition was prepared by mixing 3.00 g of copolyvidone, 3.48 g of titanium dioxide, 8.51 g of talc and 7,00 mg of Aluminum Lake Brilliant Blue in isopropyl alcohol. This polymer mixture was sprayed onto the tablets in a conventional pan coater to obtain film-coated tablets which membrane coating weighed 15 mg approximately.

The rapid release external coating was prepared by mixing 0.05 g of alprazolam, 442.05 g of microcrystalline cellulose, 31.40 g of povidone, 18.20 g of crospovidone and 3.30 g of colloidal silicon dioxide. The mixture was blended to homogeneity; then, 5.00 g of magnesium stearate was added as lubricant. This blend was applied over the film-coated tablets by compression using biconcaves, 14.0-mm diameter punches. Coating weight: 500 mg. Hardness from 8 to 14 kp.

The final coating was prepared by mixing 12.1 g of hydroxypropyl methylcellulose 2910, 3.5 g of polyethylene glycol 6000 and 4.40 g of titanium dioxide in a mixture of methylene chloride-alcohol 96° 70:30 v/v (volume/volume). This polymer mixture was sprayed onto the tablets in a conventional pan coater to obtain film-coated tablets which membrane coating weighed 20 mg approximately.

Tablets made according to the above procedure will generally have the following composition.

Component x 1 tablet	0.5 mg	1.0 mg	2.0 mg
CORE			
Alprazolam	0.475 mg	0.950 mg	1.900 mg
Polysorbate 20	0.700 mg	1.400 mg	2.800 mg
Microcrystalline Cellulose	29.225 mg	58.450 mg	116.900 mg
Sodium Chloride	57.000 mg	114.000 mg	228.000 mg
Povidone	15.000 mg	30.000 mg	60.000 mg

Polyethylene Oxide	40.000 mg	80.000 mg	160.000 mg
Hydroxypropyl methylcellulose 2208	3.500 mg	7.000 mg	14.000 mg
Colloidal Silicon Dioxide	1.900 mg	3.800 mg	7.600 mg
Magnesium Stearate	2.200 mg	4.400 mg	8.800 mg
COATING A			
Cellulose Acetate	22.000 mg	36.900 mg	51.900 mg
Polyethylene Glycol 400	1.160 mg	1.950 mg	2.740 mg
COATING B			
Copolyvidone	2.000 mg	3.000 mg	4.400 mg
Titanium Dioxide	1.650 mg	3.480 mg	5.100 mg
Talc	6.345 mg	8.513 mg	12.490 mg
Aluminium Lake Brilliant Blue	0.005 mg	0.007 mg	0.010 mg
COATING C			
Alprazolam	0.025 mg	0.050 mg	0.100 mg
Microcrystalline Cellulose	309.375 mg	442.050 mg	618.900 mg
Povidone	22.000 mg	31.400 mg	43.900 mg
Crospovidone	12.800 mg	18.200 mg	25.500 mg
Colloidal Silicon Dioxide	2.300 mg	3.300 mg	4.600 mg
Magnesium Stearate	3.500 mg	5.000 mg	7.000 mg
COATING D			
Hydroxypropylmethylcellulose 2910	9.100 mg	12.100 mg	15.100 mg
Polyethylene Glycol 6000	2.590 mg	3.500 mg	4.400 mg
Titanium Dioxide	3.310 mg	4.400 mg	5.500 mg

EXAMPLE 2

A large scale batch of Alprazolam (2 mg strength) and Risperidone (5 mg strength) tablets was prepared by mixing 2.00 g of Alprazolam, 14.00 g of Hydroxypropyl methylcellulose 2208, 228.00 g of Sodium Chloride, 116,80 g of Microcrystalline Cellulose, 60.0 g of Povidone, 160.00 g of Polyethylene Oxide (molecular weight of about 300,000). The mixture was wet with a blend of 110.00 ml of alcohol 96° and 2.80 g of Polysorbate 20. The blend was granulated and dried at 40 – 50°C for 3 hours; then, it was screened and mixed with 7.60 g of Colloidal Silicon Dioxide. The blend was mixed to homogenize and 8.80 g of Magnesium Stearate was added as lubricant. The final blend was tabletted using biconcaves, 10.50-mm diameter punches. Cores weight: 600.0 mg. Hardness from 8 to 12 kp.

