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Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
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Clarke, Modet & Cº

COLOMBIA

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

REF: EXPEDIENTE No. 06010699
FECHA DE LA SOLICITUD: Febrero 3, 2006
SOLICITANTE: GRÜNENTHAL GMBH
TITULO: FORMA DE ADMINISTRACIÓN A PRUEBA DE ABUSO

ASUNTO: SOLICITUD ESTUDIO DE FONDO

DILIA RODRÍGUEZ D´ALEMAN, en mi condición de apoderada de la Sociedad solicitante, por el presente escrito atentamente solicito a Usted que habiéndose surtido la publicación de la presente solicitud, en la Gaceta de la Propiedad Industrial No.579 de fecha Agosto 31 de 2007 y se proceda con el estudio de Fondo.

Para tal fin me permito anexar la tasa correspondiente.

Agradezco continuar con el presente trámite.

Señor Jefe,

DILIA RODRIGUEZ D´ALEMAN
C.C. 41.654.882 Bogotà
P. 753

P753 107

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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2

108

Industria y Comercio
SUPERINTENDENCIA

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 06-10699

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

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **579** DE

FECHA **31 DE AGOSTO DE 2007** EL TÉRMINO HÁBIL SEÑALADO POR LA

LEY EXPIRA EL **28 DE NOVIEMBRE DE 2007**

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.

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(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.

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PHARMACEUTICAL FORMULATION CONTAINING DYE

The present application is related to U.S. Provisional Patent Application 60/310,513, filed August 6, 2001, the entire contents of which are hereby incorporated by reference and relied upon.

BACKGROUND OF THE INVENTION

Opioid analgesics are sometimes the subject of abuse. Typically, a particular dose of an opioid analgesic is more potent when administered parenterally as compared to the same dose administered orally. Therefore, one popular mode of abuse of oral opioid formulations involves the extraction of the opioid from the dosage form, and the subsequent injection of the opioid (using any "suitable" vehicle for injection) in order to achieve a "high." Also, some formulations can be tampered with in order to provide the opioid agonist contained therein better available for illicit use. For example, a controlled release opioid agonist formulation can be crushed in order to provide the opioid contained therein available for immediate release upon oral or nasal administration. An opioid formulations can also be abusable by administration of more than the prescribed dose of the drug.

Opioid antagonists have been combined with certain opioid agonists in order to deter the parenteral abuse of opioid agonists. In the prior art, the combination of immediate release pentazocine and naloxone has been utilized in tablets available in the United States, commercially available as Talwin® Nx from Sanofi-Winthrop. Talwin®Nx contains immediate release pentazocine hydrochloride equivalent to 50 mg base and naloxone hydrochloride equivalent to 0.5 mg base. A fixed combination therapy comprising tilidine (50 mg) and naloxone (4 mg) has been available in Germany for the management of pain since 1978

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

the dosage form helps to prevent injection, inhalation, and/or oral abuse by decreasing the "attractiveness" of the dosage form to a potential abuser.

In certain embodiments of the present invention, the dosage form comprises an aversive agent such as a dye to discourage an abuser from tampering with the dosage form and thereafter inhaling, injecting, or swallowing the tampered dosage form. Preferably, the dye is released when the dosage form is tampered with and provides a noticeable color or dye which makes the act of abuse visible to the abuser and to others such that the abuser is less likely to inhale, inject and/or swallow the tampered dosage form. For example, the dye can stain the mucous membrane of the nose and/or mouth and make the act of abuse noticeable to e.g., teachers, parents, peers, etc., whereby one may not want to abuse the drug due to the possible subsequent public scrutiny. Also, an abuser may be aversed to injecting a solution containing extracted drug if the solution has a visible color.

In certain preferred embodiments, the dosage forms are controlled release oral dosage forms comprising a therapeutically effective amount of an opioid analgesic with the aversive agent described above such that the dosage form provides effective pain relief for at least about 12 hours, or at least about 24 hours when orally administered to a human patient.

In certain embodiments, may have a modified or sustained release as not to dump the aversive agent in a particular section of the gastrointestinal tract, e.g. the stomach, where it may cause an unwanted effect such as excessive irritation. The aversive agent can be combined with an enteric carrier to delay the release or combined with a carrier to provide a sustained release of the aversive agent. However, it is contemplated in the present invention that the aversive agent will not have any significant side effect (e.g., gastrointestinal side effect) even if all of the

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

selected from hydroxypropylmethylcellulose, lactose, metal stearates, and mixtures of any of the foregoing.

