

# HUMBERTO RUBIO & CIA.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-128770- -00005-0000

Fecha: 2008-06-12 11:15:56 Dep. 2020 NUECREACION  
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII  
Act. 538 PETICION Folios: 2

Señor

**SUPERINTENDENTE DE INDUSTRIA Y COMERCIO  
DIVISIÓN DE NUEVAS CREACIONES**

**E. S. D.**

**REF:** Expediente No.:  
Patente de Invención:

**06-128.770**

**"FORMAS FARMACEUTICAS  
ORALES, PROTEGIDAS FRENTE AL  
ABUSO, QUE CONTIENEN (1R,2R)-  
3-(3-DIMETHYLAMINO-1-ETHYL-  
2-METHYL-PROPYL)-PHENOL"  
GRUNENTHAL GmbH**

Titular:

**Publicada en la Gaceta de la Propiedad Industrial No. 587 de  
18 de Enero de 2008**

## SOLICITUD DE EXAMEN DE PATENTABILIDAD

**HUMBERTO RUBIO CAMACHO**, mayor de edad, domiciliado en Bogotá, D.C., identificado con la cédula de ciudadanía número 17.192.062 de Bogotá, abogado en ejercicio, portador de la Tarjeta Profesional No. 50.007, expedida por el Consejo Superior de la Judicatura, actuando en carácter de **APODERADO** de la sociedad **GRUNENTHAL GmbH**, domiciliada en Zieglerstrasse 6, 52078, Aachen, Alemania, respetuosamente solicito a esa Dependencia:

- 1.- De conformidad con lo establecido en el Artículo 44 de la Decisión 486 de la Comisión de la Comunidad Andina y estando dentro del término legal de seis (6) meses contados desde la fecha de publicación en la Gaceta No. 587 de 18 de enero de 2008, de la solicitud de la patente de la referencia, solicito se sirvan proceder a efectuar el examen de patentabilidad de la Invención.
- 2.- Para que la presente petición sea viable, estoy anexando el siguiente documento:
  - 2.1. Recibo de pago No. 08-46,549 de 11 de junio de 2008; de acuerdo con la Resolución No. 44372 de 26 de diciembre de 2.007.
- 3.- Por lo anterior solicito se continúe con el trámite correspondiente.

Atentamente,

  
**HUMBERTO RUBIO CAMACHO**  
C.C. 17.192.062 de Bogotá  
T.P. 50.007 Consejo Superior  
de la Judicatura.  
COD. 4134

**06/1249/P000605**  
Bap-

82x

**PARA USO EXCLUSIVO DE  
HUMBERTO RUBIO & CIA. LTDA.**

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

**No. 06-128770- -00005-0000**Fecha: 2008-06-12 11:15:56 Dep. 2020 NUECREACIONE  
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 890176089-2

RECIBO OFICIAL DE CAJA : 08 - 46,549  
FECHA : JUNIO 11 DE 2008

## \*\*\*\*\* CONSIGNACION \*\*\*\*\*

| DEPOSITANTE               | TIPO PAGO    | BANCO           | CUENTA    | No. PAGO | FECHA PGO  | Vr. PAGO     |
|---------------------------|--------------|-----------------|-----------|----------|------------|--------------|
| HUMBERTO RUBIO & CIA ABOG | CONSIGNACION | BANCO DE BOGOTA | 062754387 | 769731   | 10/06/2008 | 2,351,000.00 |

## \*\*\*\*\* C O N C E P T O \*\*\*\*\*

| CANT. | RENTISTICO  | CONCEPTO                              | TOTAL CONCEPTO |
|-------|-------------|---------------------------------------|----------------|
| 1     | 50005-01-01 | SOLICITUDES                           |                |
|       |             | 114 PTC CAP-II EXAMEN DE PATENTIBILID | 210,000.00     |
|       |             | TOTAL :                               | \$ 210,000.00  |

SON: DOSCIENTOS DIEZ MIL PESOS

RESPONSABLE : \_\_\_\_\_

88

**DIVISIÓN DE NUEVAS CREACIONES**

RADICACIÓN EXPEDIENTE No. 06-128770

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

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

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60/310,513 6 August 2001 (06.08.2001) US

(71) Applicant and

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(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.*

(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.

WO 03/015531 A2

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 averted 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

other aversive agents) is at least partially dispersed in the opioid, rather than separate, e.g. in a film coat. This reduces the potential of the aversive agent from being separated from the opioid during the tampering process, making the aversive agent less or not effective. For safety reasons, the amount of the dye in the present invention should not be toxic to humans.