251

US005582838A

United States Patent [19]

Rork et al.

[11] **Patent Number: 5,582,838**

[45] **Date of Patent: Dec. 10, 1996**

[54] **CONTROLLED RELEASE DRUG SUSPENSION DELIVERY DEVICE**

[75] Inventors: **Gerald S. Rork; James D. Pipkin,** both of Lawrence, Kans.

[73] Assignee: **Merck & Co., Inc.,** Rahway, N.J.

[21] Appl. No.: **363,451**

[22] Filed: **Dec. 22, 1994**

[51] **Int. Cl.^{6}** **A61K 9/24**; A61K 9/32; A61K 9/36

[52] **U.S. Cl.** **424/472**; 424/471; 424/473; 424/479; 424/480; 424/482; 424/470

[58] **Field of Search** 424/472, 473, 424/471, 470, 479, 480, 482

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,146,169	8/1964	Stephenson et al.	167/82
3,538,214	11/1970	Polli et al.	424/19
3,845,770	11/1974	Theeuwes et al.	128/260
3,916,899	11/1975	Theeuwes et al.	128/260
3,957,523	5/1976	Ohno et al.	106/189
4,160,452	7/1979	Theeuwes	128/260
4,200,098	3/1980	Ayer et al.	128/260
4,218,433	8/1980	Kooichi et al.	424/15
4,220,153	9/1980	Dresback et al.	128/260
4,235,236	11/1980	Theeuwes	128/260
4,244,941	1/1981	Lerk	424/21
4,256,108	3/1981	Theeuwes	128/260
4,285,987	8/1981	Ayer et al.	427/3
4,326,525	4/1982	Swanson et al.	128/260
4,327,725	5/1982	Cortese et al.	128/260
4,557,925	12/1985	Liadahl et al.	424/19
4,578,075	3/1986	Urquhart et al.	604/892
4,601,893	7/1986	Cardinal	424/15
4,681,583	7/1987	Urquhart et al.	604/892
4,687,660	8/1987	Baker et al.	424/465
4,743,247	5/1988	Wong	604/892.1
4,783,337	11/1988	Wong et al.	424/468
4,814,182	3/1989	Graham et al.	424/484
4,839,177	6/1989	Colombo et al.	424/482
4,851,228	7/1989	Zentner et al.	424/456
4,898,733	2/1990	DePrince et al.	424/425
4,915,954	4/1990	Ayer et al.	424/473
4,968,507	11/1990	Zentner et al.	424/465
4,971,790	11/1990	Magruder et al.	424/78
4,994,273	2/1991	Zentner et al.	424/422
4,996,060	2/1991	Eckenhoff et al.	424/473
5,004,614	4/1991	Staniforth	424/466
5,030,452	7/1991	Curatolo	424/450
5,057,321	10/1991	Edgren	424/413
5,230,895	7/1993	Czarnecki et al.	424/422
5,366,738	11/1994	Rork et al.	424/473

FOREIGN PATENT DOCUMENTS

0040457	1/1981	European Pat. Off. .
0378404	7/1990	European Pat. Off. .
0021758	1/1981	United Kingdom .
2116841	11/1983	United Kingdom .

OTHER PUBLICATIONS

Proceed. Intern. Symp. Control Rel. Bioact. Mater., 20 (1993).

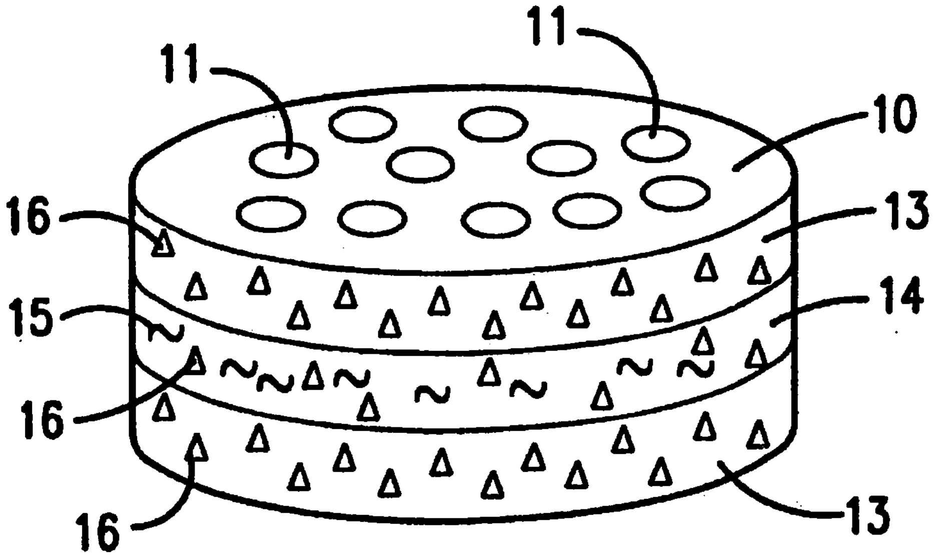
J. Pharm. Sci., 72, pp. 772–775 (1983), by Kallstrand, et al.

