137

Clarke, Modet & Cº

COLOMBIA

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

REF: EXPEDIENTE No. 06.030.701
SOLICITANTE: GRUNENTHAL GMBH

ASUNTO: PAGO TASA OFICIAL RESTABLECIMIENTO DEL DERECHO

DILIA RODRÍGUEZ D´ALEMAN, identificada como aparece al pie de mi firma, domiciliada en la carrera 11 No. 86-53, piso 6, obrando como apoderada de la sociedad solicitante de la patente de la referencia, dando alcance a mi memorial de 16 de junio de 2008, atentamente me permito anexar los recibos Nrs. 08-77,888, 08-77,889, 08-77,890 todos los anteriores de 30 de septiembre de 2008 y 08-71,858 de 9 de septiembre de 2008, por la suma de $900.000.00, correspondiente al valor de la tasa del Restablecimiento del Derecho.

Señor Superintendente,

DILIA RODRIGUEZ D´ALEMAN
C.C. 41.654.882 de Bogotá
T.P. 20824
/srr
p-755

138

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 77,888
FECHA : SEPTIEMBRE 30 DE 2008

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CLARKE MODET Y CO. COLOMBCONSIGNACION		BANCO DE BOGOTA	062754387	92970393	30/09/2008	51,690,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	91	TASA ANUAL DE MANTENIMIENTO DE PA	260,000.00
			TOTAL : $	260,000.00

SON: DOSCIENTOS SESENTA MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

P-755

139

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 77,889
FECHA : SEPTIEMBRE 30 DE 2008

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CLARKE MODET Y CO. COLOMB	CONSIGNACION	BANCO DE BOGOTA	062754387	92970393	30/09/2008	51,690,000.00

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CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
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			TOTAL : $	260,000.00

SON: DOSCIENTOS SESENTA MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

140

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 77,890
FECHA : SEPTIEMBRE 30 DE 2008

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CLARKE MODET Y CO. COLOMB	CONSIGNACION	BANCO DE BOGOTA	062754387	92970393	30/09/2008	51,690,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	91	TASA ANUAL DE MANTENIMIENTO DE PA	260,000.00
			TOTAL : $	260,000.00

SON: DOSCIENTOS SESENTA MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

141

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

CERTIFICACION DE EXCEDENTE : 00 - [illegible]
FECHA : SEPTIEMBRE [illegible]

***** D U P L I C A D O *****

SOLICITANTE	TIPO PAGO	LUGAR	CUENTA	No. P-SF	FECHA PAGO	Vr. PAGO
CLARKE MODET Y CO. COLOMBIANA/BINACIONA	BANCO DE BOGOTA	60704387	[illegible]	[illegible]		49,150,000.00

***** D E S P A C H O *****

CONCEPTO	DESCRIPCION	TOTAL CONCEPTO
500405-01-45	OTROS SERVICIOS DE PUBLICIDAD	OTROS SERVICIOS ADMINISTRATIVOS	100,000.00
		TOTAL :	[illegible]

SON: CIENTO VEINTE MIL PESOS

RESPONSABLE : _____

ANULADO DE ESTA LIQUIDACION AL EXPEDIENTE No. _____

ESTA LIQUIDACION DE DESISTENTE DE PAGO SOLO PODRA SER UTILIZADA COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PUEDE SER CUESTIONADA POR NINGUN MOTIVO.

Industria y Comercio
SUPERINTENDENCIA

142

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 06-30701

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCIÓN**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **587** DE

FECHA **18 DE ENERO DE 2008** EL TÉRMINO HÁBIL SEÑALADO POR LA LEY

EXPIRA EL **16 DE ABRIL DE 2008**

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____

D1
143

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

(19) World Intellectual Property Organization
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(21) International Application Number: PCT/US02/24549

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(30) Priority Data:
60/310,513 6 August 2001 (06.08.2001) US

(71) Applicant and
(72) Inventor: **GRUBER, Thomas** [US/US]; 511 Westchester Drive, Rockford, IL 61107 (US).

(74) Agent: **PICCIANO, Dante, J.**; Bell, Boyd & Lloyd LLC, P.O. Box 1135, Chicago, IL 60690-1135 (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, 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:
— *without international search report and to be republished upon receipt of that 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.