The controlled release coatings of the present invention may also include an exit means comprising at least one passageway, orifice, or the like. The passageway may be formed by such methods as those disclosed in U.S. Patent Nos. 3,845,770; 3,916,889; 4,063,064; and 4,088,864. The passageway can have any shape such as round, triangular, square, elliptical, irregular, etc.

Matrix Formulations

In certain embodiments of the present invention, the sustained release formulation is achieved via a matrix optionally having a controlled release coating as set forth herein. The present invention may also utilize a sustained release matrix that affords in-vitro dissolution rates of the opioid analgesic within desired ranges and releases the opioid analgesic in a pH-dependent or pH-independent manner.

A non-limiting list of suitable sustained-release materials which may be included in a sustained-release matrix according to the invention include hydrophilic and/or hydrophobic materials, such as gums, cellulose ethers, acrylic resins, protein derived materials, waxes, shellac, and oils such as hydrogenated castor oil and hydrogenated vegetable oil. However, any pharmaceutically acceptable hydrophobic or hydrophilic sustained-release material which is capable of imparting sustained-release of the opioid analgesic may be used in accordance with the present invention. Preferred sustained-release polymers include alkylcelluloses such as ethylcellulose, acrylic and methacrylic acid polymers and copolymers, and cellulose ethers, especially hydroxyalkylcelluloses (especially hydroxypropylmethylcellulose) and carboxyalkylcelluloses. Preferred acrylic and methacrylic acid polymers and copolymers include methyl methacrylate, methyl methacrylate copolymers, ethoxyethyl methacrylates, ethyl

acrylate, trimethyl ammonioethyl methacrylate, cyanoethyl methacrylate, aminoalkyl methacrylate copolymer, poly(acrylic acid), poly(methacrylic acid), methacrylic acid alkylamine copolymer, poly(methylmethacrylate), poly(methacrylicacid) (anhydride), polymethacrylate, polyacrylamide, poly(methacrylic acid anhydride), and glycidyl methacrylate copolymers. Certain preferred embodiments utilize mixtures of any of the foregoing sustained-release materials in the matrix of the invention.

The matrix also may include a binder. In such embodiments, the binder preferably contributes to the sustained-release of the opioid analgesic or pharmaceutically acceptable salt thereof from the sustained-release matrix. If an additional hydrophobic binder material is included, it is preferably selected from natural and synthetic waxes, fatty acids, fatty alcohols, and mixtures of the same. Examples include beeswax, carnauba wax, stearic acid and stearyl alcohol. This list is not meant to be exclusive. In certain preferred embodiments, a combination of two or more hydrophobic binder materials is included in the matrix formulations.

Preferred hydrophobic binder materials which may be used in accordance with the present invention include digestible, long chain (C_8-C_{50}, especially C_{12}-C_{40}), substituted or unsubstituted hydrocarbons, such as fatty acids, fatty alcohols, glyceryl esters of fatty acids, mineral and vegetable oils, natural and synthetic waxes and polyalkylene glycols. Hydrocarbons having a melting point of between 25° and 90°C are preferred. Of the long-chain hydrocarbon binder materials, fatty (aliphatic) alcohols are preferred in certain embodiments. The oral dosage form may contain up to 80% (by weight) of at least one digestible, long chain hydrocarbon.

In certain embodiments, the hydrophobic binder material may comprise natural or synthetic waxes, fatty alcohols (such as lauryl, myristyl, stearyl, cetyl or preferably cetostearyl alcohol), fatty acids, including but not limited to fatty acid esters, fatty acid glycerides (mono-,

(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

In one preferred embodiment, the ratio of, e.g., the at least one hydroxyalkyl cellulose or acrylic resin to the at least one aliphatic alcohol/polyalkylene glycol determines, to a considerable extent, the release rate of the opioid analgesic from the formulation. In certain embodiments, a ratio of the hydroxyalkyl cellulose to the aliphatic alcohol/polyalkylene glycol of between 1:1 and 1:4 is preferred, with a ratio of between 1:2 and 1:3 being particularly preferred.

In certain embodiments, the polyalkylene glycol may be, for example, polypropylene glycol, or polyethylene glycol which is preferred. The average molecular weight of the at least one polyalkylene glycol is preferably between 1,000 and 15,000, especially between 1,500 and 12,000.

Another suitable sustained-release matrix comprises an alkylcellulose (especially ethylcellulose), a C_{12} to C_{36} aliphatic alcohol and, optionally, a polyalkylene glycol.

In addition to the above ingredients, a sustained-release matrix may also contain suitable quantities of other materials, e.g., diluents, lubricants, binders, granulating aids, and glidants that are conventional in the pharmaceutical art.