Primary Examiner—James M. Spear
Attorney, Agent, or Firm—Francis P. Bigley; Mark R. Daniel

[57] **ABSTRACT**

A device is disclosed for the controlled delivery of a beneficial agent, the device consisting of (i) a core comprising at least two layers, wherein at least one layer comprises a beneficial agent and a polymer which forms microscopic gel beads upon hydration and at least one layer which comprises a polymer which forms microscopic gel beads upon hydration; and (ii) an impermeable, insoluble coating which adheres to and surrounds the core and contains apertures which provide an area for the hydration and release of the microscopic gel beads.

23 Claims, 4 Drawing Sheets



US005582838A

United States Patent [19]

Rork et al.

[11] Patent Number: 5,582,838

[45] Date of Patent: Dec. 10, 1996

[54] CONTROLLED RELEASE DRUG SUSPENSION DELIVERY DEVICE

[75] Inventors: Gerald S. Rork; James D. Pipkin, both of Lawrence, Kans.

[73] Assignee: Merck & Co., Inc., Rahway, N.J.

[21] Appl. No.: 363,451

[22] Filed: Dec. 22, 1994

[51] Int. Cl.6 .... A61K 9/24; A61K 9/22; A61K 9/36

[52] U.S. Cl. 424/473; 424/471; 424/475; 424/479; 424/480; 424/482; 424/470

[58] Field of Search 424/472, 473, 424/471, 470, 479, 480, 482

[56] References Cited

U.S. PATENT DOCUMENTS

[illegible]	8/1964	Stephenson et al.	167/82
[illegible]	11/1970	[illegible] et al.	424/19
[illegible]	11/1974	Theeuwes et al.	128/260
[illegible]	11/1975	Theeuwes et al.	128/260
[illegible]	5/1976	[illegible] et al.	106/189
[illegible]	2/1979	Theeuwes	128/260
[illegible]	3/1980	Ayer et al.	128/260
[illegible]	8/1980	Kozuka et al.	424/15
[illegible]	9/1980	Dresback et al.	128/260
[illegible]	11/1980	Theeuwes	128/260
[illegible]	1/1981	Lowe	424/21
[illegible]	3/1981	Theeuwes	128/260
[illegible]	8/1981	Ayer et al.	424/15
[illegible]	4/1982	Swanson et al.	128/260
[illegible]	5/1982	Cortese et al.	128/260
[illegible]	12/1985	[illegible] et al.	424/19
[illegible]	3/1986	Urquhart et al.	604/892
[illegible]	7/1986	Eckhardt	424/15
[illegible]	7/1987	Urquhart et al.	604/892
[illegible]	8/1987	Baker et al.	424/468
[illegible]	5/1988	Wong	604/892.1
[illegible]	12/1988	Wong et al.	424/468
4,814,182	3/1989	Graham et al.	[illegible]
4,839,177	6/1989	Colombo et al.	[illegible]
4,941,123	7/1990	Zanner et al.	[illegible]
4,898,733	2/1990	DePrince et al.	[illegible]
4,915,954	4/1990	Ayer et al.	[illegible]
[illegible]	10/1990	Zentner et al.	[illegible]
[illegible]	11/1990	Magruder et al.	[illegible]
[illegible]	2/1991	Zentner et al.	[illegible]
4,996,060	2/1991	[illegible] et al.	[illegible]
5,004,614	4/1991	Staniforth	[illegible]
5,030,452	7/1991	Conte	[illegible]
[illegible]	10/1991	Eckenhoff	[illegible]
5,230,895	7/1993	Czarnecki et al.	[illegible]
5,366,738	11/1994	Rork et al.	[illegible]

FOREIGN PATENT DOCUMENTS

0040457	1/1981	European Pat. Off.
0378404	7/1990	European Pat. Off.
[illegible]	1/1961	United Kingdom
2146541	11/1983	United Kingdom

OTHER PUBLICATIONS

Proceed. Intern. Symp. Control. Rel. Bioact. Mater., 20 (1993).