WO 03/015531 A2

(54) Title: PHARMACEUTICAL FORMULATION CONTAINING DYE

(57) **Abstract:** Methods and compositions for preventing abuse of dosage forms comprising an opioid analgesic and an aversive agent (e.g., a dye) in an effective amount to deter an abuser from administering a tampered form of the dosage form intravenously, intranasally, and/or orally are revealed.

(Valoron®N, Goedecke). A fixed combination of buprenorphine and naloxone was introduced in 1991 in New Zealand (Temgesic®Nx, Reckitt & Colman) for the treatment of pain. Purdue Pharma L.P currently markets sustained-release oxycodone in dosage forms containing 10, 20, 40, 80 and 160 mg oxycodone hydrochloride under the tradename OxyContin.

U.S. Patent Nos. 5,266,331; 5,508,042; 5,549,912 and 5,656,295 disclose sustained release oxycodone formulations. U.S. Patent Nos. 4,769,372 and 4,785,000 to Kreek describe methods of treating patients suffering from chronic pain or chronic cough without provoking intestinal dysmotility by administering 1 to 2 dosage units comprising from about 1.5 to about 100 mg of opioid analgesic or antitussive and from about 1 to about 18 mg of an opioid antagonist having little to no systemic antagonist activity when administered orally, from 1 to 5 times daily.

U.S. Patent No. 6,228,863 to Palermo et al. describes compositions and methods of preventing abuse of opioid dosage forms. PCT/US98/27257 to Kaiko et al. describes compositions and methods of preventing abuse of opioid dosage forms. U.S. Patent No. 5,472,943 to Crain et al. describes methods of enhancing the analgesic potency of bimodally acting opioid agonists by administering the agonist with an opioid antagonist.

U.S. Patent No. 3,980,766 to Shaw et al., is related to drugs which are suitable for therapy in the treatment of narcotic drug addiction by oral use, e.g., methadone, formulated to prevent injection abuse through concentration of the active component in aqueous solution by incorporating in a solid dosage or tablet form of such drug an ingestible solid having thickening properties which cause rapid increase in viscosity upon concentration of an aqueous solution thereof.

However, there still exists a need for a safe and effective treatment of pain with opioid analgesic dosage forms which are less subject to abuse than current therapies. All documents cited herein, including the foregoing, are incorporated by reference in their entireties for all purposes.

OBJECTS AND SUMMARY OF THE INVENTION

It is an object of certain embodiments of the invention to provide an oral dosage form of an opioid analgesic which is subject to less parenteral abuse than other dosage forms.

It is an object of certain embodiments of the invention to provide an oral dosage form of an opioid analgesic which is subject to less intranasal abuse than other dosage forms.

It is an object of certain embodiments of the invention to provide an oral dosage form of an opioid analgesic which is subject to less oral abuse than other dosage forms.

It is a further object of certain embodiments of the invention to provide an oral dosage form of an opioid analgesic which is subject to less diversion than other dosage forms.

It is a further object of certain embodiments of the invention to provide a method of treating pain in human patients with an oral dosage form of an opioid analgesic while reducing the abuse potential of the dosage form.

It is a further object of certain embodiments of the invention to provide a method of manufacturing an oral dosage form of an opioid analgesic such that it has less abuse potential.

These objects and others are achieved by the present invention, which is directed in part to an oral dosage form comprising an opioid analgesic; and at least one aversive agent for reducing the abuse of the opioid analgesic.

In certain embodiments of the present invention, the oral dosage forms of the present invention comprising an opioid analgesic; and an aversive agent or agents as a component(s) of

particles are about 0.2 to about 2 mm in diameter, more preferably about 0.5 to about 2 mm in diameter.

The term "parenterally" as used herein includes subcutaneous injections, intravenous injections, intramuscular injections, intrasternal injections, infusion techniques, or other methods of injection known in the art.

The term "inhaled" as used herein includes trans-mucosal, trans-bronchial, and trans-nasal abuse.

The term "dye" as used herein includes a compound used to impart an indication of abuse to an abuser administering a tampered dosage form of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The aversive agents of the present invention are preferably for use in connection with oral dosage forms including opioid analgesics, which provide valuable analgesia but which may be abused. This is particularly true for controlled release opioid analgesic products which have a large dose of opioid analgesic intended to be released over a period of time in each dosage unit. Drug abusers typically may take a controlled-release product and crush, shear, grind, chew, dissolve and/or heat, extract or otherwise damage the product so that the full contents of the dosage form become available for immediate absorption by injection, inhalation, and/or oral consumption.