In order to facilitate the preparation of a solid, sustained-release oral dosage form according to this invention, there is provided, in a further aspect of the present invention, a process for the preparation of a solid, sustained-release oral dosage form according to the present invention comprising incorporating an opioid analgesic in a sustained-release matrix. Incorporation in the matrix may be effected, for example, by:

(a) forming granules comprising at least one hydrophobic and/or hydrophilic material as set forth above (e.g., a water soluble hydroxyalkyl cellulose) together with the opioid analgesic, and an aversive agent;

Osmotic Dosage Forms

Sustained release dosage forms according to the present invention may also be prepared as osmotic dosage formulations. The osmotic dosage forms preferably include a bilayer core comprising a drug layer (containing the opioid analgesic and optionally the aversive agent) and a delivery or push layer (which may contain the aversive agent), wherein the bilayer core is surrounded by a semipermeable wall and optionally having at least one passageway disposed therein.

The expression "passageway" as used for the purpose of this invention, includes aperture, orifice, bore, pore, porous element through which the opioid analgesic can be pumped, diffuse or migrate through a fiber, capillary tube, porous overlay, porous insert, microporous member, or porous composition. The passageway can also include a compound that erodes or is leached from the wall in the fluid environment of use to produce at least one passageway. Representative compounds for forming a passageway include erodible poly(glycolic) acid, or poly(lactic) acid in the wall; a gelatinous filament; a water-removable poly(vinyl alcohol); leachable compounds such as fluid-removable pore-forming polysaccharides, acids, salts or oxides. A passageway can be formed by leaching a compound from the wall, such as sorbitol, sucrose, lactose, maltose, or fructose, to form a sustained-release dimensional pore-passageway. The passageway can have any shape, such as round, triangular, square and elliptical, for assisting in the sustained metered release of opioid analgesic from the dosage form. The dosage form can be manufactured with one or more passageways in spaced-apart relation on one or more surfaces of the dosage form. A passageway and equipment for forming a passageway are disclosed in U.S. Patent Nos. 3,845,770; 3,916,899; 4,063,064 and 4,088,864. Passageways comprising sustained-release dimensions sized, shaped and adapted as a releasing-pore formed by aqueous leaching to provide

a releasing-pore of a sustained-release rate are disclosed in U.S. Patent Nos. 4,200,098 and 4,285,987.

In certain embodiments, the bilayer core comprises a drug layer with opioid analgesic and a displacement or push layer optionally containing the aversive agent. The aversive agent may optionally be included in the drug layer instead of or in addition to being included in the push layer. In certain embodiments, the drug layer may also comprise at least one polymer hydrogel. The polymer hydrogel may have an average molecular weight of between about 500 and about 6,000,000. Examples of polymer hydrogels include but are not limited to a maltodextrin polymer comprising the formula $(C_6 H_{12} O_5)_n \cdot H_2O$, wherein n is 3 to 7,500, and the maltodextrin polymer comprises a 500 to 1,250,000 number-average molecular weight; a poly(alkylene oxide) represented by, e.g., a poly(ethylene oxide) and a poly(propylene oxide) having a 50,000 to 750,000 weight-average molecular weight, and more specifically represented by a poly(ethylene oxide) of at least one of 100,000, 200,000, 300,000 or 400,000 weight-average molecular weights; an alkali carboxyalkylcellulose, wherein the alkali is sodium or potassium, the alkyl is methyl, ethyl, propyl, or butyl of 10,000 to 175,000 weight-average molecular weight; and a copolymer of ethylene-acrylic acid, including methacrylic and ethacrylic acid of 10,000 to 500,000 number-average molecular weight.

In certain embodiments of the present invention, the delivery or push layer comprises an osmopolymer. Examples of an osmopolymer include but are not limited to a member selected from the group consisting of a polyalkylene oxide and a carboxyalkylcellulose. The polyalkylene oxide possesses a 1,000,000 to 10,000,000 weight-average molecular weight. The polyalkylene oxide may be a member selected from the group consisting of polymethylene oxide, polyethylene oxide, polypropylene oxide, polyethylene oxide having a 1,000,000 average

molecular weight, polyethylene oxide comprising a 5,000,000 average molecular weight, polyethylene oxide comprising a 7,000,000 average molecular weight, cross-linked polymethylene oxide possessing a 1,000,000 average molecular weight, and polypropylene oxide of 1,200,000 average molecular weight. Typical osmopolymer carboxyalkylcellulose comprises a member selected from the group consisting of alkali carboxyalkylcellulose, sodium carboxymethylcellulose, potassium carboxymethylcellulose, sodium carboxyethylcellulose, lithium carboxymethylcellulose, sodium carboxyethylcellulose, carboxyalkylhydroxyalkylcellulose, carboxymethylhydroxyethyl cellulose, carboxyethylhydroxyethylcellulose and carboxymethylhydroxypropylcellulose. The osmopolymers used for the displacement layer exhibit an osmotic pressure gradient across the semipermeable wall. The osmopolymers imbibe fluid into dosage form, thereby swelling and expanding as an osmotic hydrogel (also known as osmogel), whereby they push the contents of the drug layer from the osmotic dosage form.