J. Pharm. Sci., 72, pp. 772–775 (1983), by Kallstrand et al.

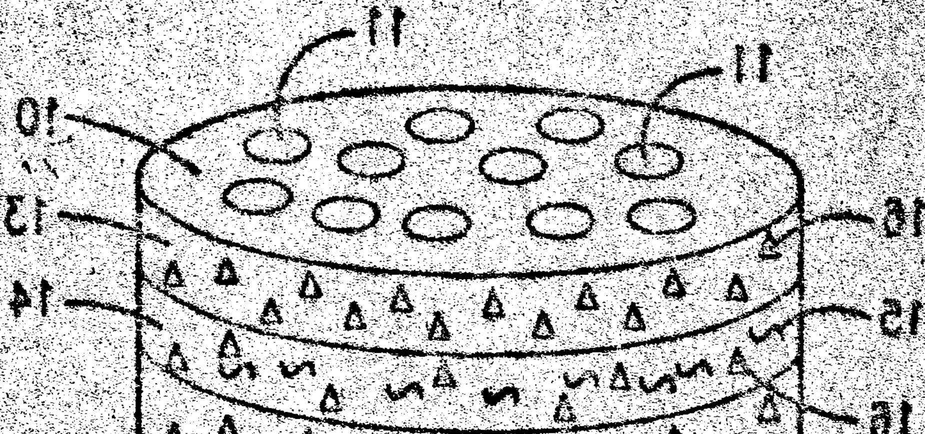
Primary Examiner—James M. Spear

Attorney, Agent, or Firm—Francis P. Bigley; Mark R. Daniel

[57] ABSTRACT

A device is disclosed for the controlled delivery of a beneficial agent, the device consisting of (i) a core comprising at least two layers, wherein at least one layer comprises a beneficial agent and a polymer which forms microscopic gel beads upon hydration and at least one layer which comprises a polymer which forms microscopic gel beads upon hydration and (ii) an impermeable, insoluble coating which adheres to and surrounds the core and contains apertures which provide an area for the hydration and release of the microscopic gel beads.

21 Claims, 4 Drawing Sheets



In vitro release rate performance of both sets of devices were measured at 37° C. in isotonic, phosphate buffer at pH 7.4 containing 0.4% w/w sodium dodecylsulfate using a USP Apparatus II at 50 rpm. The cumulative percent of lovastatin released was plotted against time and is shown in FIG. 5, using a single composition core devices with 39×0.5 mm holes (FIG. 5, #52) and 22×0.5 mm holes (FIG. 5, #51) as standards. As shown in FIG. 5, the release profiles for the two-layer device were significantly improved over the single composition core, in that in the last 20% of lovastatin was released at a more constant rate and greater than 95% of the lovastatin content was released in less than 20 hours. This is a 10–15% improvement in the cumulative percent released over the single composition core device.

EXAMPLE 2

Tablets for the controlled release of nifedipine were prepared from the following formulation:

	mg/Layer
Ingredients: Active Layer	
Nifedipine micronized	33
"CARBOPOL 974P" NF	15
Dibasic Sodium Phosphate (anhydrous)USP	37.5
Lactose Hydrous NF (spray dried)	7.5
Povidone USP K-90	2.5
Magnesium Stearate NF	0.5
	96.0
Ingredients: Inactive Layer	
AVICEL PH101	33
"CARBOPOL 974P" NF	15
Sodium Citrate Dihydrate USP	37.5
Lactose Hydrous NF (impalpable)	7.5
Povidone USP K-90	2.5
Magnesium Stearate NF	0.5
	96.0

The micronized nifedipine was combined with dibasic sodium phosphate, CARBOPOL, lactose and polyvinylpyrrolidone, mixed thoroughly then granulated using an aqueous alcoholic solvent blend (10% by volume water). The solvated mass was passed through a #20 screen then dried initially at 60° for two to four hours, then at 40° C. overnight. Magnesium stearate was sifted over the dried granulation and the total mixture passed through a #40 screen, The same procedure was used to prepare the inactive granulation with AVICEL substituted for nifedipine, The active granulation was filled into the 9/32" standard concave round die first and compressed with a force of 200–800 lbs then the inactive granulation was filled onto the lightly compressed active layer and the two layers compressed together with a force of 1500–2000 lbs. The resulting thickness was 4.3 mm and hardness was 18 kg. The tablets were coated to a thickness of 100 microns with the following coating formulation using a Uniglat Fluidized bed column spray coater.