In certain embodiments, the present invention comprises the prevention or deterrence of the abuse of opioid analgesics by the inclusion of at least one aversive agent in the dosage form with the opioid analgesic.

In certain alternative embodiments, the present invention comprises the prevention or deterrence of the abuse of drugs other than opioid analgesics which may also be the subject of

as immediate-release capsules containing 5 mg oxycodone hydrochloride. The present invention is contemplated to encompass all such formulations, with the inclusion of one or more aversive agents as described herein.

Additionally, agents other than opioid analgesics which are subject to abuse may be used in accordance with the present invention in place of the opioid analgesics in the dosage form.

Dosage Forms

The opioid analgesic formulation in combination with an aversive agent can be formulated as an immediate release formulation or controlled release oral formulation in any suitable tablet, coated tablet or multiparticulate formulation known to those skilled in the art. The controlled release dosage form may include a controlled release material which is incorporated into a matrix along with the opioid analgesic. In addition, the aversive agent may be separate from the matrix, or incorporated into the matrix.

The controlled release dosage form may optionally comprise particles containing or comprising the opioid analgesic, wherein the particles have diameters from about 0.1 mm to about 2.5 mm, preferably from about 0.5 mm to about 2 mm. Additionally, the aversive agent may be incorporated into these particles, or may be incorporated into a tablet or capsule containing these particles. Preferably, the particles are film coated with a material that permits release of the opioid analgesic at a controlled rate in an environment of use. The film coat is chosen so as to achieve, in combination with the other stated properties, a desired in-vitro release rate. The controlled release coating formulations of the present invention should be capable of producing a strong, continuous film that is smooth and elegant, capable of supporting pigments and other coating additives, non-toxic, inert, and tack-free.

In certain embodiments, the dosage forms of the present invention comprise normal release matrixes containing the opioid analgesic and the aversive agent.

Coated Beads

In certain embodiments of the present invention a hydrophobic material is used to coat inert pharmaceutical beads such as nu pariel 18/20 beads comprising an opioid analgesic, and a plurality of the resultant solid controlled release beads may thereafter be placed in a gelatin capsule in an amount sufficient to provide an effective controlled release dose when ingested and contacted by an environmental fluid, e.g., gastric fluid or dissolution media. The one or more aversive agents may also be coated onto the beads comprising the opioid analgesic, may be prepared as separate beads and then combined in a dosage form including the controlled release beads comprising an opioid analgesic, or the aversive agent may be mixed in the dosage form with the controlled release beads comprising the opioid analgesic. In preferred embodiments where the opioid analgesic and the aversive agent are mixed in a capsule as different beads, the beads have an exact or similar appearance in order to deter an abuser from manually separating the beads prior to abuse in order to avoid the aversive substance. In tablet dosage forms, the aversive agent is preferably not included as a distinct layer which can be easier to separate from the active agent, although the present invention does encompass these embodiments.

The controlled release bead formulations of the present invention slowly release the opioid analgesic, e.g., when ingested and exposed to gastric fluids, and then to intestinal fluids. The controlled release profile of the formulations of the invention can be altered, for example, by varying the amount of overcoating with the hydrophobic material, altering the manner in which a plasticizer is added to the hydrophobic material, by varying the amount of plasticizer relative to hydrophobic material, by the inclusion of additional ingredients or excipients, by altering the

(b) mixing the at least one hydrophobic and/or hydrophilic material-containing granules with at least one C_{12}-C_{36} aliphatic alcohol; and

(c) optionally, compressing and shaping the granules.

The granules may be formed by any of the procedures well-known to those skilled in the art of pharmaceutical formulation. For example, in one preferred method, the granules may be formed by wet granulating the hydroxyalkyl cellulose, opioid analgesic, and an aversive agent with water. In a particularly preferred embodiment of this process, the amount of water added during the wet granulation step is preferably between 1.5 and 5 times, especially between 1.75 and 3.5 times, the dry weight of the opioid analgesic. Optionally, the opioid analgesic and/or the aversive agent is added extragranularly.