In certain embodiments, when the dosage form is chewed, crushed or dissolved and heated in a solvent, the release of the aversive agent hinders, deters or prevents the administration of the tampered dosage form orally, intranasally, parenterally and/or sublingually.

**The opioid agonists useful in the present invention include, but are not limited to,**  
alfentanil, allylprodine, alphaprodine, anileridine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, desomorphine, dextromoramide, dezocine, diampromide, diamorphine, dihydrocodeine, dihydromorphine, dimenoxadol, dimepheptanol, dimethylthiambutene, dioxaphetyl butyrate, dipipanone, eptazocine, ethoheptazine, ethylmethylthiambutene, ethylmorphine, etonitazene, etorphine, dihydroetorphine, fentanyl and derivatives, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, ketobemidone, levorphanol, levophenacylmorphan, lofentanil, meperidine, meptazinol, metazocine, methadone, metopon, morphine, myrophine, narceine, nicomorphine, norlevorphanol, normethadone, nalorphine, nalbuphene, normorphine, norpipanone, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenadoxone, phenomorphan, phenazocine, phenoperidine, piminodine, piritramide, propheptazine, promedol, properidine, propoxyphene, sufentanil, tilidine, tramadol, mixtures of any of the foregoing, salts of any of the foregoing, and the like. In certain embodiments, the amount of the opioid agonist in the claimed opioid composition may be about 75 ng to 750 mg.

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.

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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(methacrylic acid) (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  $25^\circ$  and  $90^\circ\text{C}$  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-,

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<sub>12</sub> to C<sub>36</sub> 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;

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(b) mixing the at least one hydrophobic and/or hydrophilic material-containing granules, with at least one C<sub>12</sub>-C<sub>36</sub> 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 certain embodiments, the uncoated/coated sustained release spheroids, granules, or matrix multiparticulates containing the opioid analgesic; and the aversive agent; are cured until an endpoint is reached at which the sustained release spheroids, granules, or matrix multiparticulates provide a stable dissolution of the opioid. The curing endpoint may be determined by comparing the dissolution profile (curve) of the dosage form immediately after curing to the dissolution profile (curve) of the dosage form after exposure to accelerated storage conditions of, e.g., at least one month at a temperature of 40°C and a relative humidity of 75%. Cured formulations are described in detail in U.S. Patent Nos. 5,273,760; 5,286,493; 5,500,227; 5,580,578; 5,639,476; 5,681,585; and 6,024,982. Other examples of sustained-release formulations and coatings which may be used in accordance with the present invention include U.S. Patent Nos. 5,324,351; 5,356,467; and 5,472,712.

In addition to the above ingredients, the spheroids, granules, or matrix multiparticulates 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 amounts up to about 50% by weight of the formulation if desired. The quantities of these additional materials will be sufficient to provide the desired effect to the desired formulation.

Specific examples of pharmaceutically acceptable carriers and excipients that may be used to formulate oral dosage forms are described in the Handbook of Pharmaceutical

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Excipients, American Pharmaceutical Association (1986), incorporated by reference herein.

It has further been found that the addition of a small amount of talc to the sustained release coating reduces the tendency of the aqueous dispersion to stick during processing, and acts as a polishing 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

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**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO  
DIRECCIÓN DE NUEVAS CREACIONES**

2020  
Bogotá, D.C.,

Abogado

**HUMBERTO RUBIO CAMACHO**

Apoderado

|        |            |           |
|--------|------------|-----------|
| ASUNTO | Radicación | 06-128770 |
|        | Trámite    | 002       |
|        | Evento     | 001       |
|        | Actuación  | 430       |
|        | Oficio     | 1432      |
|        | Folios     | 22        |

Patente de Invención ☒ Patente de Modelo de Utilidad ☐

Vía Nacional ☐

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

No. Sol. Internacional PCT/EP2005/006990

Fecha de Presentación Internal. 29 de Junio de 2005

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: 5 a 34 y 40 como se radicó inicialmente

Reivindicaciones: Folios 35 a 39 como se radicó inicialmente

Prioridad: Folios: 1  
01 de Julio de 2004, DE, 100 032 103.5

**2. Análisis de la Prioridad**

La fecha de prioridad del 01 de Julio de 2004 y su correspondiente documento, son aceptados para el estudio de patentabilidad.