Film Coating Ingredients	Amount
Cellulose Acetate Butyrate (Eastman 381-20)	140 g
Triethyl Citrate NF	14 g
Methylene Chloride	3000 ml
Alcohol USP	1000 ml

The tablets were mechanically drilled with 16×0.45 mm diameter openings through the coating on the active face.

In vitro release tests were carried out at 37° C. using USP Apparatus 2 into pH 7.4 phosphate buffer containing 2% sodium dodecyl sulfate at 100 rpm. The drug released was monitored by flow-through UV spectrophotometry at 340 nm. The results of this study are shown in FIG. 6. Two or three tablets can be filled into a gelatin capsule to provide 60 or 90 mg dosages.

What is claimed is:

1. A drug delivery device for the controlled in situ production and release of a suspension containing a beneficial agent, consisting of:

(a) a compressed core which comprises at least two layers, wherein at least one layer comprises an admixture of a therapeutically effective amount for those in need thereof, of a pharmaceutically active ingredient and a polymer which upon hydration forms microscopic polymer gel beads selected from the group consisting of sodium acrylate polymers and carboxypolymethylenes prepared from acrylic acid cross-linked with allyl ethers of sucrose or pentaerythritol; and at least one other layer comprising a polymer which upon hydration forms microscopic polymer gel beads; and

(b) a water insoluble, water impermeable coating applied to the core, comprising a polymer and a plasticizer, which surrounds and adheres to the core, the polymer being selected from the group consisting of polyvinyl chloride, cellulose acetate, cellulose acetate butyrate or ethylcellulose, or combinations of these polymers, the plasticizer being selected from the group consisting of dibutylsebacate or triethylcitrate, the coating having apertures, exposing between about 5 and about 75% of the core surface.

2. The device of claim **1** wherein the polymer of the compressed core is selected from carboxypolymethylenes prepared from acrylic acid cross-linked with allyl ethers of sucrose or penterythritol and the pharmaceutically acceptable salts thereof.

3. The device of claim **1** wherein the amount of beneficial agent in the core comprises from about 1% to about 75% by weight of the core mixture.

4. The device of claim **1** wherein the beneficial agent is an HMG CoA reductase inhibitor.

5. The device of claim **4** wherein the beneficial agent is chosen from the group consisting of lovastatin, pravastatin and simvastatin.

6. The device of claim **1** wherein the beneficial agent is lovastatin.

7. The device of claim **1** wherein the beneficial agent is nifedipine.

8. The device of claim **1** wherein the amount of polymer, which upon hydration produces polymer gel beads in the core comprises from about 75% to about 10% by weight of the core mixture.

9. The device of claim **1**, wherein the core mixture further comprises a polymer hydration modulating agent selected from the group consisting of acids, bases, salts sugars, surfactants and soluble polymers.

10. The device of claim **9**, wherein the polymer hydration modulating agent is selected from the group consisting of sodium citrate, betamine hydrochloride, sodium bicarbonate, sodium carbonate and arginine.

11. The device of claim **1** wherein the insoluble, impermeable coating is selected from polyvinyl chloride, cellulose acetate, cellulose acetate butyrate or ethylcellulose.

12. The device of claim **1** wherein the apertures in the coating range in diameter from about 0.5 mm to about 2 mm.

253

253

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
13 March 2003 (13.03.2003)

PCT

(10) International Publication Number
WO 03/020246 A1

(51) International Patent Classification⁷: **A61K 9/22**, 9/28, 9/44

(21) International Application Number: PCT/EP02/09274

(22) International Filing Date: 20 August 2002 (20.08.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0120835.4 28 August 2001 (28.08.2001) GB

(71) Applicant *(for all designated States except US)*: **SMITHKLINE BEECHAM P.L.C.** [GB/GB]; 980 Great West Road, Brentford, Middlesex TW8 9GS (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **CLARKE, Allan, J.** [US/US]; GlaxoSmithKline, 709 Swedeland Road, King of Prussia, PA 19406 (US). **GLINECKE, Robert** [DE/US]; GlaxoSmithKline, 709 Swedeland Road, King of Prussia, PA 19406 (US). **LI, Chi, Leung** [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). **MARTINI, Luigi, G.** [GB/GB]; GlaxoSmithKline, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB).