A sustained-release matrix can also be prepared by, e.g., melt-granulation or melt-extrusion techniques. Generally, melt-granulation techniques involve melting a normally solid hydrophobic binder material, e.g., a wax, and incorporating a powdered drug therein. To obtain a sustained release dosage form, it may be necessary to incorporate a hydrophobic sustained-release material, e.g. ethylcellulose or a water-insoluble acrylic polymer, into the molten wax hydrophobic binder material. Examples of sustained-release formulations prepared via melt-granulation techniques are found, e.g., in U.S. Patent No. 4,861,598.

The additional hydrophobic binder material may comprise one or more water-insoluble wax-like thermoplastic substances possibly mixed with one or more wax-like thermoplastic substances being less hydrophobic than said one or more water-insoluble wax-like substances. In order to achieve sustained release, the individual wax-like substances in the formulation should be substantially non-degradable and insoluble in gastrointestinal fluids during the initial

Biomaterials 23 (2002) 1113–1119

Dissolution behaviour of hydrophilic matrix tablets containing two different polyethylene oxides (PEOs) for the controlled release of a water-soluble drug. Dimensionality study

L. Maggi*, L. Segale, M.L. Torre, E. Ochoa Machiste, U. Conte

Department of Pharmaceutical Chemistry, University of Pavia, Via Taramelli 12, I-27100 Pavia, Italy

Received 7 February 2001; accepted 1 June 2001

Abstract

Hydrophilic matrix tablets containing polyethylene oxides as the retarding polymer have been successfully employed in the controlled release of drugs. To evaluate the relative influence of drug diffusion and polymer erosion mechanisms in the drug delivery process, we studied the hydration behaviour of matrix tablets containing a water-soluble drug and PEOs of two different molecular weights: Polyox WSRN 1105 ($M_w = 0.9 \times 10^6$) and Polyox WSRN 301 ($M_w = 4 \times 10^6$). The hydration rate, the extent of swelling, and the erosion rate of matrices containing the polymer, the drug and tableting excipients were evaluated in comparison to tablets made of pure polymer. The results of these studies on function of the release behaviour were then discussed.

The results show that the higher molecular weight PEO swells to a greater extent and tends to form, upon hydration, a stronger gel, which is therefore less liable to erosion, if compared to the lower molecular weight PEO. This difference in the erosion behaviour can explain the different efficiencies of the two polymeric products in modulating the delivery rate of the water-soluble drug. Moreover, the presence of other soluble components (drug and excipients) in the dosage form enhances the erosion trend of the tablets with a consequent reduction of the efficiency of the polymer in drug release control.

Keywords: Polyethylene oxides; Swelling erosion characteristics; Dissolution behaviour; Morphological modifications

1. Introduction

High molecular weight polyethylene oxides (PEOs) have been successfully employed in controlled release swellable matrices [1–3]. The use of oral controlled release matrices made of hydrophilic polymers that swell and form a gel layer upon contact with water, and then erode slowly, thus modulating the drug delivery rate, has been extensively investigated [4]. The polymers employed are hydrophilic, linear, uncrosslinked molecules; when matrices containing these types of polymer come into contact with water, forces of attraction (chiefly hydrogen bonding) start acting between polymer and water. Due to the high water-affinity of the polymer, these forces are likely to be preferred over polymer–polymer interactions; the forces holding the polymer segments together are therefore reduced and the polymer chains can swell [5]. Water diffuses into the matrix and when its concentration reaches a threshold value, the polymer swells and a gel layer is formed at the matrix surface. In the gel phase, polymer chains slowly begin to unfold and gradually become solvated; however, the presence of physical entanglements between neighbouring chains hinder polymer dissolution [6]. At the outermost surface, the polymer is diluted to the point where the chains disentangle, the polymer has no longer structural integrity and dissolves as single molecules or as discrete agglomerates, i.e. erosion [7,8]. This complex gelatinous layer forms a diffusional barrier that retards further water uptake but can also modulate drug release rate. Water-soluble drugs are mainly released by diffusion of dissolved drug molecules across the gel layer, while poorly water-soluble drugs are more likely released through erosion of the gel [9]. The contribution of these two phenomena to the overall drug release process is influenced not only by drug solubility,

*Corresponding author. Tel.: +39-382-507779; fax: +39-382-507382.

E-mail address: lauretta.maggi@unipv.it (L. Maggi).

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PII: S0142-9612(01)00223-X

but also by the physical and mechanical properties of the gel layer that forms around the tablet. When the release mechanism involves the synchronisation of swelling and erosion rates, the matrix may provide zero-order release kinetics [10,11].