The push layer may also include one or more osmotically effective compounds also known as osmagents and as osmotically effective solutes. They imbibe an environmental fluid, for example, from the gastrointestinal tract, into dosage form and contribute to the delivery kinetics of the displacement layer. Examples of osmotically active compounds comprise a member selected from the group consisting of osmotic salts and osmotic carbohydrates. Examples of specific osmagents include but are not limited to sodium chloride, potassium chloride, magnesium sulfate, lithium phosphate, lithium chloride, sodium phosphate, potassium sulfate, sodium sulfate, potassium phosphate, glucose, fructose and maltose.

The push layer may optionally include a hydroxypropylalkylcellulose possessing a 9,000 to 450,000 number-average molecular weight. The hydroxypropylalkylcellulose is represented

by a member selected from the group consisting of hydroxypropylmethylcellulose, hydroxypropylethylcellulose, hydroxypropyl isopropyl cellulose, hydroxypropylbutylcellulose, and hydroxypropylpentylcellulose.

The push layer may also optionally comprise an antioxidant to inhibit the oxidation of ingredients. Some examples of antioxidants include but are not limited to a member selected from the group consisting of ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, a mixture of 2 and 3 tertiary-butyl-4-hydroxyanisole, butylated hydroxytoluene, sodium isoascorbate, dihydroguaretic acid, potassium sorbate, sodium bisulfate, sodium metabisulfate, sorbic acid, potassium ascorbate, vitamin E, 4-chloro-2,6-ditertiary butylphenol, alphatocopherol, and propylgallate.

In certain alternative embodiments, the dosage form comprises a substantially homogenous core comprising opioid analgesic, an aversive agent, a pharmaceutically acceptable polymer (e.g., polyethylene oxide), optionally a disintegrant (e.g., polyvinylpyrrolidone), optionally an absorption enhancer (e.g., a fatty acid, a surfactant, a chelating agent, a bile salt, etc.). The substantially homogenous core is surrounded by a semipermeable wall having a passageway (as defined above) for the release of the opioid analgesic, and the aversive agent.

In certain embodiments, the semipermeable wall comprises a member selected from the group consisting of a cellulose ester polymer, a cellulose ether polymer and a cellulose ester-ether polymer. Representative wall polymers comprise a member selected from the group consisting of cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, mono-, di- and tricellulose alkenylates, and mono-, di- and tricellulose alkinylates. The poly(cellulose) used for the present invention comprises a number-average molecular weight of 20,000 to 7,500,000.

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

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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,

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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

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado
DILIA MARÍA RODRÍGUEZ D'ALEMÁN
Apoderado

ASUNTO		
	Radicación	06-010699
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	
	Folios	21 868

Patente de Invención ■ Patente de Modelo de Utilidad ☐

Vía Nacional ☐

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

No. Sol. Internacional PCT/EP2004/008793
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: 36 a 70 y 76 como se radicó inicialmente
Reivindicaciones:	Folios 71 a 75 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 administración termoformada sin extrusión a prueba de abuso, con una dureza de al menos de 500N.

El problema planteado en esta solicitud es cómo obtener una forma de administración termoformada sin extrusión 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 sin extrusión 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.

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.

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 sin extrusión, 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)

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 las cuales pueden ser preparadas por granulación por fusión (Ver página 19, línea 11).

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 a prueba de abuso.

D2 describe una manera de solucionar el problema técnico, pues enseña tabletas de matriz hidrofílica que contienen entre otros como polímero óxido de polietileno, los cuales se emplean en liberación controlada y que presentan una dureza entre 10 y 30kN para las formulaciones enseñadas (Ver columna 2, página 1114)

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) aplicando la fuerza de compresión necesaria" 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, puesto que 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

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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 29 ENE. 2010

CONCEPTO TÉCNICO No. 04239	**EXAMINADOR TÉCNICO** Código No. 202070

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado
DILIA MARÍA RODRÍGUEZ D'ALEMÁN
Apoderado

ASUNTO	Radicación	06-010699
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	869
	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 CESPEDES DE VERGEL
Directora de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha 29 ENE. 2010

CONCEPTO TÉCNICO No. 04239	**EXAMINADOR TÉCNICO** Código No. 202070