(74) Agent: **WALKER, Ralph, Francis**; GlaxoSmithKline, Corporate Intellectual Property CN925.1, 980 Great West Road, Brentford, Middlesex TW8 9GS (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
- *with international search report*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/020246 A1

(54) Title: INJECTION MOLDING PROCESS FOR THE PREPARATION OF AN ORAL DELIVERY DEVICE FOR A PHARMACEUTICALLY ACTIVE AGENT

(57) Abstract: An injection moulding process for the preparation of an oral delivery device comprising a core which contains a pharmaceutically active agent, having a coating with one or more openings leading to such a core. The invention also relates to devices produced by the process, and to injection moulds suitable for performing the process.

processing conditions to achieve this are specified in the literature. For these reasons, it is believed that typical operational conditions would be between temperatures of 25 - 300°C, more typically 50 - 250°C and especially 50 - 150°C. Preferably the injection moulding pressure should be less than 6000psi (ca. 400-450 kg/cm^2) to avoid damage to a tablet core within the mould cavity, typically pressures of 200 to 1000 psi (ca. 14-70 kg/cm^2), more typically 400 to 600 psi (ca. 30-45 kg/cm^2) have been found suitable. Conversely the tablet core should be made of materials and using suitable conditions that the core can withstand such pressures within the mould without breaking or crumbling.

The material of the outer coating may be any material which blocks (either permanently of for a suitable time period) exposure of the core to an environmental fluid, e.g. a gastro-intestinal fluid, and is not removed by dissolution or otherwise disrupted before a predetermined duration for controlled, delayed or sustained release of the active material in the core has occurred. Alternatively, the coating material may be selected because of aesthetic considerations. Any pharmaceutically acceptable fluid mouldable material which exhibits thermoplastic properties can be used as an outer coating for the tablet core, and suitable materials include thermoplastic organic polymers. Those skilled in the art of injection moulding characterise the flow properties of polymeric materials according to a melt flow index which ranges from 1 g/10min (very poor flow) to 50 g/10min (very high flow). It has been found that materials that exhibit a melt flow index in the range of 15 – 30 g/10min are particularly suitable for use in this invention. Representative materials and their blends suitable for use as a coating material in this invention include those listed in US-A-5,004,614. Preferred coating materials include the polymethacrylate copolymers, natural waxes and lipids, and biodegradable polymers in general. Other suitable polymer materials include polyvinyl acetates, such as the 40 and 20 grades thereof, cellulose acetate, butyrate and phthalate, EVA (ethylene vinyl acetate) or HPC (hydroxypropyl cellulose), silicones, or copolymers of methacrylic acid, methylmethacrylate, and methyl acrylate, such as that known as 4135F, available from Röhm polymers, or a blend based on 4135F. 4135F comprises a methacrylic acid, methylmethacrylate, methyl acrylate copolymer in a typical ratio 25:65:10 with a dissolution threshold of pH greater than 7.2.

Accordingly in a further aspect, the present invention provides a device adapted for oral delivery of a pharmaceutically active agent, when made by a process as described herein. Typically such a device comprises a core which includes a pharmaceutically active agent covered by an outer coating which includes one or more openings communicating from the exterior of the device to the core characterised in that the outer coating is a polymeric material exhibiting a melt flow

Claims:

1. A process for the preparation of a device comprising a core which includes a pharmaceutically active agent covered by an outer coating which includes one or more opening communicating from the exterior of the device to the core characterised in that the outer coating is applied by injection moulding said coating around said core.

2. A process according to claim 1 which comprises;
providing a core of the device comprising a pharmaceutically active agent;
locating said core within a mould cavity surrounding the core, said mould cavity defining the required dimensions of the outer coating and also defining the required position, shape and dimensions of the one or more opening;
injecting a fluid mouldable material into said mould cavity;
allowing the material to set to thereby form the outer coating;
separating the formed device from the mould cavity.