**3. Objeto de la invención**

Título de la solicitud: formas farmacéuticas orales, protegidas frente al abuso, que contienen (1R,2R)-3-(3-dimetilamino-1-etil-2-metil-propil)-fenol.

El objeto de la presente solicitud de patente de invención consiste en una forma farmacéutica oral, protegida frente al abuso, que contienen (1R,2R)-3-(3-dimetilamino-1-etil-2-metil-propil)-fenol para una administración única diaria.

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El problema planteado en esta solicitud es cómo obtener una forma farmacéutica oral protegidas frente al abuso, que contienen (1R, 2R)-3-(3-dimetilamino-1-etil-2-metil-propil)-fenol para una administración única diaria.

Para solucionar este problema técnico la solicitud en estudio proporciona una forma farmacéutica oral protegida frente al abuso, que contienen (1R, 2R)-3-(3-dimetilamino-1-etil-2-metil-propil)-fenol para una administración única diaria

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

#### 4. De la solicitud de Patente

##### 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 la forma de liberación de la forma farmacéutica, de liberación controlada, sostenida y/o retardada, sin embargo no se encuentran caracterizadas a lo largo del capítulo reivindicatorio y donde la forma farmacéutica obtenida sea para una administración única diaria. Además, no se encuentran sustentadas mediante ejemplos en la descripción que presenten la mejor forma de realizar 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: 01 de Julio de 2004

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es: 01/07/2004 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,<br>Biomaterials 23<br>(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 (artículo 18 D486)

La reivindicación 1 consiste en:

Forma farmacéutica oral, protegida frente al abuso, con una resistencia de rotura al menos 500N, y con una liberación controlada de (1R,2R)-3-(3-dimetilamino-1-etil-2-metil-propil)-fenol para una administración única diaria.

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porque comprende el principio activo y/o al menos una de sus sales o derivados (A) farmacéuticamente aceptables, al menos un polímero (C) sintético y/o natural, opcionalmente al menos un adyuvante de matriz de liberación sostenida y/o opcionalmente al menos un recubrimiento de liberación retardada, al menos otro adyuvante (B) fisiológicamente compatible, 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 susceptibles de abuso (Ver página 15, líneas 16-17), auxiliares de formulación (Ver página 18, líneas 13-15), polímeros de liberación sostenida (Ver página 15, líneas 18-22, 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 granulación, mezcla y compresión (Ver página 18 (últimas líneas) y página 19 (líneas 1-3).

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) y el fármaco en la formulación el cual es (1R, 2R)-3-(3-dimetilamino-1-etil-2-metil-propil)-fenol.

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 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 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 de liberación controlada a prueba de abuso con una dureza de al menos de 500N para el componente (C) y/o (D)" variaría "los

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proporciones del polímero con el fin de obtener una dureza de al menos 500N (0.5kN) como 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 y el intercambio de otro principio activo de abuso La reivindicación 1 no tiene Nivel Inventivo. Además los principios activos no se encuentran limitados en las formulaciones de D1 (Ver página 8, línea 8), por lo tanto cualquier persona medianamente versada en la materia a la luz de dicho documento utilizaría cualquier otro fármaco opiode; tal como (1R, 2R)-3-(3-dimetilamino-1-etil-2-metil-propil)-fenol. 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 \_\_\_\_\_

|                                  |                                                |
|----------------------------------|------------------------------------------------|
| <b>CONCEPTO TÉCNICO No. 0285</b> | <b>EXAMINADOR TÉCNICO</b><br>Código No. 202070 |
|----------------------------------|------------------------------------------------|

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO**  
**DIRECCIÓN DE NUEVAS CREACIONES**

2020  
Bogotá, D.C.,

Abogado  
**HUMBERTO RUBIO CAMACHO**  
Apoderado

|        |            |           |
|--------|------------|-----------|
| ASUNTO | Radicación | 06-128770 |
|        | Trámite    | 002       |
|        | Evento     | 001       |
|        | Actuación  | 430       |
|        | Oficio     | 001433    |
|        | 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.* **155** (2000), pp. 238-239.
- C.J. Kim, Effects of drug solubility, drug loading and polymer molecular weight on drug release from Polyox<sup>®</sup> 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 05 FEB 2010

**CONCEPTO TÉCNICO No. 0285**

**EXAMINADOR TÉCNICO**  
Código No. 202070