Previous works have demonstrated that laminated films [12] or small tablets [2] containing a drug and polyethylene oxide (PEO) characterised by molecular weight (in the range 0.6×10^6–2×10^6) can generate comparable swelling and erosion rates. In contrast, matrices containing higher molecular weight PEOs did not show any synchronisation of swelling and erosion, and drug release seems to be related more to swelling rather than to erosion rate [13].

In this work, the dissolution behaviour of matrix tablets containing PEOs of two different molecular weights was studied: the aim is to evaluate the efficiency of PEOs in modulating drug release rate, its morphological behaviour, and to study the prevailing release mechanisms. The swelling and erosion characteristics of the two different polymers were evaluated on tablets made of pure polymer while, to verify the effects of soluble components on the behaviour of the polymers under study and the swelling erosion characteristics of matrices containing the polymer, a soluble model drug (diltiazem hydrochloride), and tableting excipients were studied. The morphological behaviour during dissolution of such dosage forms was compared to the drug release profiles and evaluated in terms of drug release modulation efficiency.

Finally, the influence of the compression force applied to the tablets on the overall dissolution behaviour of these delivery devices was evaluated and discussed.

2. Experimental

2.1. Materials

Diltiazem hydrochloride was supplied by Profarmaco S.p.A. (Milan, Italy). PEOs (Polyox WSRN 1105, $M_w = 0.9 \times 10^6$, and Polyox WSRN 301, $M_w = 4 \times 10^6$) were kindly donated by Union Carbide Corp. (Danbury, CT, USA). The other excipients were lactose, magnesium stearate (C. Erba, Milan, Italy), and colloidal silicon oxide (Syloid 244, Grace GmbH, Worms, Germany).

2.2. Methods

Two different formulations (coded A1 and B1) were prepared by mixing the drug, the hydrophilic polymer and the excipients for 30 min (Turbula T2A, Bachofen, Basel, CH). The compositions of the two different mixtures are reported in Table 1.

Table 1
Percent composition of the two hydrophilic matrix formulations

Formulation	A1	B1
PEO M_w: 0.9×10^6 (Polyox WSRN 1105)	38.2	
PEO M_w: 4×10^6 (Polyox WSRN 301)	/	38.2
Diltiazem hydrochloride	49.3	49.3
Lactose	11.0	11.0
Magnesium stearate	1.0	1.0
Colloidal silicon dioxide	0.5	0.5

The true density of the two pure polymers and of the two formulations was measured (AccuPyc 1330, Micrometric, Norcross, GA).

The tablets were prepared by direct compression of the two formulations or of the two pure polymers using a single-punch tableting machine (Kilian, Coln, D) instrumented with piezoelectric load washers (Kistler, Winterthur, CH) for compression force measurements [14] and equipped with flat punches diameter 9.5 mm. 366 mg of powder, accurately weighed, was introduced into the die and the automatic compression cycle was activated. The compression force was adjusted at two different levels: 10 and 30 kN.

All the tablets weighed 366 mg ± 1%; A1 and B1 matrices contain 180 mg of diltiazem hydrochloride as active agent. The thickness and diameter of the tablets produced were measured. The porosity was calculated through tablet volume and true density of the different powders.

To verify the effects of the application of a certain compression force level on the solid state of the polymer (crystalline or amorphous), DSC thermographs of the pure polymers before and after compression at the two different forces were recorded (DSC 821E, Mettler Toledo GmbH, Schwerzenbach, CH). The samples were heated from 30 °C to 130 °C; heating rate 10 °C/min.

The crushing strength of the tablets was measured with a suitable apparatus equipped with a high sensitive load washer (Kistler, Winterthur, CH) [14].