3. A process according to claim 1 or 2 wherein a moulding pressure less than 400-450 kg/cm^2 is used.

4. A process according to claim 2 or 3 wherein the mould has a cavity in which the tablet core may be located with a space around the said core to define the required shape and dimensions of the coating, with one or more internal member extending from the interior surface of the mould cavity to abut the said core and to define the shape and position of the said one or more opening.

5. A process according to claim 4 wherein one or more internal member is resiliently mounted so as to be able to move reciprocally resiliently inward and outward relative to the mould cavity.

6. A process according to claim 5 wherein the resilient mounting of the internal member is such as to apply a resilient pressure of up to 14 kg/cm^2 to the tablet core, or to be resiliently moveable under such a pressure applied thereto.

7. A process according to claim 5, 5 or 6 wherein an internal member is provided with a vacuum conduit passing therethrough to the outside of the mould, by which reduced pressure may be applied to a tablet core in contact with the member to assist in retaining the core in place in the mould.

256

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogada
JIMENA ESCOBAR URIBE
(Apoderado)

ASUNTO
Radicación 05054294
Trámite 002
Evento 001
Actuación 430
Oficio № 4391
Folios 019

Patente de Invención ☒ Patente de Modelo de Utilidad ☐

Vía Nacional ☒

Vía PCT (fase nacional) ☐ Cap.I ☐ Cap. II ☐

No. Sol. Internacional No aplica
Fecha de Presentación Internacional No aplica

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados:

1.1. Descripción: (Folios: 9 a 106) como se radicó inicialmente.

1.2. Reivindicaciones: 1 a 20 (Folios: 107 a 110) como se radicó inicialmente.

1.3. Prioridad: 04/06/2004, US 10/860.972.

2. Análisis de la Prioridad:

La prioridad de la presente solicitud corresponde al objeto reivindicado.

3. Objeto de la invención:

La presente solicitud se titula: “Forma de dosificación de liberación inmediata que comprende cubierta que tiene aberturas en la misma”.

El objeto de la presente solicitud se refiere a una forma de dosificación que provee

liberación inmediata de un ingrediente activo. La forma de dosificación comprende un núcleo sólido y una cubierta que rodea al núcleo. La cubierta tiene una o más aberturas en la misma.

Según la descripción, se conocen ciertas formas de dosificación que contienen aberturas o relieves. Por ejemplo, se conocen en la técnica formas de dosificación de "bomba osmótica" para la administración de ingredientes farmacéuticamente activos.

En el capítulo reivindicatorio se reclama lo siguiente:

Reivindicaciones 1 a 20 (folios: 107 a 110): Una forma de dosificación que contiene por lo menos un ingrediente activo, que comprende un núcelo y una cubierta que rodea por lo menos una porción del núcleo...; la cubierta es fácilmente soluble en fluidos gastrointestinales y la forma de dosificación provee liberación inmediata de por lo menos un ingrediente activo tras el contacto de la forma de dosificación con un medio líquido.

El problema planteado en esta solicitud es la necesidad de formas de liberación inmediata de fármacos.

La solución propuesta por la presente solicitud consiste en formas de dosificación de liberación inmediata de un núcleo sólido y una cubierta que rodea al núcleo y que tiene una o más aberturas en la misma.

El objeto de la solicitud definido anteriormente se clasificó en la IPC A61K 9/30, 9/28.

4. **Análisis de la(s) Oposición(es):** *(artículo 43 D. 486)*

No se presentaron oposiciones al objeto reivindicado.

5. **Determinación del Estado de la Técnica:**

La fecha que se ha tenido en cuenta para determinar el Estado de la Técnica es:

Fecha de presentación de la solicitud prioritaria 4-06-2004.

Teniendo en cuenta la fecha indicada, se buscaron documentos del estado de la técnica relacionados, con fecha de publicación anterior a esta.

Se encontró como anterioridades que pueden afectar la patentabilidad del objeto de la presente solicitud:

Nº	Documento	Título	Fecha de Publicación
D1	WO 2004/028513	Immediate release dosage form comprising Shell having openings therein	8 de abril de 2004
D2	WO 01/51040	Osmotic device containing alprazolam and an antipsychotic agent	19 de Julio de 2001
D3	US 5582838	Controlled release drug suspension delivery device	10 de diciembre de 1996
D4	WO 03/020246	Injection molding process for the preparation of an oral delivery device for a pharmaceutically active agent	13 de marzo de 2003