In vitro dissolution tests were performed in 1 l of distilled water at 37 °C, with the USP apparatus 2 (paddle), at 100 rpm (six replicates). The amount of diltiazem released was measured by UV detection at 236 nm (Spectracomp 602, Advanced Products, Milan, Italy). The release data were fitted using the familiar empirical equation proposed by Korsmeyer and Peppas [15],

$$\frac{M_t}{M_\infty} = kt^n, \tag{1}$$

where M_t/M_∞ is the fractional drug released, t the release time, k is a kinetic constant and n the diffusion exponent characteristic of the release mechanism. For a cylindrical matrix, $0.89 < n < 1.0$ indicates a zero order release, while $0.45 < n < 0.89$ shows anomalous release

152

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado
DILIA MARÍA RODRÍGUEZ D'ALEMÁN
Apoderado

ASUNTO	Radicación	06-030701
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	875
	Folios	13

Patente de Invención [■] Patente de Modelo de Utilidad [ ]

Vía Nacional [ ]

Vía PCT (fase nacional) [■] Cap.I [■] Cap. II [ ]

No. Sol. Internacional PCT/EP2004/008792
Fecha de Presentación Internal. 05 de Agosto de 2004

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

Descripción:	Folios: 32 a 62 y 69 como se radicó inicialmente
Reivindicaciones:	Folios 63 a 70 como se radicó inicialmente
Prioridad:	Folios: 1 06 de Agosto de 2003, DE, 10336400.5

2. Análisis de la Prioridad

La fecha de prioridad del 08 de Agosto de 2003 y su correspondiente documento, son aceptados para el estudio de patentabilidad.

3. Objeto de la invención

Título de la solicitud: forma de administración a prueba de abuso

El objeto de la presente solicitud de patente de invención consiste en una forma de

El problema planteado en esta solicitud es cómo obtener una forma de administración termoformada mediante extrusión, sin la alteración de la coloración, a prueba de abuso, con una dureza de al menos de 500N"

Para solucionar este problema técnico la solicitud en estudio proporciona una forma de administración termoformada mediante extrusión, sin la alteración de la coloración, a prueba de abuso, con una dureza de al menos de 500N.

IPC: A61K 9/20, 31/485, 31/515, 31/5513

4. De la solicitud de Patente

Descripción (artículo 28 D. 486)
El solicitante no anexa la figura No 1 del documento original en la solicitud nacional. El resumen según Folio 69 se refiere a la invención "sin extrusión", diferente a lo expresado en el capítulo reivindicatorio y descripción en cuanto al objeto de la invención.

Reivindicaciones (artículo 30 D 486)
La reivindicación 1 se encuentra caracterizada donde el componente (C) o (D) opcionalmente presente, con una dureza *de al menos* 500N. El término utilizado como *de al menos* se encuentra impreciso y amplio, frente al parámetro de la dureza. La reivindicación 1 se refiere a *sin alteración de la coloración,* el cual es un resultado alcanzado con la invención.

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: 06 de Agosto de 2003

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es: 06/08/2003 se encontraron los siguientes documentos del estado de la técnica relacionados, que pueden afectar la patentabilidad del objeto de la presente solicitud:

Nº	Documento	Título	Fecha de publicación
D1	WO 03/015531	Pharmaceutical formulation containing dye	27/02/2003
D2	Maggi et al, Biomaterials 23 (2002) 1113–1119	Dissolution behaviour of hydrophilic matrix tablets containing two different polyethylene oxides (PEOs) for the controlled release of a water-soluble drug. Dimensionality study	2002

6. Análisis de patentabilidad (artículo 14 D486)

Nivel inventivo (artículo18 D486)

La reivindicación 1 consiste en:

> Forma de administración termoformada mediante extrusión, sin la alteración de coloración, a prueba de abuso, caracterizada porque tiene, además de uno o más principios (A) activos susceptibles de abuso, así como opcionalmente sustancias (B) auxiliares fisiológicamente aceptables, al menos un polímero (C) sintético o natural y opcionalmente al menos una cera (D), teniendo el componente (C) y el componente (D) opcionalmente presente una dureza de al menos 500N.

El Estado de la Técnica más cercano es **D1**, que da a conocer formulaciones farmacéuticas a prueba de abuso (Ver página 1, líneas 5-18) (Ver página 3) (Ver página 4, líneas 1-5) (Ver página 6, líneas 13-21). Entre las formas de dosificación, pueden ser entre otras de liberación controlada en tabletas, tabletas cubiertas o una formulación multiparticulada (Ver página 11, líneas 8-12); perlas cubiertas (Ver página 12, líneas 3); de matriz (Ver página 15), y formas de dosificación osmótica (Ver páginas 30-34)

Las formas de dosificación controlada pueden contener opcionalmente partículas, donde el agente aversivo puede ser incorporado en las partículas o puede ser incorporado en una tableta o en una cápsula. (Ver página 11, líneas 13-17);

La cubierta empleada en las formulaciones de liberación controlada son capaces de producir un film continuo y fuerte que es capaz de soportar pigmentos y otros aditivos (Ver página 11, último párrafo)

Entre las formulaciones de matriz se encuentran las de liberación sostenida con una capa de liberación controlada, donde se incluyen los principios activos (Ver página 15, líneas 16-17), auxiliares de formulación (Ver página 18, líneas 13-15), polímeros de liberación sostenida (Ver página 15, líneas18-22, ver página 16, líneas 1-6) y opcionalmente puede incluir un aglutinante el cual puede ser seleccionado de ceras naturales o sintéticas (Ver página 16, 6-11) y donde las matrices pueden ser preparadas por extrusión de fusión (Ver página 19, líneas 11-12).

La composición objeto de esta solicitud se diferencia de las composiciones de **D1**, en que especifica la dureza de al menos 500N para el componente (C) y (D).

El hecho de incluir el parámetro de la dureza en las composiciones que se daban a conocer en **D1**, causa que se dificulte o impida la pulverización de las formas de administración con principios activos susceptibles de abuso.

El Problema Técnico Objetivo era cómo obtener una forma de administración termoformada sin extrusión donde se dificulte o impida la pulverización de las formas de administración con principios activos susceptibles de abuso.

D2 describe una manera de solucionar el problema técnico, pues enseña tabletas de

La reivindicación es obvia, porque el Experto en la Materia enfrentado al problema de "obtener una forma de administración termoformada sin extrusión a prueba de abuso con una dureza de al menos de 500N para el componente (C) y/o (D)", variaría "las proporciones del polímero con el fin de obtener una dureza de al menos 500N (0.5kN)" cómo se revela en **D2**, en las composiciones que se enseñan en **D1**, logrando de esta forma la composición objeto de esta solicitud, con una dureza de al menos de 500N. Por tanto, el hecho que sea la tableta más dura, no hace que sea inventiva.La reivindicación 1 no tiene Nivel Inventivo. Las reivindicaciones dependientes 2-30, no mencionan alguna característica que haga inventiva a la forma de administración de la reivindicación 1, por lo cual se considera que no tienen nivel inventivo.

7. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

N°	Documento N°	Reivindicaciones afectadas	Requisito que afecta
D1	WO 03/015531	1-30	Nivel Inventivo
D2	Maggi et al, Biomaterials 23 (2002) 1113–1119	1-30	Nivel Inventivo

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 60 días contados a partir de la fecha de 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 quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL
Directora de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha _____

CONCEPTO TÉCNICO No. 0281	**EXAMINADOR TÉCNICO** Código No. 202070

156

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado
DILIA MARÍA RODRÍGUEZ D'ALEMÁN
Apoderado

ASUNTO	Radicación	06-030701
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	883
	Folios	01

Como resultado del examen de búsqueda de anterioridades y con fundamento en el artículo 46 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. SOLICITUD DE SUMINISTRO DE INFORMACIÓN

Como consecuencia de la búsqueda de anterioridades de materia relacionada con la de la presente invención, se determinó que existen en el estado de la técnica los siguientes documentos, que eventualmente afectarían los requisitos de patentabilidad de esta solicitud:

- L. Maggi et al, High molecular weight polyethylene oxides (PEOs) as an alternative to HPMC in controlled release dosage forms. *Int. J. Pharm.* **195** (2000), pp. 229-238.
- C.J. Kim , Effects of drug solubility, drug loading and polymer molecular weight on drug release from Polyox ® tablets. *Drug. Dev. Ind. Pharm.* **24** (1998), pp. 645-651.
- Zhang et al, *Pharm. Dev. Tech,* 1999, 4, 241-250

Siendo que las publicaciones referenciadas hacen parte del resultado del examen de búsqueda realizado para la solicitud WO equivalente a esta solicitud colombiana aquí estudiada, y no siendo viable la consecución de dichos artículos por este despacho, se requiere que el solicitante, en virtud de lo establecido en el artículo 46 de la Decisión 486 de la Comisión de la Comunidad Andina, proporcione las publicaciones completas, con lo que podrá realizarse un análisis absoluto de la patentabilidad de la invención correspondiente a la presente solicitud.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto (5), del título primero de la circular única N° 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL
Directora de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha