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SOLIDAS DE ACETATO DE BAZEDOXIFENO

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FORMULARIO ÚNICO DE SOLICITUD DE PATENTE PCT ENTRADA EN FASE NACIONAL

1

SOLICITUD DE :

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Patente de Invención

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Patente de Modelo de Utilidad

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Capítulo I.

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Capítulo II.

2

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IDENTIFICACION

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Número

3

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Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página

10

ANEXOS

00002

- ☒ Comprobante de pago de la tasa de presentación de la solicitud
- ☐ Documento que acredite la existencia y representación legal cuando el solicitante sea persona jurídica
- ☐ Poderes, si fuere el caso
- ☐ Documento de cesión del inventor al solicitante o a su causante
- ☐ Declaraciones
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☐ Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen preliminar (IPEA)
- ☐ Traducción del examen preliminar internacional efectuado por la IPEA
- ☐ De ser el caso, copia del contrato de acceso
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- ☐ De ser el caso, certificado de depósito del material biológico
- ☐ Arte final 12 x 12
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud
- ☐ De ser el caso, modificaciones efectuadas a la solicitud internacional.
- ☒ Otros: Reporte de Búsqueda Internacional, Opinión Escrita, Notificación de presentación de documento de Prioridad y Extractos

11

FIGURA CARACTERISTICA

12

Solicito la concesión de la patente,

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***** CONCEPTO *****

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(54) Title: BAZEDOXIFENE ACETATE SOLID DISPERSION FORMULATIONS

(57) Abstract: The present invention is directed to solid dispersions of bazedoxifene acetate, compositions containing the same, preparations thereof, and uses thereof.

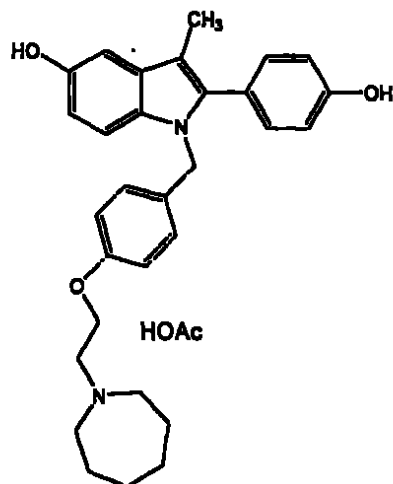
BAZEDOXIFENE ACETATE SOLID DISPERSION FORMULATIONS

FIELD OF THE INVENTION

The present invention relates to solid dispersions and compositions thereof of the selective estrogen receptor modulator 1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol acetic acid (bazedoxifene acetate).

BACKGROUND OF THE INVENTION

Bazedoxifene acetate (1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol acetic acid), having the chemical formula shown below:



belongs to the class of drugs typically referred to as selective estrogen receptor modulators (SERMs). Consistent with its classification, bazedoxifene demonstrates affinity for estrogen receptors (ER) but shows tissue selective estrogenic effects. For example, bazedoxifene acetate demonstrates little or no stimulation of uterine response in preclinical models of uterine stimulation. Conversely, bazedoxifene acetate demonstrates an estrogen agonist-like effect in preventing bone loss and reducing cholesterol in an ovariectomized rat model of osteopenia. In an MCF-7 cell line (human breast cancer cell line), bazedoxifene acetate behaves as an estrogen antagonist. These data demonstrate that bazedoxifene acetate is estrogenic on bone and cardiovascular lipid parameters and antiestrogenic on uterine and mammary tissue and thus has the potential for treating a number of different disease or disease-like states wherein the estrogen receptor is involved.

U.S. Pat. Nos. 5,998,402 and 6,479,535 report the preparation of bazedoxifene acetate. The synthetic preparation of bazedoxifene acetate has also appeared in the general literature. See, for example, Miller et al., *J. Med. Chem.*, 2001, 44, 1654-1657. Further description of the drug's biological activity has appeared in the general literature as well (e.g. Miller, et al. *Drugs of the Future*, 2002, 27(2), 117-121). Formulations of bazedoxifene acetate are also reported in U.S. Pat. App. Pub. No. 2002/0031548 A1.

Because drug formulations showing, for example, improved bioavailability are consistently sought, there is an ongoing need for new formulations of existing drug molecules. The solid dispersions of bazedoxifene acetate and compositions containing the same described herein helps meet these and other needs.

SUMMARY OF THE INVENTION

In some embodiments, the present invention provides a solid dispersion comprising bazedoxifene acetate dispersed in a dispersing agent.

In some embodiments, the present invention provides a composition comprising the solid dispersion described herein and a pharmaceutically acceptable carrier.

In some embodiments, the present invention provides a dosage form comprising the solid dispersion described herein.

In some embodiments, the present invention provides a method of preparing the solid dispersion described herein, comprising: a) combining bazedoxifene acetate and a dispersing agent in solution; and b) removing solvent to yield the solid dispersion.

In some embodiments, the present invention provides a method of preparing the solid dispersion described herein, comprising: a) combining bazedoxifene acetate with melted dispersing agent to form a liquid mixture; and b) solidifying the liquid mixture to form the solid dispersion.

In some embodiments, the present invention provides a method of treating a mammal having a disease or syndrome associated with estrogen deficiency or excess of estrogen comprising administering to the mammal a therapeutically effective amount of the solid dispersion of described herein.

In some embodiments, the present invention provides a method of treating a mammal having a disease or disorder associated with proliferation or abnormal development of endometrial tissues comprising administering to the mammal a therapeutically effective amount of the solid dispersion described herein.

In some embodiments, the present invention provides a method of lowering cholesterol in a mammal comprising administering to the mammal a therapeutically effective amount of the solid dispersion described herein.

5 In some embodiments, the present invention provides a method of inhibiting bone loss in a mammal comprising administering to the mammal a therapeutically effective amount of the solid dispersion described herein.

In some embodiments, the present invention provides a method of treating breast cancer in a mammal comprising administering to the mammal a therapeutically effective amount of the solid dispersion described herein.

) In some embodiments, the present invention provides a method of treating postmenopausal woman for one or more vasomotor disturbances comprising administering to the postmenopausal woman a therapeutically effective amount of the solid dispersion of described herein.

5 The present invention further provides the solid dispersions of the invention for use in therapy.

The present invention further provides use of the solid dispersions of the invention for the preparation of a medicament.

BRIEF DESCRIPTION OF THE DRAWINGS

) Figure 1 shows a plot comparing dissolution rates of bazedoxifene acetate as a crystalline solid and as a solid dispersion with PVP according to Example 3.

Figure 2 shows a plot comparing bioavailability of bazedoxifene acetate in dogs for formulations containing dispersion and non-dispersion formulations according to Example 4.

5 DETAILED DESCRIPTION

The present invention provides, *inter alia*, bazedoxifene acetate (BZA) solid dispersions and compositions thereof having improved properties relating to solubility, bioavailability and the like. The solid dispersions of the invention have increased solubility and bioavailability compared with, for example, crystalline BZA or microcrystalline BZA.

0 The increased bioavailability associated with solid BZA dispersions has numerous advantages including allowing for administration of lower dosages, thereby lessening chances for adverse side effects and reducing subject variability.

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The compositions of the invention contain, for example, BZA dispersed in a dispersing agent. In some embodiments, the weight ratio of BZA to dispersing agent is about 1:99 to about 99:1. In some embodiments, the weight ratio of BZA to dispersing agent is about 1:99 to about 75:25 or about 1:99 to about 60:40. In further embodiments, the weight ratio of BZA to dispersing agent is about 1:99 to about 15:85; about 1:99 to about 10:90; or about 1:99 to about 5:95. In further embodiments, the weight ratio of BZA to dispersing agent is about 5:95. In further embodiments, the weight ratio of BZA to dispersing agent is about 25:75 to about 75:25, about 40:60 to about 60:40 or about 1:1. In some embodiments, the weight ratio of BZA to dispersing agent is about 1:1.

The "dispersing agent," as used herein, refers to any substance or mixture of substances that acts as a dispersing medium for molecules/particles of bazedoxifene acetate. The dispersing agent is typically composed of a pharmaceutically acceptable substance that does not substantially interfere with the pharmaceutical action of BZA. The phrase "pharmaceutically acceptable" is employed herein to refer to those substances which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. In some embodiments, the dispersing agent is a solid at room temperature (e.g., about 22 °C). In further embodiments, the dispersing agent melts at a temperature between about 30 and 100 °C. In further embodiments, the dispersing agent is soluble in an organic solvent.

Non-limiting examples of suitable dispersing agents include polymers such as celluloses (e.g., carboxymethylcelluloses, methylcelluloses, hydroxypropylcelluloses, hydroxypropylmethylcelluloses); hyaluronates; alginates; polysaccharides, heteropolysaccharides (pectins); poloxamers; poloxamines; ethylene vinyl acetates; polyethylene glycols; dextrans; polyvinylpyrrolidones; chitosans; polyvinylalcohols; propylene glycols; polyvinylacetates; phosphatidylcholines (lecithins); miglyols; polylactic acid; polyhydroxybutyric acid; mixtures of two or more thereof, copolymers thereof, derivatives thereof, and the like. Further example dispersing agents include copolymer systems such as polyethylene glycol-polylactic acid (PEG-PLA), polyethylene glycol-polyhydroxybutyric acid (PEG-PHB), polyvinylpyrrolidone-polyvinylalcohol (PVP-PVA), and derivatized copolymers such as copolymers of N-vinyl purine (or pyrimidine) derivatives and N-vinylpyrrolidone.

In some embodiments, the dispersing agent contains polyvinylpyrrolidone (PVP) or derivative thereof. PVP is a polyamide that forms complexes with a wide variety of

substances and is considered to be chemically and physiologically inert. Examples of suitable PVPs include polyvinylpyrrolidones having an average molecular weight from about 10,000 to about 50,000. In some embodiments, the polyvinylpyrrolidone has an average molecular weight of about 10,000 to about 20,000. In further embodiments, the polyvinylpyrrolidone has a molecular weight of about 15,000 to about 20,000. An example suitable PVP is PVP K-17 (PLASDONE povidone, ISP Technologies, Ltd.). In some embodiments, the dispersing agent consists essentially of PVP or derivative thereof.

In some embodiments, the dispersing agent contains a block co-polymer of ethylene and propylene glycol, often referred to as a Poloxamer. Some suitable example Poloxamers include Poloxamer 188 (LUTROL F 68, BASF), Poloxamer 407 (LUTROL F 127, BASF), and the like. In some embodiments, the dispersing agent is Poloxamer 188.

In some embodiments, the dispersing agent contains a polyethylene glycol (PEG). Suitable PEGs include PEG 200, 300, 400, 600, 1000, 1450, 3350, 4000, 6000, 8000, 10000, 20000, mixtures thereof and the like. In some embodiments, the dispersing agent is PEG 1450.

The BZA dispersions of the invention can be made by any of numerous methods that result in, for example, a solid dispersion of amorphous BZA. In an example method, BZA (in any form, e.g., crystalline, amorphous, etc.) and the dispersing agent can be dissolved in a dispersing solvent (together, or separately and then combined) in the weight ratio desired and then the dispersing solvent is removed to yield the desired solid dispersion. The dispersing solvent can be an aqueous solvent or organic solvent. Suitable organic solvents include alcohols, ethers, hydrocarbons, halogenated hydrocarbons, nitriles, mixtures thereof, and the like. In some embodiments, the organic solvent is a volatile solvent such as methanol, ethanol, isopropanol, diethyl ether, pentane, hexane, benzene, dichloromethane, acetonitrile, mixtures thereof and the like. In some embodiments, the organic solvent is an alcohol such as methanol, ethanol, n-propanol, isopropanol, mixtures thereof and the like. In some embodiments, the organic solvent is ethanol.

In another example, BZA and dispersing agent can be combined in the desired weight ratio when either or both the BZA and dispersing agent is (are) in liquid form (e.g., a melt), and then the liquid mixture is solidified to form the desired solid dispersion. According to such embodiments, the BZA and dispersing agent can be combined when at least one of the BZA and dispersing agent is melted. The resulting mixture is then solidified by cooling to a temperature sufficient to solidify the mixture. In some embodiments, the mixture is cooled to about 25 °C or below. In some embodiments, BZA is combined with melted dispersing agent

and the resulting mixture cooled to a temperature below the melting point of the mixture to form the solid dispersion. In further embodiments, the dispersing agent is heated to a temperature between about 30 and 200 °C, between about 30 and 150 °C, or between about 30 and 100 °C, which is a temperature that is at or above the melting point of the dispersing agent. In further embodiments, the dispersing agent is heated to a temperature above about 30, above about 40, above about 50, above about 60, above about 70, above about 80 or above about 90 °C. These and other methods are routine techniques suitable for the preparation of the BZA dispersions of the invention.

In some embodiments, the solid dispersions of the invention are characterized by an equilibrium solubility in 0.0005 M acetic acid at a temperature of about 20 to about 26 °C that is greater than that for crystalline or microcrystalline bazedoxifene acetate. In further embodiments, the solid dispersions of the invention are characterized by an equilibrium solubility in 0.0005 M acetic acid at a temperature of about 20 to about 26 °C that is at least about 8, at least about 10, at least about 12, at least about 14, at least about 16, or at least about 19 mg/mL. Equilibrium solubility can be measured by routine methods in the art such as described in Example 2.

In some embodiments, the solid dispersions of the invention are characterized such that a dosage form comprising about 10 mg total of bazedoxifene acetate in a solid dispersion is characterized by an AUC_{0-24} greater than about 140, greater than about 150, greater than about 160, greater than about 170, or greater than about 180 ng·hr/mL when orally administered to mammal. In further embodiments, the solid dispersions of the invention are characterized such that a dosage form comprising about 10 mg total of bazedoxifene acetate in a solid dispersion is characterized by:

- a) an AUC_{0-24} of about 140 to about 250 ng·hr/mL;
- b) a C_{max} of about 12 to about 30 ng/mL; and
- c) a t_{max} of about 1.0 to about 3.5 hr;

when orally administered to mammal. Methods for measuring the pharmacokinetic parameters AUC_{0-24} (area under curve for 24 hours), C_{max} , and t_{max} are well known in the art and described, for example, in Example 4.

Dosage and Formulation

The solid dispersions described herein can be formulated for administration to a patient in any of a variety of ways. In some embodiments, the solid dispersions can be administered alone, i.e., without the addition of excipients or other additives. For example,

solid dosage forms (e.g., tablet, capsules etc.) containing greater than about 95%, greater than about 98%, or greater than about 99% (by weight) of solid dispersion described herein can be directly administered to a patient.

5 In some embodiments, the solid dispersions are combined with one or more pharmaceutically acceptable carriers (excipients) to form a pharmaceutical composition for administration to a patient. The composition can contain any amount of solid dispersion. In some embodiments, the compositions contains about 1 to about 99 % by weight of the solid dispersion. In further embodiments, the composition contains about 1 to about 50% by weight of the solid dispersion. In yet further embodiments, the composition contains about 1
0 to about 30% by weight of the solid dispersion. In yet further embodiments, the composition contains about 1 to about 20% by weight of the solid dispersion. In yet further embodiments, the composition contains about 1 to about 10% by weight of the solid dispersion.

Formulations containing the present solid dispersions can be administered in daily doses ranging from 0.1 mg to 1000 mg of bazedoxifene acetate to a person in need. Preferred
5 dose ranges vary from 10 mg/day to about 600 mg/day, more preferably from 10 mg/day to about 60 mg/day. The dosing can be either in a single dose or two or more divided doses per day. Such doses can be administered in any manner that facilitates the compound's entry into the bloodstream including orally, via implants, parenterally, vaginally, rectally, and transdermally.

0 Transdermal administrations include all administrations across the surface of the body and the inner linings of body passages including epithelial and mucosal tissues. Such administration may be in the form of a lotion, cream, colloid, foam, patch, suspension, and the like.

Oral formulations containing the present solid dispersions can comprise any
5 conventionally used oral forms, including tablets, capsules, buccal forms, troches, lozenges and oral liquids, suspensions, and the like. Capsules or tablets of containing the present solid dispersion can also be combined with mixtures of other active compounds or inert fillers and/or diluents such as the pharmaceutically acceptable starches (e.g. corn, potato or tapioca starch), sugars, artificial sweetening agents, powdered celluloses, such as crystalline and
0 microcrystalline celluloses, flours, gelatins, gums, etc.

Tablet formulations can be made by conventional compression, wet granulation, or dry granulation methods and utilize pharmaceutically acceptable diluents (fillers), binding agents, lubricants, disintegrants, suspending or stabilizing agents, including, but not limited to, magnesium stearate, stearic acid, talc, sodium lauryl sulfate, microcrystalline cellulose,

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carboxymethylcellulose calcium, polyvinylpyrrolidone, gelatin, alginic acid, acacia gum, xanthan gum, sodium citrate, complex silicates, calcium carbonate, glycine, dextrin, sucrose, sorbitol, dicalcium phosphate, calcium sulfate, lactose, kaolin, mannitol, sodium chloride, talc, dry starches and powdered sugar. Oral formulations used herein may utilize standard delay or time release formulations or spansules. Suppository formulations may be made from traditional materials, including cocoa butter, with or without the addition of waxes to alter the suppositories melting point, and glycerin. Water soluble suppository bases, such as polyethylene glycols of various molecular weights, may also be used.

Film coatings useful with the present formulations are known in the art and generally consist of a polymer (usually a cellulosic type of polymer), a colorant and a plasticizer. Additional ingredients such as wetting agents, sugars, flavors, oils and lubricants can be included in film coating formulations to impart certain characteristics to the film coat. The compositions and formulations herein may also be combined and processed as a solid, then placed in a capsule form, such as a gelatin capsule.

The filler or diluent can comprise any substance known in the art that is useful for the preparation of solid oral formulations. Pharmaceutically acceptable fillers can be selected from, for example, lactose, microcrystalline cellulose, sucrose, mannitol, calcium phosphate, calcium carbonate, powdered cellulose, maltodextrin, sorbitol, starch, xylitol, and the like.

The present formulations can also include disintegrant agents. These disintegrants can be selected from those known in the art, including pregelatinized starch, sodium starch glycolate and the like. Other useful disintegrants include croscarmellose sodium, crospovidone, starch, alginic acid, sodium alginate, clays (e.g. veegum or xanthan gum), cellulose floc, ion exchange resins, or effervescent systems, such as those utilizing food acids (such as citric acid, tartaric acid, malic acid, fumaric acid, lactic acid, adipic acid, ascorbic acid, aspartic acid, erythorbic acid, glutamic acid, and succinic acid) and an alkaline carbonate component (such as sodium bicarbonate, calcium carbonate, magnesium carbonate, potassium carbonate, ammonium carbonate, etc.). The disintegrant(s) useful herein can comprise from about 4% to about 40% of the composition by weight, preferably from about 15% to about 35%, more preferably from about 20% to about 35%.

Some components can have multiple functions in the formulations of this invention, acting e.g. as both a filler and a disintegrant, and its function in a specific formulation may be singular even though its properties may allow multiple functionality.

The pharmaceutical formulations and excipient systems herein can also contain an antioxidant or a mixture of antioxidants, such as ascorbic acid. Other antioxidants which can

be used include sodium ascorbate and ascorbyl palmitate, optionally in conjunction with an amount of ascorbic acid. An example range for the antioxidant(s) is from about 0.05% to about 15% by weight, from about 0.5% to about 15% by weight, or from about 0.5% to about 5% by weight. In some embodiments, the pharmaceutical formulations contain substantially no antioxidant.

Pharmaceutical compositions of the present solid dispersions can also be formulated with steroidal estrogens, such as conjugated estrogens, USP. The amount of bazedoxifene acetate used in the formulation can be adjusted according to the particular solid dispersion used, the amount and type of steroidal estrogen in the formulation as well as the particular therapeutic indication being considered. In general, the bazedoxifene acetate can be used in an amount sufficient to antagonize the effect of the particular estrogen to the level desired. The dose range of conjugated estrogens can be from about 0.3 mg to about 2.5 mg, about 0.3 mg to about 1.25 mg, or about 0.3 mg to about 0.625 mg. An example range for amount of bazedoxifene acetate in a combination formulation is about 10 mg to about 40 mg. For the steroidal estrogen mestranol, a daily dosage can be from about 1 μ G to about 150 μ G, and for ethynyl estradiol a daily dosage of from about 1 μ G to 300 μ G can be used. In some embodiments, the daily dose is between about 2 μ G and about 150 μ G.

An example oral formulation contains the present solid dispersion and the following excipient systems:

- a) a filler and disintegrant together comprising from about 1% to about 99% by weight (wt) of the total formulation, preferably between about 20% and about 85% of the formulation, of which from about 4% to about 45% by weight of the total formulation; and
- b) a lubricant comprising from about 0.2% to about 15% of the composition (wt), where the lubricant is magnesium stearate or other metallic stearates (e.g. calcium stearate or zinc stearate), fatty acid esters (e.g. sodium stearyl fumarate), fatty acids (e.g. stearic acid), fatty alcohols, glyceryl behenate, mineral oil, paraffins, hydrogenated vegetable oils, leucine, polyethylene glycols, metallic lauryl sulfates or sodium chloride.

The percentages listed above for the filler, disintegrant, and lubricants are based on final pharmaceutical composition. The remainder of the final composition is comprised of the solid dispersion and a pharmaceutically acceptable surface covering, such as a coating or capsule, as described herein. In some embodiments of this invention, the solid dispersion comprises from about 1 % to about 99 %, about 10 to about 95 %, or about 20 to about 90%

by weight, of the final composition; and the coating or capsule comprises up to about 8 %, by weight, of the formulation.

Additional numerous various excipients, dosage forms, dispersing agents and the like that are suitable for use in connection with the solid dispersions of the invention are known in the art and described in, for example, *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, Pa., 1985, which is incorporated herein by reference in its entirety.

Methods

As described in U.S. Pat. No. 5,998,402, bazedoxifene and salts thereof are selective estrogen agonists with affinity for the estrogen receptor. Unlike other types of estrogen agonists, bazedoxifene and salts thereof are antiestrogenic in the uterus and can antagonize the trophic effects of estrogen agonists in uterine tissues. Accordingly, the solid dispersions of the invention, and compositions containing the same, can find many uses related to treating disease states or syndromes associated with an estrogen deficiency or an excess of estrogen. They may also be used in methods of treatment for diseases or disorders which result from proliferation or abnormal development, actions or growth of endometrial or endometrial-like tissues.

Bazedoxifene acetate has the ability to behave like an estrogen agonist by lowering cholesterol and preventing bone loss. Accordingly, the solid dispersion is useful for treating many maladies which result from estrogen effects and estrogen excess or deficiency including osteoporosis, prostatic hypertrophy, male pattern baldness, vaginal and skin atrophy, acne, dysfunctional uterine bleeding, endometrial polyps, benign breast disease, uterine leiomyomas, adenomyosis, ovarian cancer, infertility, breast cancer, endometriosis, endometrial cancer, polycystic ovary syndrome, cardiovascular disease, contraception, Alzheimer's disease, cognitive decline and other CNS disorders, as well as certain cancers including melanoma, prostate cancer, cancers of the colon, CNS cancers, among others. Additionally, the solid dispersion can be used for contraception in pre-menopausal women, as well as hormone replacement therapy in post-menopausal women (such as for treating vasomotor disturbances such as hot flush) or in other estrogen deficiency states where estrogen supplementation would be beneficial. It can also be used in disease states where amenorrhea is advantageous, such as leukemia, endometrial ablations, chronic renal or hepatic disease or coagulation diseases or disorders.

The solid dispersions of the invention can also be used in methods of inhibition of bone loss, which can result from an imbalance in an individual's formation of new bone tissues and the resorption of older tissues, leading to a net loss of bone. Such bone depletion results in a range of individuals, particularly in post-menopausal women, women who have undergone bilateral oophorectomy, those receiving or who have received extended corticosteroid therapies, those experiencing gonadal dysgenesis, and those suffering from Cushing's syndrome. Special needs for bone, including teeth and oral bone, replacement can also be addressed using the present solid dispersion in individuals with bone fractures, defective bone structures, and those receiving bone-related surgeries and/or the implantation of prosthesis. In addition to the problems described above, the solid dispersion can be used in treatments for osteoarthritis, hypocalcemia, hypercalcemia, Paget's disease, osteomalacia, osteomalacia, multiple myeloma and other forms of cancer having deleterious effects on bone tissues.

Methods of treating the diseases and syndromes listed herein are understood to involve administering to an individual in need of such treatment a therapeutically effective amount of the solid dispersion of the invention, or composition containing the same. As used herein, the term "treating" in reference to a disease is meant to refer to preventing, inhibiting and/or ameliorating the disease.

As used herein, the term "individual" or "patient," used interchangeably, refers to any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans.

As used herein, the phrase "therapeutically effective amount" refers to the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response in a tissue, system, animal, individual or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes one or more of the following:

(1) preventing the disease; for example, preventing a disease, condition or disorder in an individual that may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease;

(2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., arresting or slowing further development of the pathology and/or symptomatology); and

X

(3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual that is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (i.e., reversing the pathology and/or symptomatology).

The invention will be described in greater detail by way of specific examples. The following examples are offered for illustrative purposes, and are not intended to limit the invention in any manner. Those of skill in the art will readily recognize a variety of noncritical parameters which can be changed or modified to yield essentially the same results.

EXAMPLES

0 Example 1: Preparation of Bazedoxifene Acetate Solid Dispersions

Solid dispersion formulations of bazedoxifene acetate were prepared according to the procedures set forth below. The dispersions were all found to be amorphous (non crystalline) by X-ray powder diffraction, which is in contrast to a physical mixture of BZA and dispersing reagent which was shown to contain crystalline BZA.

5

Example 1.1 Bazedoxifene Acetate Solid Dispersion with PVP (1:1 w/w)

To a solution of 3.0004 g of PVP K17 (PLASDONE, Povidone USP, Polyvinylpyrrolidone, ISP Technologies Inc.) in 55 mL of ethanol (EM Science) was added 3.0891 g of bazedoxifene acetate. Another 20 mL of ethanol was added and the resulting suspension was warmed to 65 °C for 5 minutes until a clear brown solution was observed. Solvents were evaporated under reduced pressure at room temperature to dryness. The yellow flakes were collected and grinded with mortar and pestle to give 5.6 g of brown-creamy powder.

25 Example 1.2: Bazedoxifene Acetate Solid Dispersion with PVP (1:1 w/w)

To a solution of 2.1091 g of PVP K17 (PLASDONE, Povidone USP, Polyvinylpyrrolidone, ISP Technologies Inc.) in 4 mL of ethanol was added 2.1028 g of bazedoxifene acetate. Another 2 mL of ethanol was added to form a milky suspension. Another 44 mL of ethanol was added (total of 50 mL) and the mixture was heated to 65 °C for 5 min to make a yellow solution. Solvents were evaporated under reduced pressure at room temperature to dryness to give a yellow-brown solid.

30

Example 1.3: Bazedoxifene Acetate Solid Dispersion with PVP (1:1 w/w)

To a solution of 3.00519 g of PVP K17 in 15 mL of ethanol was added 3.00671 g of bazedoxifene acetate with mixing. Another 60 mL of ethanol was added and the mixture was warmed to 65 °C for 5 minutes to get a clear yellow-brown solution. Solvents were evaporated under reduced pressure at room temperature to dryness. The yellow-brown solid was grinded with mortar and pestle to give yellow-creamy fine powder.

Example 1.4: Bazedoxifene Acetate Solid Dispersion with PVP (5% w/w active)

To a solution of 0.9509 g of PVP K-17 (PLASDONE, Povidone USP, Polyvinylpyrrolidone, ISP Technologies Inc.) in 1 mL of ethanol (EM Science) was added 0.0499 g of bazedoxifene acetate. A thick yellow solution was formed and 0.5 mL of ethanol was added to the mixture to form a yellow viscous solution. Solvents were evaporated under reduced pressure at room temperature to dryness. The yellow solid material was collected and grinded with mortar and pestle.

Example 1.5: Bazedoxifene Acetate Solid Dispersion with Poloxamer 188 (5% w/w active)

To a solution of 0.9503 g of Poloxamer 188 (BASF; polyoxypropylene-polyoxyethylene copolymer) in 1.5 mL of ethanol and 0.5 mL of de-ionized water, was added 0.0503 g of bazedoxifene acetate to form a colorless solution. Solvents were evaporated under reduced pressure at room temperature to dryness. The creamy solid material was collected.

Example 1.6: Bazedoxifene Acetate Solid Dispersion with Poloxamer 188 (5% w/w active)

To Poloxamer 188 (0.9540 g; BASF) melted at 60 °C was added 0.0502 g of bazedoxifene acetate with mixing to form a clear liquid. The liquid was cooled to room temperature.

Example 1.7: Bazedoxifene Acetate Solid Dispersion with PEG 1450 (5% w/w active)

To a solution of 0.9522 g of PEG 1450 (Union Carbide) in 1.5 mL of ethanol heated to 40 °C was added 0.0510 g of bazedoxifene acetate to form a clear solution. Solvents were evaporated under reduced pressure to dryness to form white waxy material.

Example 1.8: Bazedoxifene Acetate Solid Dispersion with PEG 1450 (5% w/w active)

To 0.9448 g of melted PEG 1450 at 70 °C was added 0.0504 g of bazedoxifene acetate with mixing to form a clear liquid. The liquid was cooled to room temperature.

5 Example 2: Equilibrium Solubility of Bazedoxifene Acetate Solid Dispersions

A few milligrams of each of the dispersions of Examples 1.1 to 1.8 were placed in 2 mL of 0.0005 M acetic acid, held at room temperature (about 20-26 °C), rotated at 50 rotation/min for 18 hours, and filtered through 0.45 µm (Nylon Acrodisc) filter. After 10x dilution with mobile phase, 10 µL was injected to HPLC. The HPLC was carried out with the

3 following parameters:

Column: Inertsil 5 ODS-2 150x 4.6 mm

Flow rate: 1.5 mL/min

Detector: UV at 220 nm

Temperature: Ambient

5 Mobile Phase: 320 mL of acetonitrile and 680 mL of a solution containing 6.8 g of monobasic potassium phosphate in 2 L water, pH adjusted to 3.0 with 85% phosphoric acid).

Results are provided in Table II below. Bazedoxifene solid dispersion with PVP (5% w/w active), gave the highest equilibrium solubility.

3 **Table II**

Dispersion Example No.	Equilibrium Solubility
1.1 (ethanol; PVP; 1:1 w/w)	13.9 mg/mL
1.4 (ethanol; PVP; 5% w/w active)	20.1 mg/mL
1.5 (ethanol; Poloxamer 188; 5% w/w active)	2.9 mg/mL
1.6 (melt; Poloxamer 188; 5% w/w active)	8.1 mg/mL
1.7 (ethanol; PEG 1450; 5% w/w active)	2.3 mg/mL
1.8 (melt; PEG 1450; 5% w/w active)	5.3 mg/mL

Example 3: Intrinsic Dissolution Rate of Bazedoxifene Acetate versus Bazedoxifene Acetate Solid Dispersion with PVP (1:1 w/w)

5 Pellets of each of bazedoxifene acetate and bazedoxifene acetate solid dispersion (PVP; 1:1 w/w, see Example 1) were prepared by compressing 100 mg of each in a die

(Wood's Apparatus) at 1000 psi pressure for 1 minute with a Carver press. The pellets were then fitted into a dissolution apparatus which resulted in a single exposed surface of pellet with a surface area of 0.5 cm². The dissolution rate in 900 mL of 0.0005 M acetic acid was determined using the USP method (apparatus 2) with a rotation of 50 rpm at 37 °C. From the concentration of mg/mL (by HPLC) versus time profile, the apparent intrinsic dissolution rate was determined.

The intrinsic dissolution rates of bazedoxifene acetate and bazedoxifene acetate solid dispersion with PVP (1:1 w/w) were 0.018 mg/cm²-min and 0.18 mg/cm²-min, respectively. The bazedoxifene acetate solid dispersion is about 10 times faster than the non-dispersed material. Results are shown in Figure 1.

Example 4: Preliminary Pharmacokinetic Analysis of Bazedoxifene Acetate Solid Dispersions in Dogs

Bioavailability of bazedoxifene acetate formulations was evaluated in dogs. Six female dogs (6.2-10.5 kg) were divided into three groups, 2 dogs per group. To each group of dogs, a single dose equivalent to 10 mg of bazedoxifene acetate was administered orally as one of three formulations:

Formulation A) 1/2 of one 20 mg tablet (Table III);

Formulation B) one 10 mg capsule of bazedoxifene acetate solid dispersion according to Ex. 1.1 where the capsule has the same formula as for formulation A but without SLS (Table IV); and

Formulation C) one 10 mg capsule containing bazedoxifene acetate solid dispersion according to Ex. 1.1 (i.e., without excipients) (Table V).

The study was conducted as a randomized, crossover study. The formulations were administered following an overnight fast, and food was offered following the four hour blood sample. Blood samples were drawn at 0 (predose), 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hours after dosing; and plasma was separated and assayed for bazedoxifene acetate content.

The compositions of batches A, B and C are provided below in Tables III, IV, and V, respectively. Capsules were prepared by mixing components in bag blends and filling the capsule manually (a Capsogel #2 CS, white opaque capsule).

Results are provided in Table VI and Figure 2. As can be seen from the AUC (area under curve) data, bioavailability of bazedoxifene acetate when formulated as a dispersion was found to be about 50% higher than for non-dispersion formulations.

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Table III
Formulation A

Ingredient	% w/w	mg/tablet
bazedoxifene acetate, micronized	4.843	20.00
lactose, NF	35.208	145.40
microcrystalline cellulose (Avicel PH 101)	33.898	140.00
pregelatinized starch, NF (Starch 1500)	13.559	56.00
sodium lauryl sulfate (SLS)	1.453	6.00
sodium starch glycolate, NF	5.811	24.00
ascorbic acid	1.453	6.00
silicon dioxide (Syloid 244 FP)	0.145	0.60
magnesium stearate, NF	0.484	2.00
White Opadry 1	3.148	13.00
Total	100.00	413.00

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Table IV
Formulation B

Ingredient	% w/w	mg/capsule	g/16 gram batch
bazedoxifene acetate solid dispersion of Example 1.1 (45.191 % use at value)	11.23	22.13	1.6850
lactose, NF	31.00	61.07	4.6500
microcrystalline cellulose (Avicel PH 101)	35.53	70.00	5.3299
pregelatinized starch, NF (Starch 1500)	14.21	28.00	2.1320
sodium starch glycolate, NF	8.09	12.00	0.9137
ascorbic acid	1.52	3.00	0.2284
silicon dioxide (Syloid 244 FP)	0.15	0.30	0.0228
magnesium stearate, NF	0.25	0.50	0.0381
Total	100.00	197.00	15.0000

5

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Table V
Formulation C

Ingredient	% w/w	mg/capsule
bazedoxifene acetate solid dispersion of Example 1.1 (45.191 % use at value)	100	22.13

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Table VI
Mean (%CV) Bazedoxifene Acetate Pharmacokinetic Parameters in Dogs Following
Single Dose Oral Administration Equivalent to 10 mg Bazedoxifene Acetate

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Parameter	Formulation A Tablet	Formulation B Solid Dispersion Capsule without SLS	Formulation C Solid Dispersion Capsule without excipients
AUC ₀₋₂₄ (ng·hr/mL)	124 (19)	188 (52)	173 (56)
C _{max} (ng/mL)	21.8 (43)	26.0 (37)	16.9 (57)
t _{max} (hr)	2.33 (120)	1.42 (65)	2.42 (59)

5

Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims. Each of the publications and, references, including books and patents, cited in the present application is incorporated herein by reference in its entirety.

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What is claimed is:

1. A solid dispersion comprising bazedoxifene acetate dispersed in a dispersing agent.
2. The solid dispersion of claim 1 wherein said bazedoxifene acetate in said solid dispersion is amorphous.
3. The solid dispersion of claim 1 or 2 wherein said dispersing agent comprises a cellulose, hyaluronate, alginate, polysaccharide, heteropolysaccharide, poloxamers, poloxamines, ethylene vinyl acetate, polyethylene glycol, dextran, polyvinylpyrrolidone, chitosan, polyvinylalcohol, propylene glycol, polyvinylacetate, phosphatidylcholines, miglyol, polylactic acid, polyhydroxybutyric acid, mixtures of two or more thereof or copolymers thereof.
4. The solid dispersion of claim 3 wherein said dispersing agent comprises polyvinylpyrrolidone, poloxamer or polyethylene glycol.
5. The solid dispersion of claim 4 wherein said dispersing agent comprises polyvinylpyrrolidone.
6. The solid dispersion of claim 4 wherein said dispersing agent comprises Poloxamer 188.
7. The solid dispersion of claim 4 wherein said dispersing agent comprises PEG 1450.
8. The solid dispersion of any one of claims 1 to 7 wherein the weight ratio of bazedoxifene acetate to dispersing agent is about 1:99 to about 75:25.
9. The solid dispersion of any one of claims 1 to 7 wherein the weight ratio of bazedoxifene acetate to dispersing agent is about 1:99 to about 60:40.
10. The solid dispersion of any one of claims 1 to 7 wherein the weight ratio of bazedoxifene acetate to dispersing agent is about 1:99 to about 10:90.

11. The solid dispersion of any one of claims 1 to 7 wherein the weight ratio of bazedoxifene acetate to dispersing agent is about 5:95.
12. The solid dispersion of any one of claims 1 to 7 wherein the weight ratio of bazedoxifene acetate to dispersing agent is about 40:60 to about 60:40.
13. The solid dispersion of any one of claims 1 to 7 wherein the weight ratio of bazedoxifene acetate to dispersing agent is about 1:1.
14. The solid dispersion of any one of claims 1 to 7 having an equilibrium solubility in 0.0005 M acetic acid at a temperature of about 20 to about 26 °C of at least about 8 mg/mL.
15. The solid dispersion of any one of claims 1 to 7 wherein a dosage form comprising about 10 mg total of bazedoxifene acetate in the form of said solid dispersion is characterized by an AUC₀₋₂₄ greater than about 140 ng·hr/mL when orally administered to mammal.
16. The solid dispersion of any one of claims 1 to 7 wherein a dosage form comprising about 10 mg total of bazedoxifene acetate in the form of said solid dispersion is characterized by:
- a) an AUC₀₋₂₄ of about 140 to about 250 ng·hr/mL;
 - b) a C_{max} of about 12 to about 30 ng/mL; and
 - c) a t_{max} of about 1.0 to about 3.5 hr;
- when orally administered to mammal.
17. A method of preparing the solid dispersion of any one of claims 1 to 16 comprising:
- a) combining bazedoxifene acetate and said dispersing agent in solution, wherein said solution comprises a solvent; and
 - b) removing said solvent to yield said solid dispersion.
18. The method of claim 17 wherein said solvent is an organic solvent.
19. The method of claim 18 wherein said organic solvent comprises an alcohol.
20. The method of claim 19 wherein said alcohol comprises ethanol.

21. A solid dispersion prepared by the method of any one of claims 17 to 20.
22. A method of preparing the solid dispersion of any one of claims 1 to 16 comprising:
 - a) combining bazedoxifene acetate with melted dispersing agent to form a liquid mixture; and
 - b) solidifying said liquid mixture to form said solid dispersion.
23. The method of claim 22 wherein said melted dispersing agent is prepared by heating said dispersing agent to a temperature above about 30 °C.
24. The method of claim 22 or 23 wherein said solidifying is carried out by cooling said liquid mixture to a temperature at or below about 25 °C.
25. A solid dispersion prepared by the method of any one of claims 22 to 24.
26. A composition comprising the solid dispersion of anyone of claims 1 to 16, 21 or 25 and a pharmaceutically acceptable carrier.
27. The composition of claim 26 comprising about 1 to about 99 % by weight of said solid dispersion.
28. The composition of claim 26 comprising about 1 to about 50% by weight of said solid dispersion.
29. The composition of claim 26 comprising about 1 to about 30% by weight of said solid dispersion.
30. The composition of claim 26 comprising about 1 to about 20% by weight of said solid dispersion.
31. The composition of claim 26 comprising about 1 to about 10% by weight of said solid dispersion.

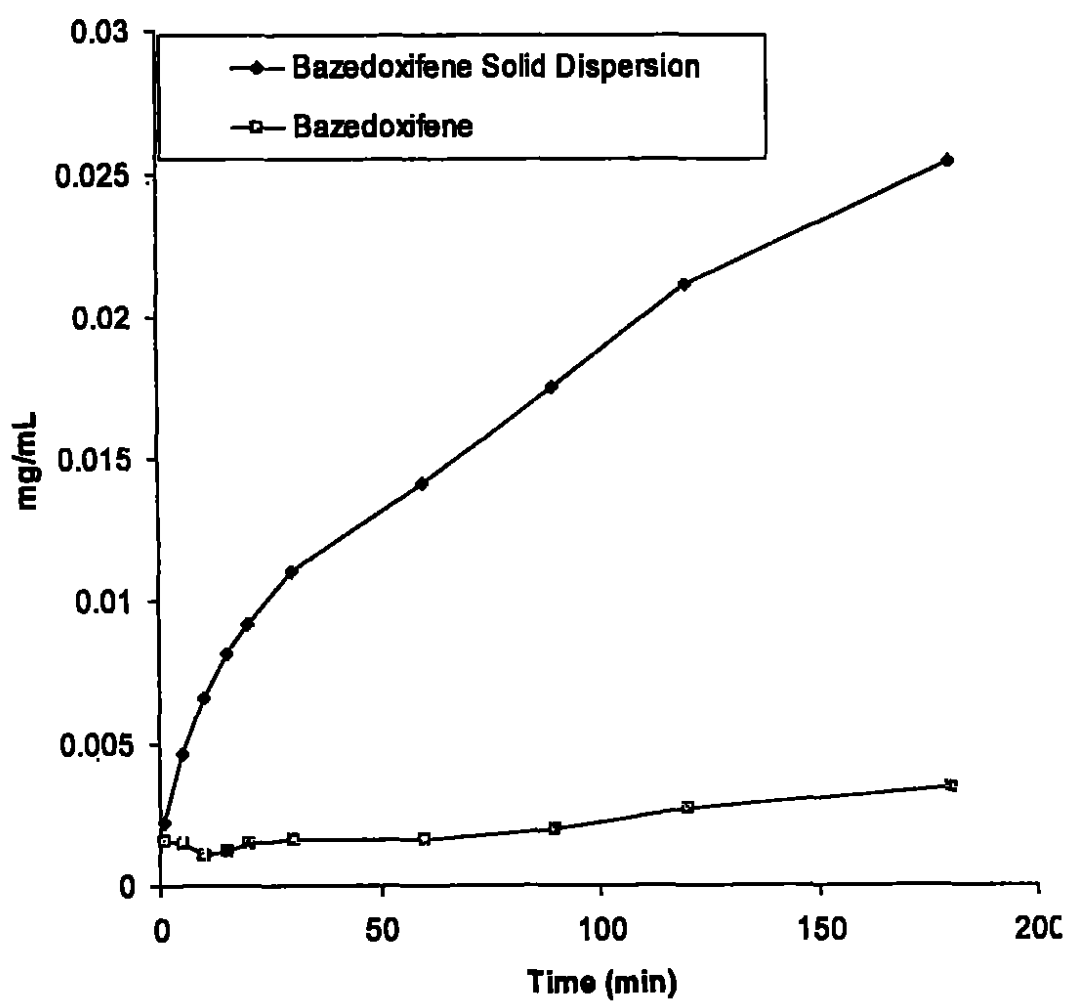
32. A dosage form comprising the solid dispersion of any one of claims 1 to 16, 21 or 25.
33. The dosage form of claim 32 wherein said dosage form is for oral, transdermal, or implantation administration.
34. The dosage form of claim 32 wherein said dosage form is a tablet or capsule.
35. A method of treating a mammal having a disease or syndrome associated with estrogen deficiency or excess of estrogen comprising administering to said mammal a therapeutically effective amount of the solid dispersion of any one of claims 1 to 16, 21 or 25.
36. A method of treating a mammal having a disease or disorder associated with proliferation or abnormal development of endometrial tissues comprising administering to said mammal a therapeutically effective amount of the solid dispersion of any one of claims 1 to 16, 21 or 25.
37. A method of lowering cholesterol in a mammal comprising administering to said mammal a therapeutically effective amount of the solid dispersion of any one of claims 1 to 16, 21 or 25.
38. A method of inhibiting bone loss in a mammal comprising administering to said mammal a therapeutically effective amount of the solid dispersion of any one of claims 1 to 16, 21 or 25.
39. A method of treating breast cancer in a mammal comprising administering to said mammal a therapeutically effective amount of the solid dispersion of any one of claims 1 to 16, 21 or 25.
40. A method of treating postmenopausal woman for one or more vasomotor disturbances comprising administering to said postmenopausal woman a therapeutically effective amount of the solid dispersion of any one of claims 1 to 16, 21 or 25.
41. The method of claim 40 wherein said vasomotor disturbance is hot flush.

42. The use of a solid dispersion according to any one of claims 1 to 16, 21 or 25 in the manufacture of a medicament for the treatment of a disease or syndrome associated with estrogen deficiency or excess of estrogen, a disease or disorder associated with proliferation or abnormal development of endometrial tissues, lowering cholesterol, inhibiting bone loss, or treating breast cancer.

1/2

FIGURE 1

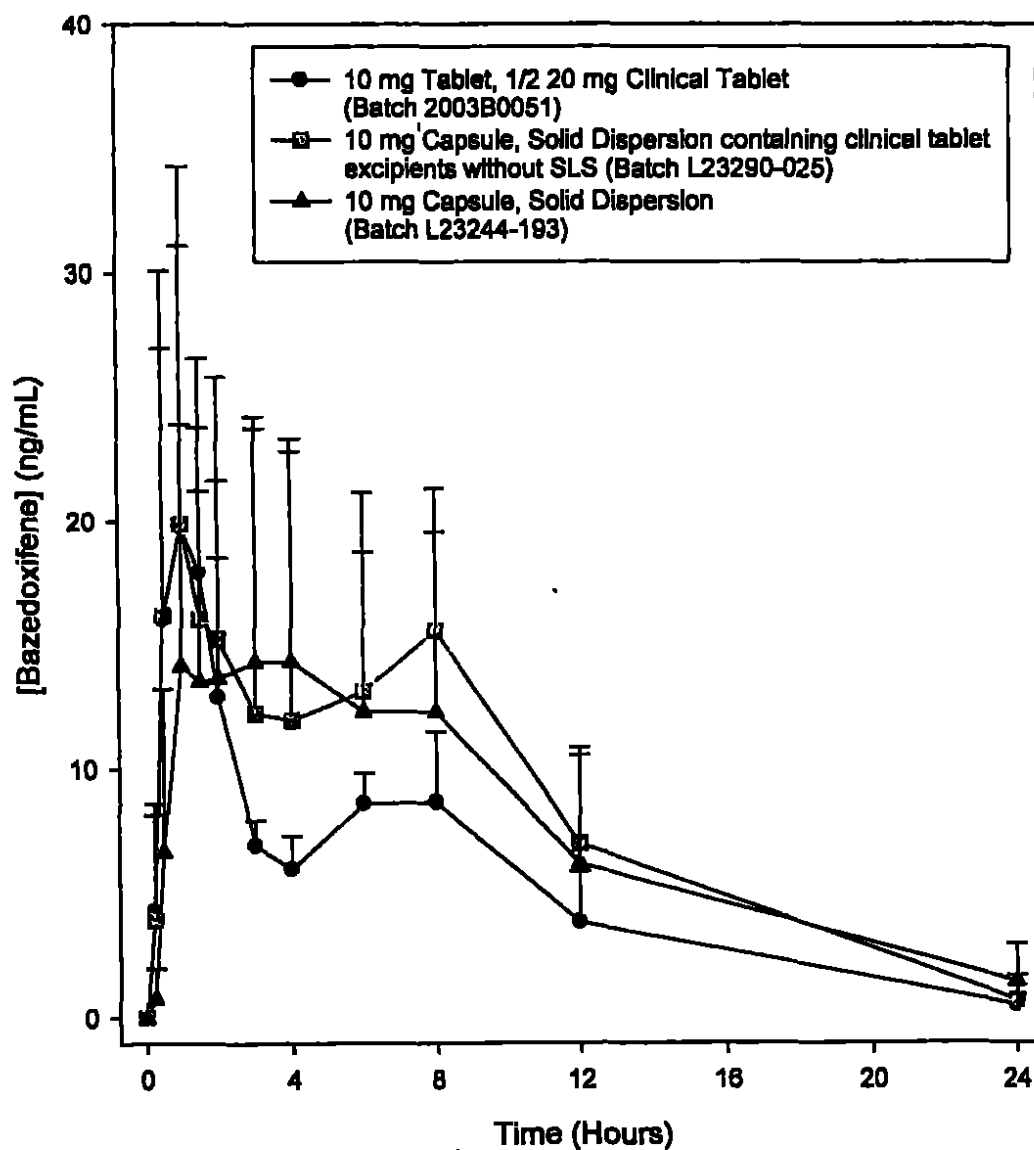
**BZA, Intrinsic Dissolution in 0.0005M Acetic acid
at 37C (average)**



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FIGURE 2

Mean Plasma Bazedoxifene Levels in Dogs (n=6)
Following Oral Administration of 10 mg Bazedoxifene



FORMULACIONES DE DISPERSIONES SOLIDAS DE ACETATO DE
BAZEDOXIFENO

CAMPO DE LA INVENCION

5

La presente invención se refiere a dispersiones sólidas y composiciones de las mismas del modulador selectivo del receptor de estrógenos, ácido 1-[4-(2-azepan-1-il-etoxi)-bencil]-2-(4-hidroxifenil)-3-metil-1H-indol-5-ol acético (acetato de bazedoxifeno).

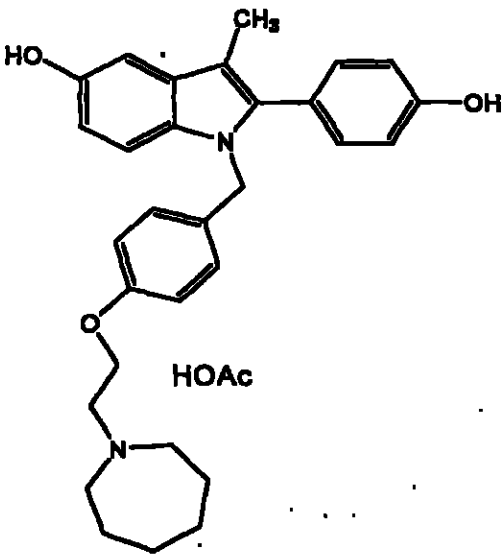
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ANTECEDENTES DE LA INVENCION

El acetato de bazedoxifeno (ácido 1-[4-(2-azepan-1-il-etoxi)-bencil]-2-(4-hidroxifenil)-3-metil-1H-indol-5-ol acético), que tiene la fórmula química mostrada a continuación:

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pertenece a la clase de fármacos típicamente referida como moduladores selectivos del receptor de estrógenos (SERM). Consistente con su clasificación, el bazedoxifeno demuestra afinidad para receptores de estrógeno (ER) pero muestra efectos estrogénicos selectivos de tejido. Por ejemplo, el acetato de bazedoxifeno demuestra poca o ninguna estimulación

de respuesta uterina en modelos preclínicos de estimulación uterina. De manera contraria, el acetato de bazedoxifeno demuestra un efecto de tipo agonista de estrógeno en la prevención de pérdida ósea y reducción de colesterol en un modelo de osteopenia de rata ovariectomizada. En una línea
5 de células MCF-7 (línea celular de cáncer de mama en humanos), el acetato de bazedoxifeno se comporta como un antagonista de estrógenos. Estos datos demuestran que el acetato de bazedoxifeno es estrogénico en parámetros lipídicos cardiovasculares y de hueso y antiestrogénico en tejido uterino y mamario y por lo tanto, tiene el potencial de tratar un número de
10 diferentes estados de enfermedad o de enfermedades en donde está implicado el receptor de estrógenos.

Las patentes de E.U.A. Nos. 5,998,402 y 6,479,535 informan la preparación de acetato de bazedoxifeno. La preparación sintética de acetato de bazedoxifeno también ha aparecido en la bibliografía general. Ver, por
15 ejemplo, Miller et al., J. Med. Chem., 2001, 44, 1654-1657. Una descripción adicional de la actividad biológica del fármaco ha aparecido también en la bibliografía general (por ejemplo, Miller, et al. Drugs of the Future, 2002, 27(2), 117-121). Las formulaciones de acetato de bazedoxifeno también se informan en la publicación de solicitud de patente de E.U.A. No. 2002/0031548 A1.

20 Debido a que se busca de manera consistente formulaciones de fármaco que muestren, por ejemplo, biodisponibilidad mejorada, existe la continua necesidad de nuevas formulaciones de moléculas de fármaco existentes. Las dispersiones sólidas de acetato de bazedoxifeno y composiciones que contienen el mismo aquí descritas ayuda a satisfacer éstas y otras
25 necesidades.

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BREVE DESCRIPCION DE LA INVENCION

En algunas modalidades, la presente invención provee una dispersión sólida que comprende acetato de bazedoxifeno disperso en un agente de dispersión.

- 5 En algunas modalidades, la presente invención provee una composición que comprende la dispersión sólida descrita en la presente y un vehículo farmacéuticamente aceptable.

En algunas modalidades, la presente invención provee una forma de dosificación que comprende la dispersión sólida descrita en la presente.

- 10 En algunas modalidades, la presente invención provee un método para preparar la dispersión sólida descrita en la presente, que comprende: a) combinar acetato de bazedoxifeno y un agente de dispersión en solución; y b) remover solvente para producir la dispersión sólida.

- En algunas modalidades, la presente invención provee un método para
15 preparar la dispersión sólida descrita en la presente, que comprende: a) combinar acetato de bazedoxifeno con agente de dispersión fundido para formar una mezcla líquida; y b) solidificar la mezcla líquida para formar la dispersión sólida.

- En algunas modalidades, la presente invención provee un método para tratar
20 a un mamífero que tenga una enfermedad o síndrome relacionado con deficiencia de estrógenos o exceso de estrógenos, que comprende administrar al mamífero una cantidad terapéuticamente efectiva de la dispersión sólida descrita en la presente.

- En algunas modalidades, la presente invención provee un método para tratar
25 a un mamífero que tenga una enfermedad o trastorno asociado con proliferación o desarrollo anormal de tejidos endometriales, que comprende administrar al mamífero una cantidad terapéuticamente efectiva de la dispersión sólida descrita en la presente.

En algunas modalidades, la presente invención provee un método para reducir el colesterol en un mamífero que comprende administrar al mamífero una cantidad terapéuticamente efectiva de la dispersión sólida descrita en la presente.

- 5 En algunas modalidades, la presente invención provee un método para inhibir pérdida ósea en un mamífero, que comprende administrar al mamífero una cantidad terapéuticamente efectiva de la dispersión sólida descrita en la presente.

- En algunas modalidades, la presente invención provee un método para tratar
10 cáncer de mama en un mamífero, que comprende administrar al mamífero una cantidad terapéuticamente efectiva de la dispersión sólida descrita en la presente.

- En algunas modalidades, la presente invención provee un método para tratar a mujeres postmenopáusicas para una o más alteraciones vasomotoras, que
15 comprende administrar a la mujer postmenopáusica una cantidad terapéuticamente efectiva de la dispersión sólida descrita en la presente.

La presente invención provee adicionalmente las dispersiones sólidas de la invención para uso en terapia.

- La presente invención provee además el uso de las dispersiones sólidas de la
20 invención para la preparación de un medicamento.

BREVE DESCRIPCION DE LOS DIBUJOS

- La figura 1 muestra una gráfica que compara las velocidades de disolución de
25 acetato de bazedoxifeno como un sólido cristalino y como una dispersión sólida con PVP de acuerdo con el ejemplo 3; y

la figura 2 muestra una gráfica que compara la biodisponibilidad de acetato de bazedoxifeno en perros para formulaciones que contienen formulaciones de dispersión y de no dispersión de acuerdo con el ejemplo 4.

DESCRIPCION DETALLADA DE LA INVENCION

La presente invención provee, *inter alia*, dispersiones sólidas de acetato de
5 bazedoxifeno (BZA) y composiciones de las mismas que tienen propiedades
mejoradas en cuanto a la solubilidad, biodisponibilidad y similares. Las
dispersiones sólidas de la invención tienen una solubilidad y biodisponibilidad
incrementada en comparación, por ejemplo, con BZA cristalino o BZA
microcristalino. La biodisponibilidad incrementada relacionada con
10 dispersiones sólidas de BZA tienen numerosas ventajas que incluyen permitir
la administración de dosificaciones más bajas, reduciendo de esta manera las
oportunidades de efectos secundarios adversos y reduciendo la variabilidad
del sujeto.

Las composiciones de la invención contienen, por ejemplo, BZA disperso en
15 un agente de dispersión. En algunas modalidades, la relación en peso de BZA
a agente de dispersión es de aproximadamente 1:99 a aproximadamente
99:1. En algunas modalidades, la relación en peso de BZA a agente de
dispersión es de aproximadamente 1:99 a aproximadamente 75:25 o
aproximadamente 1:99 a aproximadamente 60:40. En modalidades
20 adicionales, la relación en peso de BZA a agente de dispersión es de
aproximadamente 1:99 a aproximadamente 15:85; aproximadamente 1:99 a
aproximadamente 10:90; o aproximadamente 1:99 a aproximadamente 5:95.
En otras modalidades, la relación en peso de BZA a agente de dispersión es
aproximadamente 5:95. En modalidades adicionales, la relación en peso de
25 BZA a agente de dispersión es aproximadamente 25:75 a aproximadamente
75:25, aproximadamente 40:60 a aproximadamente 60:40 o aproximadamente
1:1. En algunas modalidades, la relación en peso de BZA a agente de
dispersión es aproximadamente 1:1.

El "agente de dispersión", como se utiliza en la presente, se refiere a cualquier sustancia o mezcla de sustancias que actúa como un medio de dispersión para moléculas/partículas de acetato de bazedoxifeno. El agente de dispersión por lo regular está compuesto de una sustancia farmacéuticamente aceptable que no interfiere sustancialmente con la acción farmacéutica de BZA. La frase "farmacéuticamente aceptable" se emplea en la presente para referirse a aquellas sustancias las cuales son, dentro del alcance del sano juicio médico, adecuadas para uso en contacto con los tejidos de seres humanos y animales sin excesiva toxicidad, irritación, respuesta alérgica, u otro problema o complicación, proporcional con una relación razonable de beneficio/riesgo. En algunas modalidades, el agente de dispersión es un sólido a temperatura ambiente (por ejemplo, aproximadamente 22°C). En modalidades adicionales, el agente de dispersión se funde a una temperatura entre aproximadamente 30 y 100°C. En modalidades adicionales, el agente de dispersión es soluble en un solvente orgánico.

Los ejemplos no limitativos de agentes de dispersión adecuados incluyen polímeros tales como celulosas (por ejemplo, carboximetilcelulosas, metilcelulosas, hidroxipolipilcelulosas, hidroxipropilmetilcelulosas); hialuronatos; alginatos; polisacáridos, heteropolisacáridos (pectinas); poloxámeros; poloxaminas; etilenos-acetatos de vinilo; polietilenglicoles; dextranos; polivinilpirrolidonas; quitosanos; alcoholes polivinílicos; propilenglicoles; acetatos de polivinilo; fosfatidilcolinas (lecitinas); miglioles; ácido poliláctico; ácido polihidroxibutírico; mezclas de dos o más de los mismos, copolímeros de los mismos, derivados de los mismos, y similares. Otros ejemplos de agentes de dispersión incluyen sistemas de copolímero tales como polietilenglicol-ácido poliláctico (PEG-PLA), polietilenglicol-ácido polihidroxibutírico (PEG-PHB), polivinilpirrolidona-alcohol polivinílico (PVP-PVA), y copolímeros derivados tales como copolímeros de derivados N-vinil purina (o pirimidina) y N-vinilpirrolidona.

En algunas modalidades, el agente de dispersión contiene polivinilpirrolidona (PVP) o derivados de la misma. PVP es una poliamida que forma complejos con una amplia variedad de sustancias y se considera que es química y fisiológicamente inerte. Ejemplos de PVP adecuadas incluyen

5 polivinilpirrolidonas que tienen un peso molecular promedio de aproximadamente 10,000 a aproximadamente 50,000. En algunas modalidades, la polivinilpirrolidona tiene un peso molecular promedio de aproximadamente 10,000 a aproximadamente 20,000. En modalidades adicionales, la polivinilpirrolidona tiene un peso molecular de

10 aproximadamente 15,000 a aproximadamente 20,000. Un ejemplo adecuado de PVP es PVP K-17 (PLASDONE povidona, ISP Technologies, Ltd). En algunas modalidades, el agente de dispersión consiste esencialmente en PVP o su derivado.

En algunas modalidades, el agente de dispersión contiene un copolímero de

15 bloque de etileno y propilenglicol, con frecuencia referido como un poloxámero. Algunos ejemplos adecuados de poloxámeros incluyen Poloxámero 188 (LUTROL F-68, BASF), Poloxámero 407 (LUTROL F 127, BASF), y similares. En algunas modalidades, el agente de dispersión es Poloxámero 188.

20 En algunas modalidades, el agente de dispersión contiene un polietilenglicol (PEG). Los PEG adecuados incluyen PEG 200, 300, 400, 600, 1000, 1450, 3350, 4000, 6000, 8000, 10000, 20000, mezclas de los mismos y similares. En algunas modalidades, el agente de dispersión es PEG 1450.

Las dispersiones de BZA de la invención se pueden realizar a través de

25 cualquiera de numerosos métodos que dan como resultado, por ejemplo, una dispersión sólida de BZA amorfo. En un método ejemplar, BZA (en cualquier forma, por ejemplo, cristalina, amorfa, etc.) y el agente de dispersión se pueden disolver en un solvente de dispersión (junto, o por separado y luego combinarse) en la relación en peso deseada y posteriormente se remueve el

solvente de dispersión para producir la dispersión sólida deseada. El solvente de dispersión puede ser un solvente acuoso o un solvente orgánico. Los solventes orgánicos adecuados incluyen alcoholes, éteres, hidrocarburos, hidrocarburos halogenados, nitrilos, mezclas de los mismos, y similares. En algunas modalidades, el solvente orgánico es un solvente volátil tal como metanol, etanol, isopropanol, dietil éter, pentano, hexano, benceno, diclorometano, acetonitrilo, mezclas de los mismos y similares. En algunas modalidades, el solvente orgánico es un alcohol tal como metanol, etanol, n-propanol, isopropanol, mezclas de los mismos y similares. En algunas modalidades, el solvente orgánico es etanol.

En otro ejemplo, BZA y el agente de dispersión se pueden combinar en la relación en peso deseada cuando cualquiera o ambos del BZA y agente de dispersión está o están en forma líquida (por ejemplo, un material fundido), y posteriormente la mezcla líquida se solidifica para formar la dispersión sólida deseada. De acuerdo con tales modalidades, el BZA y el agente de dispersión se pueden combinar cuando por lo menos uno del BZA y el agente de dispersión está fundido. La mezcla resultante posteriormente se solidifica mediante enfriamiento a una temperatura suficiente para solidificar la mezcla. En algunas modalidades, la mezcla se enfría a aproximadamente 25°C o menos. En algunas modalidades, el BZA se combina con agente de dispersión fundido y la mezcla resultante se enfría a una temperatura inferior al punto de fusión de la mezcla para formar la dispersión sólida. En modalidades adicionales, el agente de dispersión se calienta a una temperatura entre aproximadamente 30 y 200°C, entre aproximadamente 30 y 150°C, o entre aproximadamente 30 y 100°C, la cual es una temperatura que está en o por encima del punto de fusión del agente de dispersión. En modalidades adicionales, el agente de dispersión se calienta a una temperatura superior a aproximadamente 30, superior a aproximadamente 40, superior a aproximadamente 50, superior a aproximadamente 60, superior a

aproximadamente 70, superior a aproximadamente 80 o superior a aproximadamente 90°C. Estos y otros métodos son técnicas rutinarias adecuadas para la preparación de las dispersiones de BZA de la invención.

En algunas modalidades, las dispersiones sólidas de la invención están
5 caracterizadas por una solubilidad de equilibrio en ácido acético 0.0005 M a una temperatura de aproximadamente 20 a aproximadamente 26°C que es superior a aquella para acetato de bazedoxifeno cristalino o microcristalino. En modalidades adicionales, las dispersiones sólidas de la invención están
10 caracterizadas por una solubilidad de equilibrio en ácido acético 0.0005 M a una temperatura de aproximadamente 20 a aproximadamente 26°C que es por lo menos aproximadamente 8, por lo menos aproximadamente 10, por lo menos aproximadamente 12, por lo menos aproximadamente 14, por lo menos aproximadamente 16, o por lo menos aproximadamente 19 mg/mL. La solubilidad de equilibrio puede ser medida a través de métodos rutinarios en la
15 técnica tales como se describe en el ejemplo 2.

En algunas modalidades, las dispersiones sólidas de la invención están caracterizadas para que una forma de dosificación que comprende aproximadamente 10 mg totales de acetato de bazedoxifeno en una dispersión sólida esté caracterizada por una AUC_{0-24} mayor a
20 aproximadamente 140, mayor a aproximadamente 150, mayor a aproximadamente 160, mayor a aproximadamente 170, o mayor a aproximadamente 180 ng-hr/mL cuando se administra oralmente al mamífero. En modalidades adicionales, las dispersiones sólidas de la invención están caracterizadas para que una forma de dosificación que comprende
25 aproximadamente 10 mg totales de acetato de bazedoxifeno en una dispersión sólida esté caracterizada por:

- a) una AUC_{0-24} de aproximadamente 140 a aproximadamente 250 ng-hr/mL;
- b) una C_{max} de aproximadamente 12 a aproximadamente 30 ng/mL; y
- c) un t_{max} de aproximadamente 1.0 a aproximadamente 3.5 hr;

cuando se administra oralmente a un mamífero. Los métodos para medir los parámetros farmacocinéticos AUC_{0-24} (área bajo la curva durante 24 horas), C_{max} , y t_{max} son conocidos en la técnica y se describen, por ejemplo, en el ejemplo 4.

5

Dosificación y formulación

- Las dispersiones sólidas descritas en la presente pueden ser formuladas para administración a un paciente en cualquiera de una variedad de formas. En algunas modalidades, las dispersiones sólidas pueden ser administradas
- 10 solas, es decir, sin la adición de excipientes u otros aditivos. Por ejemplo, las formas de dosificación sólidas (por ejemplo, tabletas, cápsulas, etc.) que contienen más de aproximadamente 95%, más de aproximadamente 98%, o más de aproximadamente 99% (en peso) de dispersión sólida descrita en la presente pueden ser directamente administradas a un paciente.
- 15 En algunas modalidades, las dispersiones sólidas se combinan con uno o más vehículos (excipientes) farmacéuticamente aceptables para formar una composición farmacéutica para administración a un paciente. La composición puede contener cualquier cantidad de dispersión sólida. En algunas modalidades, las composiciones contienen aproximadamente 1 a
- 20 aproximadamente 99% en peso de la dispersión sólida. En modalidades adicionales, las composiciones contienen aproximadamente 1 a aproximadamente 50% en peso de la dispersión sólida. Incluso en otras modalidades, la composición contiene aproximadamente 1 a
- 25 aproximadamente 30% en peso de la dispersión sólida. Incluso en modalidades adicionales, la composición contiene aproximadamente 1 a aproximadamente 20% en peso de la dispersión sólida. En modalidades adicionales, la composición contiene aproximadamente 1 a aproximadamente 10% en peso de la dispersión sólida.

Las formulaciones que contienen las dispersiones sólidas de la presente invención pueden ser administradas en dosis diarias que varían de 0.1 mg a 1000 mg de acetato de bazedoxifeno a una persona que lo necesita. Las escalas de dosis preferidas varían de 10 mg/día a aproximadamente 600 mg/día, de preferencia de 10 mg/día a aproximadamente 60 mg/día. La dosificación puede ser ya sea en una dosis única o dos o más dosis divididas por día. Tales dosificaciones pueden ser administradas en cualquier manera que facilite la entrada del compuesto a la corriente sanguínea incluyendo la forma oral, a través de implantes, la forma parenteral, vaginal, rectal y transdérmica.

Las administraciones transdérmicas incluyen todas las administraciones a través de la superficie del cuerpo y los revestimientos internos de pasos corporales incluyendo tejidos epiteliales y de la mucosa. Dicha administración puede ser en forma de una loción, crema, coloide, espuma, parche, suspensión y similares.

Las formulaciones orales que contienen las dispersiones sólidas de la presente invención pueden comprender cualquier forma oral convencionalmente utilizada, incluyendo tabletas, cápsulas, formas bucales, trociscos, comprimidos y líquidos orales, suspensiones, y similares. Las cápsulas o tabletas que contienen la dispersión sólida de la presente invención también se pueden combinar con mezclas de otros compuestos activos o llenadores inertes y/o diluyentes tales como los almidones farmacéuticamente aceptables (por ejemplo, almidón de maíz, papa o tapioca), azúcares, agentes edulcorantes artificiales, celulosas en polvo, tales como celulosas cristalinas y microcristalinas, harinas, gelatinas, gomas, etc.

Las formulaciones en tableta se pueden realizar a través de métodos convencionales de compresión, granulación en húmedo, o granulación en seco y utilizar diluyentes (llenadores) farmacéuticamente aceptables, agentes de aglutinamiento, lubricantes, desintegrantes, agentes de suspensión o

estabilización, que incluyen pero no se limitan a estearato de magnesio, ácido esteárico, talco, laurilsulfato de sodio, celulosa microcristalina, carboximetilcelulosa de calcio, polivinilpirrolidona, gelatina, ácido algínico, goma de acacia, goma de xantano, citrato de sodio, silicatos complejos, 5 carbonato de calcio, glicina, dextrina, sacarosa, sorbitol, fosfato dicálcico, sulfato de calcio, lactosa, caolín, manitol, cloruro de sodio, talco, almidones secos y azúcar en polvo. Las formulaciones orales usadas en la presente invención pueden utilizar formulaciones estándar de liberación retardada o en tiempo o spansules o cápsulas de liberación prolongada. Las formulaciones 10 en supositorio se pueden hacer a partir de materiales tradicionales, que incluyen manteca de cacao, con o sin adición de ceras para alterar el punto de fusión de los supositorios, y glicerina. También se pueden utilizar bases de supositorio solubles en agua, tales como polietilenglicoles de diversos pesos moleculares.

15 Los revestimientos de película útiles con las formulaciones de la presente invención se conocen en la técnica y generalmente consisten en un polímero (por lo general un tipo celulósico de polímero), un colorante y un plastificador. Ingredientes adicionales tales como agentes de humectación, azúcares, saborizantes, aceites y lubricantes se pueden incluir en formulaciones de 20 revestimiento de película para impartir ciertas características a la capa de película. Las composiciones y formulaciones en la presente también se pueden combinar y procesar como un sólido, posteriormente se pueden colocar en forma de cápsula, tal como una cápsula de gelatina.

El llenador o diluyente puede comprender cualquier sustancia conocida en la 25 técnica que sea útil para la preparación de formulaciones orales sólidas. Los llenadores farmacéuticamente aceptables pueden ser seleccionados por ejemplo, de lactosa, celulosa microcristalina, sacarosa, manitol, fosfato de calcio, carbonato de calcio, celulosa en polvo, maltodextrina, sorbitol, almidón, xilitol y similares.

Las formulaciones de la presente también pueden incluir agentes desintegrantes. Estos desintegrantes se pueden seleccionar de aquellos conocidos en la técnica, que incluyen almidón pregelatinizado, glicolato de almidón de sodio, y similares. Otros desintegrantes útiles incluyen

5 croscarmelosa de sodio, crospovidona, almidón, ácido algínico, alginato de sodio, arcillas (por ejemplo, veegum o goma de xantano), flóculo de celulosa, resinas de intercambio iónico, o sistemas efervescentes, tales como aquellos que utilizan ácidos alimenticios (tales como ácido cítrico, ácido tartárico, ácido málico, ácido fumárico, ácido láctico, ácido adípico, ácido ascórbico, ácido

10 aspártico, ácido eritórbico, ácido glutámico y ácido succínico) y un componente de carbonato alcalino (tal como bicarbonato de sodio, carbonato de calcio, carbonato de magnesio, carbonato de potasio, carbonato de amonio, etc.). El desintegrante o desintegrantes útiles en la presente invención pueden comprender de aproximadamente 4% a aproximadamente

15 40% de la composición en peso, de preferencia de aproximadamente 15% a aproximadamente 35%, preferiblemente de aproximadamente 20% a aproximadamente 35%.

Algunos componentes pueden tener funciones múltiples en las formulaciones de esta invención, que actúan, por ejemplo como un llenador y como un

20 desintegrante, y su función en una formulación específica puede ser singular aún cuando sus propiedades puedan permitir una funcionalidad múltiple.

Las formulaciones farmacéuticas y sistemas excipientes en la presente también pueden contener un antioxidante o una mezcla de antioxidantes, tales como ácido ascórbico. Otros antioxidantes los cuales pueden ser utilizados

25 incluyen ascorbato de sodio y palmitato de ascorbilo, opcionalmente junto con una cantidad de ácido ascórbico. Una escala ejemplar para el antioxidante o antioxidantes es de aproximadamente 0.05% a aproximadamente 15% en peso, de aproximadamente 0.5% a aproximadamente 15% en peso, o de aproximadamente 0.5% a aproximadamente 5% en peso. En algunas

modalidades, las formulaciones farmacéuticas no contienen sustancialmente un antioxidante.

Las composiciones farmacéuticas de las dispersiones sólidas de la presente invención también pueden ser formuladas con estrógenos esteroideos, tales como estrógenos conjugados, USP. La cantidad de acetato de bazedoxifeno utilizada en la formulación se puede ajustar de acuerdo con la dispersión sólida particular utilizada, la cantidad y tipo de estrógeno esteroideo en la formulación así como la indicación terapéutica particular que es considerada. En general, el acetato de bazedoxifeno puede ser utilizado en una cantidad suficiente para antagonizar el efecto del estrógeno particular al nivel deseado. La escala de dosis de estrógenos conjugados puede ser de aproximadamente 0.3 mg a aproximadamente 2.5 mg, aproximadamente 0.3 mg a aproximadamente 1.25 mg, o aproximadamente 0.3 mg a aproximadamente 0.625 mg. Una escala ejemplar para cantidad de acetato de bazedoxifeno en una formulación de combinación es aproximadamente 10 mg a aproximadamente 40 mg. Para el estrógeno esteroideo mestranol, una dosificación diaria puede ser de aproximadamente 1 μ G a aproximadamente 150 μ G, y para etinil estradiol, se puede utilizar una dosificación diaria de aproximadamente 1 μ G a 300 μ G. En algunas modalidades, la dosis diaria está entre aproximadamente 2 μ G y aproximadamente 150 μ G.

Un ejemplo de formulación oral contiene la dispersión sólida de la presente invención y los siguientes sistemas de excipientes:

- a) un llenador y desintegrante juntos que comprenden de aproximadamente 1% a aproximadamente 99% en peso (p) de la formulación total, de preferencia entre aproximadamente 20% y aproximadamente 85% de la formulación, o de aproximadamente 4% a aproximadamente 45% en peso de la formulación total; y
- b) un lubricante que comprende de aproximadamente 0.2% a aproximadamente 15% de la composición (p), en donde el lubricante es

estearato de magnesio u otros estearatos metálicos (por ejemplo, estearato de calcio o estearato de zinc), ésteres de ácido graso (por ejemplo, estearil fumarato de sodio), ácidos grasos (por ejemplo, ácido esteárico), alcoholes grasos, behenato de glicerilo, aceite mineral, parafinas, aceites vegetales
5 hidrogenados, leucina, polietilenglicoles, laurilsulfatos metálicos o cloruro de sodio.

Los porcentajes arriba indicados para el llenador, desintegrante, y lubricantes se basan en la composición farmacéutica final. El resto de la composición final está conformada por la dispersión sólida y una cubierta de superficie
10 farmacéuticamente aceptable, tal como un revestimiento o cápsula, como se describe en la presente. En algunas modalidades de esta invención, la dispersión sólida comprende de aproximadamente 1% a aproximadamente 99%, aproximadamente 10 a aproximadamente 95%, o aproximadamente 20 a aproximadamente 90% en peso, de la composición final; y el revestimiento o
15 cápsula comprende hasta aproximadamente 8% en peso de la formulación.

Otros numerosos y diversos excipientes, formas de dosificación, agentes de dispersión y similares que son adecuados para uso con respecto a las dispersiones sólidas de la invención se conocen en la técnica y se describen por ejemplo, en Remington's Pharmaceutical Sciences, 17a ed., Mack
20 Publishing Company, Easton, Pa., 1985, la cual se incorpora en su totalidad a la presente como referencia.

Métodos

Como se describe en la patente de E.U.A. No. 5,998,402, bazedoxifeno y
25 sales del mismo son agonistas selectivos de estrógeno con afinidad para el receptor de estrógenos. A diferencia de otros tipos de agonistas de estrógeno, bazedoxifeno y sales del mismo son antiestrogénicos en el útero y pueden antagonizar los efectos tróficos de los agonistas de estrógeno en tejidos uterinos. Por consiguiente, las dispersiones sólidas de la invención, y las

composiciones que contienen las mismas, pueden encontrar muchos usos relacionados con el tratamiento de estados de enfermedad o síndromes relacionados con una deficiencia de estrógenos o un exceso de estrógenos. También pueden ser utilizadas en métodos de tratamiento para enfermedades o trastornos que resultan de la proliferación o desarrollo anormal, acciones o crecimiento de tejidos endometriales o de tipo endometrial.

El acetato de bazedoxifeno tiene la capacidad de comportarse como un agonista de estrógenos al reducir el colesterol y evitar la pérdida ósea. En consecuencia, la dispersión sólida es útil para tratar muchas enfermedades que resultan de efectos de estrógenos y exceso de estrógenos o deficiencia que incluyen osteoporosis, hipertrofia prostática, calvicie de distribución masculina o hereditaria, atrofia vaginal y de la piel, acné, hemorragia uterina disfuncional, pólipos endometriales, enfermedad de mama benigna, leiomiomas uterinos, adenomiosis, cáncer ovárico, infertilidad, cáncer de mama, endometriosis, cáncer endometrial, síndrome de ovario poliquístico, enfermedad cardiovascular, anticoncepción, enfermedad de Alzheimer, deterioro cognitivo y otros trastornos del SNC, así como ciertos cánceres que incluyen melanoma, cáncer de próstata, cánceres del colon, cánceres del SNC, entre otros. Adicionalmente, la dispersión sólida se puede utilizar para anticoncepción en mujeres premenopáusicas, así como terapia de reemplazo hormonal en mujeres postmenopáusicas (como por ejemplo para tratar alteraciones vasomotoras tales como bochornos) o en otros estados de deficiencia de estrógenos en donde sería benéfica la suplementación de estrógenos. También se puede utilizar en estados de enfermedad en donde la amenorrea es ventajosa, tales como leucemia, ablaciones endometriales, enfermedad crónica renal o hepática o enfermedades o trastornos de coagulación.

Las dispersiones sólidas de la invención también se pueden utilizar en métodos para inhibir la pérdida ósea, la cual puede resultar de un

desequilibrio en la formación de nuevos tejidos óseos de un individuo y la resorción de tejidos más antiguos, que conduce a una pérdida neta de hueso. Dicho agotamiento óseo da como resultado una escala de individuos, particularmente en mujeres postmenopáusicas, mujeres que se han sometido a ooforectomía bilateral, aquellas que reciben o que han recibido terapias prolongadas de corticosteroides, aquellas que experimentan disgénesis gonadal, y aquellas que padecen de síndrome de Cushing. Las necesidades especiales para reemplazo óseo, incluyendo hueso oral y dientes, también pueden ser tratadas utilizando la dispersión sólida de la presente invención en individuos con fracturas de hueso, estructuras óseas defectuosas, y aquellos que reciben cirugías relacionadas con los huesos y/o el implante de prótesis. Además de los problemas antes descritos, la dispersión sólida puede ser utilizada en tratamientos para osteoartritis, hipocalcemia, hipercalcemia, enfermedad de Paget, osteomalacia, osteomalisteresis, mieloma múltiple y otras formas de cáncer que tienen efectos nocivos en los tejidos óseos.

Se entiende que los métodos para tratar las enfermedades y síndromes listados en la presente invención implican la administración a un individuo en necesidad de dicho tratamiento de una cantidad terapéuticamente efectiva de la dispersión sólida de la invención, o composición que contiene la misma.

Como se utiliza en la presente, el término “tratar” con referencia a una enfermedad, pretende referirse a la prevención, inhibición y/o mejora de la enfermedad.

Como se utiliza en la presente, el término "individuo" o "paciente", utilizado de manera intercambiable, se refiere a cualquier animal, incluyendo mamíferos, de preferencia ratones, ratas, otros roedores, conejos, perros, gatos, cerdos, ganado, ovejas, caballos, o primates, y con mayor preferencia humanos.

Como se utiliza en la presente, la frase “cantidad terapéuticamente efectiva”, se refiere a la cantidad de compuesto activo o agente farmacéutico que produce la respuesta biológica o medicinal en un tejido, sistema, animal,

individuo o humano que busca un investigador, veterinario, doctor u otro médico, que incluye una o más de las siguientes:

(1) prevenir la enfermedad; por ejemplo, prevenir una enfermedad, condición o trastorno en un individuo que puede estar predispuesto a la enfermedad, condición o trastorno pero que aún no experimenta o despliega la patología o sintomatología de la enfermedad;

(2) inhibir la enfermedad; por ejemplo, inhibir una enfermedad, condición o trastorno en un individuo que está experimentando o desplegando la patología o sintomatología de la enfermedad, condición o trastorno (es decir, detener o reducir la velocidad del desarrollo adicional de la patología y/o sintomatología); y

(3) mejorar la enfermedad; por ejemplo, mejorar una enfermedad, condición o trastorno en un individuo que está experimentando o desplegando la patología o sintomatología de la enfermedad, condición o trastorno (es decir, revertir la patología y/o sintomatología).

La invención se describirá con mayor detalle a través de ejemplos específicos. Los siguientes ejemplos se ofrecen para efectos ilustrativos, y no pretenden limitar de manera alguna la invención. Los expertos en la técnica fácilmente reconocerán una variedad de parámetros no críticos los cuales pueden ser cambiados o modificados para producir esencialmente los mismos resultados.

EJEMPLOS

EJEMPLO 1

Preparación de dispersiones sólidas de acetato de bazedoxifeno

25

Se prepararon formulaciones sólidas de dispersión de acetato de bazedoxifeno de acuerdo con los procedimientos expuestos más adelante. Se encontró que todas las dispersiones eran amorfas (no cristalinas) a través de

difracción de polvo por rayos X, lo cual difiere a una mezcla física de BZA y reactivo de dispersión la cual demostró contener BZA cristalino.

EJEMPLO 1.1

5 Dispersión sólida de acetato de bazedoxifeno con PVP (1:1 p/p)

A una solución de 3.0004 g de PVP K17 (PLASDONE, Povidona USP, Polivinilpirrolidona, ISP Technologies Inc.) en 55 mL de etanol (EM Science) se añadieron 3.0891 g de acetato de bazedoxifeno. Se añadieron otros 20 mL
10 de etanol y la suspensión resultante se calentó a 65°C durante 5 minutos hasta que se observó una solución de color café claro. Los solventes se evaporaron bajo presión reducida a temperatura ambiente hasta secar. Las laminillas amarillas se recolectaron y trituraron con mortero y mazo para dar 5.6 g de polvo de color café-crema.

15

EJEMPLO 1.2

Dispersión sólida de acetato de bazedoxifeno con PVP (1:1 p/p)

A una solución de 2.1091 g de PVP K17 (PLASDONE, Povidona USP, Polivinilpirrolidona, ISP Technologies Inc.) en 4 mL de etanol, se añadieron
20 2.1028 g de acetato de bazedoxifeno. Se añadieron otros 2 mL de etanol para formar una suspensión lechosa. Se añadieron otros 44 mL de etanol (total de 50 mL) y la mezcla se calentó a 65°C durante 5 minutos para hacer una solución de color amarillo. Los solventes se evaporaron bajo presión reducida
25 a temperatura ambiente hasta secar para dar un sólido color amarillo-café.

EJEMPLO 1.3

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Dispersión sólida de acetato de bazedoxifeno con PVP (1:1 p/p)

A una solución de 3.00519 g de PVP K17 en 15 mL de etanol, se añadieron
5 3.00671 g de acetato de bazedoxifeno con mezcla. Se añadieron otros 60 mL
de etanol y la mezcla se calentó a 65°C durante 5 minutos para obtener una
solución de color amarillo-café clara. Los solventes se evaporaron bajo
presión reducida a temperatura ambiente hasta secar. El sólido de color
amarillo-café se trituró con mortero y mazo para dar un polvo fino de color
10 amarillo-crema.

EJEMPLO 1.4**Dispersión sólida de acetato de bazedoxifeno con PVP (5% p/p activo)**

15 A una solución de 0.9509 g de PVP K-17 (PLASDONE, Povidona USP,
Polivinilpirrolidona, ISP Technologies Inc.) en 1 mL de etanol (EM Science) se
añadió 0.0499 g de acetato de bazedoxifeno. Se formó una solución espesa
de color amarillo y se añadió 0.5 mL de etanol a la mezcla para formar una
solución viscosa de color amarillo. Los solventes se evaporaron bajo presión
20 reducida a temperatura ambiente hasta secar. El material sólido de color
amarillo se recolectó y trituró con mortero y mazo.

EJEMPLO 1.5

25 **Dispersión sólida de acetato de bazedoxifeno con Poloxámero 188 (5%
p/p activo)**

A una solución de 0.9503 g de Poloxámero 188 (BASF; copolímero de
polioxipropileno-polioxietileno) en 1.5 mL de etanol y 0.5 mL de agua

desionizada, se añadió 0.0503 g de acetato de bazedoxifeno para formar una solución incolora. Los solventes se evaporaron bajo presión reducida a temperatura ambiente hasta secar. Se recolectó el material sólido de color crema.

5

EJEMPLO 1.6**Dispersión sólida de acetato de bazedoxifeno con Poloxámero 188 (5% p/p activo)**

Al Poloxámero 188 (0.9540 g; BASF) fundido a 60°C se añadió 0.0502 g de acetato de bazedoxifeno con mezcla para formar un líquido transparente. El líquido se enfrió a temperatura ambiente.

10

EJEMPLO 1.7**Dispersión sólida de acetato de bazedoxifeno con PEG 1450 (5% p/p activo)**

15

A una solución de 0.9522 g de PEG 1450 (Union Carbide) en 1.5 mL de etanol calentada a 40°C se añadió 0.0510 g de acetato de bazedoxifeno para formar una solución transparente. Los solventes se evaporaron bajo presión reducida hasta secar para formar un material ceroso de color blanco.

20

EJEMPLO 1.8**Dispersión sólida de acetato de bazedoxifeno con PEG 1450 (5% p/p activo)**

25

A 0.9448 g de PEG 1450 fundido a 70°C se añadió 0.0504 g de acetato de bazedoxifeno con mezcla para formar un líquido transparente. El líquido se enfrió a temperatura ambiente.

EJEMPLO 2

**Solubilidad de equilibrio de dispersiones sólidas de acetato de
bazedoxifeno**

5 Unos cuantos miligramos de cada una de las dispersiones de los ejemplos 1.1
a 1.8 se colocaron en 2 mL de ácido acético 0.0005 M, se mantuvieron a
temperatura ambiente (aproximadamente 20-26°C), se hicieron girar a 50
rotaciones/minuto durante 18 horas, y se filtraron a través de filtro de 0.45 µm
(Nylon Acrodisc). Después de 10x de dilución con fase móvil, se inyectaron 10
10 µL a HPLC. La HPLC se llevó a cabo con los siguientes parámetros:

Columna: Inertsil 5 ODS-2 150 x 4.6 mm
Velocidad de flujo: 1.5 mL/min
Detector: UV a 220 nm
Temperatura: Ambiente

15 Fase móvil: 320 mL de acetonitrilo y 680 mL de una solución
que contiene 6.8 g de fosfato de potasio monobásico en 2 L de agua, el pH se
ajustó a 3.0 con ácido fosfórico al 85%).

Los resultados se proveen a continuación en el cuadro II. La dispersión sólida
de bazedoxifeno con PVP (5% p/p activo) dio la solubilidad de equilibrio más
20 alta.

CUADRO II

25

Ejemplo de Dispersión No.	Solubilidad de Equilibrio
1.1 (etanol; PVP; 1:1 p/p)	13.9 mg/mL
1.4 (etanol; PVP; 5% p/p activo)	20.1 mg/mL
1.5 (etanol; Poloxámero 188; 5% p/p activo)	2.9 mg/mL
1.6 (material fundido; Poloxámero 188; 5% p/p activo)	8.1 mg/mL
1.7 (etanol; PEG 1450; 5% p/p activo)	2.3 mg/mL
1.8 (material fundido; PEG 1450; 5% p/p activo)	5.3 mg/mL

30

EJEMPLO 3

Velocidad de disolución intrínseca de acetato de bazedoxifeno con respecto a dispersión sólida de acetato de bazedoxifeno con PVP (1:1

5 **p/p)**

Se prepararon pellas de cada uno de acetato de bazedoxifeno y dispersión sólida de acetato de bazedoxifeno (PVP; 1:1 p/p, ver ejemplo 1) al comprimir 100 mg de cada uno en un troquel (Wood's Apparatus) a una presión de 70.3 kg/cm² durante un minuto con una prensa Carver. Las pellas posteriormente se colocaron en un aparato de disolución lo cual dio como resultado una sola superficie de pella expuesta con un área superficial de 0.5 cm². La velocidad de disolución en 900 mL de ácido acético 0.0005 M se determinó utilizando el método USP (aparato 2) con una rotación de 50 rpm a 37°C. A partir de la concentración de mg/mL (a través de HPLC) con respecto al perfil del tiempo, se determinó la velocidad de disolución intrínseca aparente.

Las velocidades de disolución intrínsecas de acetato de bazedoxifeno y dispersión sólida de acetato de bazedoxifeno con PVP (1:1 p/p fueron 0.018 mg/cm²-min y 0.18 mg/cm²-min, respectivamente. La dispersión sólida de acetato de bazedoxifeno es aproximadamente 10 veces más rápida que el material no disperso. Los resultados se muestran en la figura 1.

EJEMPLO 4

Análisis farmacocinético preliminar de dispersiones sólidas de acetato de bazedoxifeno en perros

25

Se evaluó la biodisponibilidad de formulaciones de acetato de bazedoxifeno en perros. Seis perros hembra (6.2-10.5 kg) se dividieron en tres grupos, dos perros por grupo. A cada grupo de perros, se administró oralmente una dosis

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- sencilla equivalente a 10 mg de acetato de bazedoxifeno como una de tres formulaciones:
- Formulación A) 1/2 de una tableta de 20 mg (cuadro III);
- Formulación B) una cápsula de 10 mg de dispersión sólida de acetato de bazedoxifeno de acuerdo con el ejemplo 1.1 en donde la cápsula tiene la misma fórmula que la formulación A pero sin SLS (cuadro IV); y
- Formulación C) una cápsula de 10 mg que contiene dispersión sólida de acetato de bazedoxifeno de acuerdo con el ejemplo 1.1 (es decir, sin excipientes) (cuadro V).
- El estudio se llevó a cabo como un estudio de cruce, aleatorio. Las formulaciones se administraron después de un ayuno durante la noche, y se ofreció alimento después de la muestra de sangre de cuatro horas. Las muestras de sangre se retiraron a 0 (predosis), 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 y 24 horas después de dosificación; y el plasma se separó y analizó para determinar el contenido de acetato de bazedoxifeno.
- Las composiciones de los lotes A, B y C se proveen a continuación en los cuadros III, IV y V, respectivamente. Se prepararon cápsulas al mezclar componentes en combinaciones de bolsa y rellenar la cápsula manualmente (un Capsogel #2 CS, cápsula opaca blanca).
- Los resultados se proveen en el cuadro VI y figura 2. Como se puede ver a partir de los datos de AUC (área bajo la curva), se encontró que la biodisponibilidad de acetato de bazedoxifeno cuando se formula como una dispersión es aproximadamente 50% superior que para formulaciones de no dispersión.

25

CUADRO III
Formulación A

Ingrediente	% p/p	mg/tableta
Acetato de bazedoxifeno, micronizado	4.843	20.00
Lactosa, NF	35.206	145.40
Celulosa microcristalina (Avicel PH 101)	33.898	140.00
Almidón pregelatinizado, NF (Starch 1500)	13.559	58.00
Laurilsulfato de sodio (SLS)	1.453	6.00
Glicolato de almidón de sodio, NF	5.811	24.00
Acido ascórbico	1.453	6.00
Dióxido de silicio (Syloid 244 FP)	0.145	0.60
Estearato de magnesio, NF	0.484	2.00
Opadry blanco 1	3.148	13.00

CUADRO IV**Formulación B**

	Ingrediente	% p/p	mg/cápsula	g/lote 15 gramos
	Dispersión sólida de acetato de bazedoxifeno del Ejemplo 1.1 (45.191% uso en valor)	11.23	22.13	1.6850
5	Lactosa, NF	31.00	61.07	4.6500
	Celulosa microcristalina (Avicel PH 101)	35.53	70.00	5.3299
	Almidón pregelatinizado, NF (Starch 1500)	14.21	28.00	2.1320
	Glicolato de almidón de sodio, NF	6.09	12.00	0.9137
	Ácido ascórbico	1.52	3.00	0.2284
	Dióxido de silicio (Syloid 244 FP)	0.15	0.30	0.0228
	Estearato de magnesio, NF	0.25	0.50	0.0381
	Total	100.00	197.00	15.0000

10

CUADRO V**Formulación C**

Ingrediente	% p/p	mg/cápsula
Dispersión sólida de acetato de bazedoxifeno del Ejemplo 1.1 (45.191% uso en valor)	100	22.13

15

CUADRO VI

Parámetros farmacocinéticos medios (% CV) de acetato de bazedoxifeno en perros después de administración oral de dosis sencilla equivalente a 10 mg de acetato de bazedoxifeno

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Parámetro	Formulación A Tableta	Formulación B Cápsula de dispersión sólida sin SLS	Formulación C Cápsula de dispersión sólida sin excipientes
AUC ₀₋₂₄ (ng·hr/mL)	124 (19)	188 (52)	173 (56)
C _{max} (ng/mL)	21.8 (43)	26.0 (37)	16.9 (57)
T _{max} (hr)	2.33 (120)	1.42 (65)	2.42 (59)

25

Diversas modificaciones de la invención, además de aquellas descritas en la presente, serán evidentes para los expertos en la técnica a partir de la descripción anterior. Dichas modificaciones también están destinadas a estar incluidas en el alcance de las reivindicaciones anexas. Cada una de las

publicaciones y referencias, incluyendo libros y patentes, citadas en la presente solicitud, se incorporan en su totalidad a la presente como referencia.

5

NOVEDAD DE LA INVENCION

REIVINDICACIONES

- 1.- Una dispersión sólida que comprende acetato de bazedoxifeno disperso en
10 un agente de dispersión.
- 2.- La dispersión sólida de conformidad con la reivindicación 1, caracterizada además porque dicho acetato de bazedoxifeno en dicha dispersión sólida es amorfo.
- 3.- La dispersión sólida de conformidad con la reivindicación 1 o 2,
15 caracterizada además porque dicho agente de dispersión comprende una celulosa, hialuronato, alginato, polisacárido, heteropolisacárido, poloxámeros, poloxaminas, etileno-acetato de vinilo, polietilenglicol, dextrano, polivinilpirrolidona, quitosano, alcohol polivinílico, propilenglicol, acetato de polivinilo, fosfatidilcolina, migliol, ácido poliláctico, ácido polihidroxitúrico,
20 mezclas de dos o más de los mismos o copolímeros de los mismos.
- 4.- La dispersión sólida de conformidad con la reivindicación 3, caracterizada además porque dicho agente de dispersión comprende polivinilpirrolidona, poloxámero o polietilenglicol.
- 5.- La dispersión sólida de conformidad con la reivindicación 4, caracterizada
25 además porque dicho agente de dispersión comprende polivinilpirrolidona.
- 6.- La dispersión sólida de conformidad con la reivindicación 4, caracterizada además porque dicho agente de dispersión comprende Poloxámero 188.
- 7.- La dispersión sólida de conformidad con la reivindicación 4, caracterizada además porque dicho agente de dispersión comprende PEG 1450.

- 8.- La dispersión sólida de conformidad con cualquiera de las reivindicaciones 1 a 7, caracterizada además porque la relación en peso de acetato de bazedoxifeno a agente de dispersión es aproximadamente 1:99 a aproximadamente 75:25.
- 5 9.- La dispersión sólida de conformidad con cualquiera de las reivindicaciones 1 a 7, caracterizada además porque la relación en peso de acetato de bazedoxifeno a agente de dispersión es aproximadamente 1:99 a aproximadamente 60:40.
- 10 10.- La dispersión sólida de conformidad con cualquiera de las reivindicaciones 1 a 7, caracterizada además porque la relación en peso de acetato de bazedoxifeno a agente de dispersión es aproximadamente 1:99 a aproximadamente 10:90.
- 15 11.- La dispersión sólida de conformidad con cualquiera de las reivindicaciones 1 a 7, caracterizada además porque la relación en peso de acetato de bazedoxifeno a agente de dispersión es aproximadamente 5:95.
- 12.- La dispersión sólida de conformidad con cualquiera de las reivindicaciones 1 a 7, caracterizada además porque la relación en peso de acetato de bazedoxifeno a agente de dispersión es aproximadamente 40:60 a aproximadamente 60:40.
- 20 13.- La dispersión sólida de conformidad con cualquiera de las reivindicaciones 1 a 7, caracterizada además porque la relación en peso de acetato de bazedoxifeno a agente de dispersión es aproximadamente 1:1.
- 14.- La dispersión sólida de conformidad con cualquiera de las reivindicaciones 1 a 7, caracterizada además porque tiene una solubilidad de equilibrio en ácido acético 0.0005 M a una temperatura de aproximadamente 25 20 a aproximadamente 26°C de por lo menos aproximadamente 8 mg/mL.
- 15.- La dispersión sólida de conformidad con cualquiera de las reivindicaciones 1 a 7, caracterizada además porque una forma de dosificación que comprende aproximadamente 10 mg totales de acetato de

bazedoxifeno en forma de dicha dispersión sólida está caracterizada por una AUC_{0-24} superior a aproximadamente 140 ng-hr/mL cuando se administra oralmente a un mamífero.

16.- La dispersión sólida de conformidad con cualquiera de las
5 reivindicaciones 1 a 7, caracterizada además porque una forma de dosificación que comprende aproximadamente 10 mg totales de acetato de bazedoxifeno en forma de dicha dispersión sólida está caracterizada por: a) una AUC_{0-24} de aproximadamente 140 a aproximadamente 250 ng-hr/mL; b) una C_{max} de aproximadamente 12 a aproximadamente 30 ng/mL; y c) un t_{max}
10 de aproximadamente 1.0 a aproximadamente 3.5 horas; cuando se administra oralmente a un mamífero.

17.- Un método para preparar la dispersión sólida de cualquiera de las reivindicaciones 1 a 16 que comprende: a) combinar acetato de bazedoxifeno y dicho agente de dispersión en solución, en donde dicha solución comprende
15 un solvente; y b) remover dicho solvente para producir dicha dispersión sólida.

18.- El método de conformidad con la reivindicación 17, caracterizado además porque dicho solvente es un solvente orgánico.

19.- El método de conformidad con la reivindicación 18, caracterizado además porque dicho solvente orgánico comprende un alcohol.

20 20.- El método de conformidad con la reivindicación 19, caracterizado además porque dicho alcohol comprende etanol.

21.- Una dispersión sólida preparada a través del método de cualquiera de las reivindicaciones 17 a 20.

22.- Un método para preparar la dispersión sólida de cualquiera de las
25 reivindicaciones 1 a 16 que comprende: a) combinar acetato de bazedoxifeno con agente de dispersión fundido para formar una mezcla líquida; y b) solidificar dicha mezcla líquida para formar dicha dispersión sólida.

- 23.- El método de conformidad con la reivindicación 22, caracterizado además porque dicho agente de dispersión fundido se prepara al calentar dicho agente de dispersión a una temperatura superior a aproximadamente 30°C.
- 24.- El método de conformidad con la reivindicación 22 o 23, caracterizado
5 además porque dicha solidificación se lleva a cabo al enfriar dicha mezcla líquida a una temperatura en o inferior a aproximadamente 25°C.
- 25.- Una dispersión sólida preparada a través del método de cualquiera de las reivindicaciones 22 a 24.
- 26.- Una composición que comprende la dispersión sólida de cualquiera de las
10 reivindicaciones 1 a 16, 21 o 25 y un vehículo farmacéuticamente aceptable.
- 27.- La composición de conformidad con la reivindicación 26, caracterizada además porque comprende aproximadamente 1 a aproximadamente 99% en peso de dicha dispersión sólida.
- 28.- La composición de conformidad con la reivindicación 26, caracterizada
15 además porque comprende aproximadamente 1 a aproximadamente 50% en peso de dicha dispersión sólida.
- 29.- La composición de conformidad con la reivindicación 26, caracterizada además porque comprende aproximadamente 1 a aproximadamente 30% en peso de dicha dispersión sólida.
- 20 30.- La composición de conformidad con la reivindicación 26, caracterizada además porque comprende aproximadamente 1 a aproximadamente 20% en peso de dicha dispersión sólida.
- 31.- La composición de conformidad con la reivindicación 26, caracterizada además porque comprende aproximadamente 1 a aproximadamente 10% en
25 peso de dicha dispersión sólida.
- 32.- Una forma de dosificación que comprende la dispersión sólida de cualquiera de las reivindicaciones 1 a 16, 21 o 25.

33.- La forma de dosificación de conformidad con la reivindicación 32, caracterizada además porque dicha forma de dosificación es para administración oral, transdérmica o por implante.

34.- La forma de dosificación de conformidad con la reivindicación 32,
5 caracterizada además porque dicha forma de dosificación es una tableta o cápsula.

35.- Un método para tratar a un mamífero que tiene una enfermedad o síndrome relacionado con deficiencia de estrógenos o exceso de estrógenos, que comprende administrar a dicho mamífero una cantidad terapéuticamente
10 efectiva de la dispersión sólida de cualquiera de las reivindicaciones 1 a 16, 21 o 25.

36.- Un método para tratar a un mamífero que tiene una enfermedad o trastorno relacionado con proliferación o desarrollo anormal de tejidos endometriales, que comprende administrar a dicho mamífero una cantidad
15 terapéuticamente efectiva de la dispersión sólida de cualquiera de las reivindicaciones 1 a 16, 21 o 25.

37.- Un método para reducir el colesterol en un mamífero, que comprende administrar a dicho mamífero una cantidad terapéuticamente efectiva de la dispersión sólida de cualquiera de las reivindicaciones 1 a 16, 21 o 25.

20 38.- Un método para inhibir pérdida ósea en un mamífero, que comprende administrar a dicho mamífero una cantidad terapéuticamente efectiva de la dispersión sólida de cualquiera de las reivindicaciones 1 a 16, 21 o 25.

39.- Un método para tratar cáncer de mama en un mamífero, que comprende administrar a dicho mamífero una cantidad terapéuticamente efectiva de la
25 dispersión sólida de cualquiera de las reivindicaciones 1 a 16, 21 o 25.

40.- Un método para tratar a mujeres postmenopáusicas para una o más alteraciones vasomotoras, que comprende administrar a dichas mujeres postmenopáusicas una cantidad terapéuticamente efectiva de la dispersión sólida de cualquiera de las reivindicaciones 1 a 16, 21 o 25.

41.- El método de conformidad con la reivindicación 40, caracterizado además porque dicha alteración vasomotora es el bochomo.

42.- El uso de una dispersión sólida de cualquiera de las reivindicaciones 1 a 16, 21 o 25, en la elaboración de un medicamento para el tratamiento de una
5 enfermedad o síndrome relacionado con deficiencia de estrógenos o exceso de estrógenos, una enfermedad o trastorno relacionado con proliferación o desarrollo anormal de tejidos endometriales, reducción del colesterol, inhibición de pérdida ósea, o tratamiento de cáncer de mama.

RESUMEN DE LA INVENCION

La presente invención se refiere a dispersiones sólidas de acetato de
bazedoxifeno, composiciones que contienen el mismo, preparaciones del
5 mismo, y usos del mismo.

Traducción de figuras:

~~00001~~

FIGURA 1

BZA, Intrinsic Dissolution in 0.0005M acetic acid at 37C (average) – BZA,

5 Disolución Intrínseca en Acido Acético 0.0005M a 37°C (promedio)

Bazedoxifene Solid Dispersion – Dispersión Sólida de Bazedoxifeno

Bazedoxifene – Bazedoxifeno

Time – Tiempo

FIGURA 2

Mean plasma bazedoxifene levels in dogs (n=6) following oral administration of

10 mg Bazedoxifene – Niveles medios de bazedoxifeno en plasma en perros
(n=6) después de administración oral de 10 mg de bazedoxifeno.

10 mg Tablet, 1/2 20 mg clinical tablet (Batch 2003B0051) – Tableta de 10 mg,

15 1/2 tableta clínica de 20 mg (Lote 2003B0051)

10 mg capsule, solid dispersion containing clinical tablet excipients without
SLS (Batch L23290-025) – Cápsula de 10 mg, dispersión sólida que contiene
excipientes de tableta clínica sin SLS (Lote L23290-025)

10 mg capsule, solid dispersion (Batch L23244-193) - Cápsula de 10 mg,

20 dispersión sólida (Lote L23244-193)

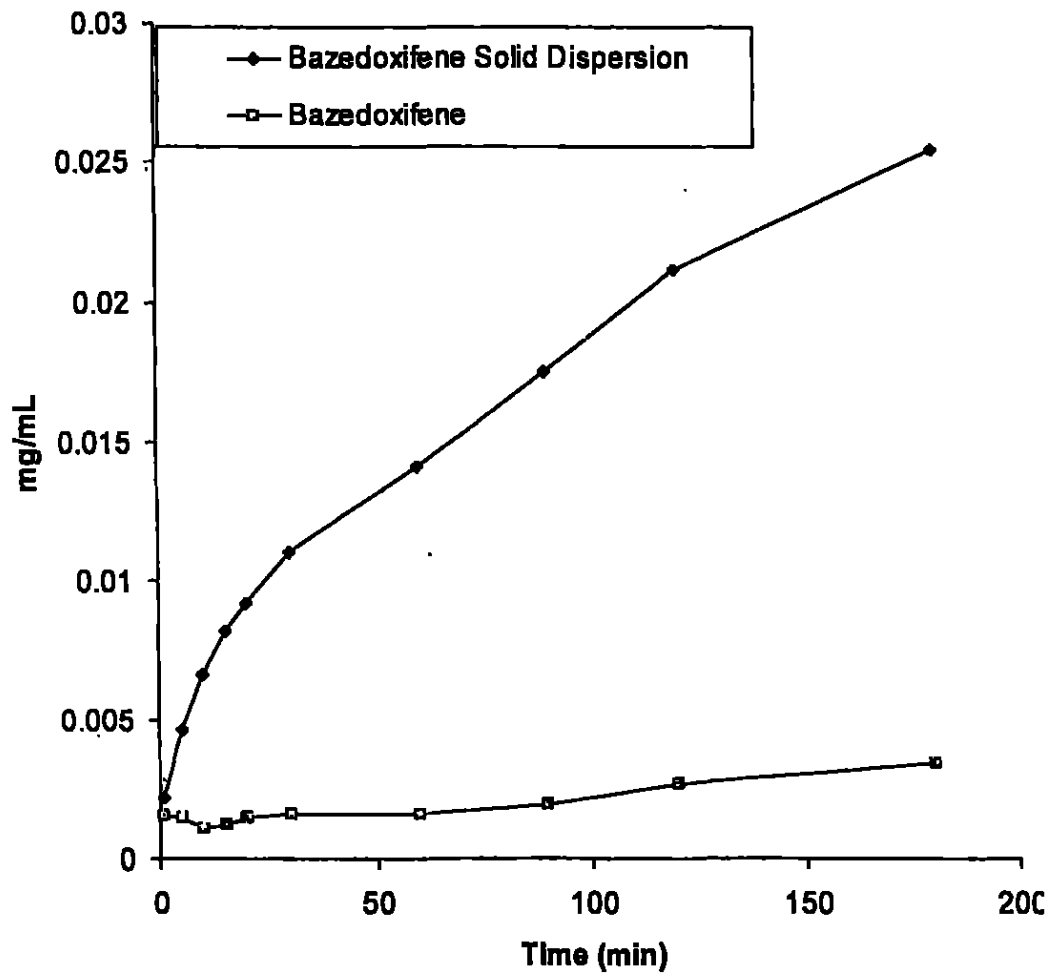
Bazedoxifene – Bazedoxifeno

Time (Hours) – Tiempo (Horas)

12

FIGURE 1

**BZA, Intrinsic Dissolution in 0.0005M Acetic acid
at 37C (average)**

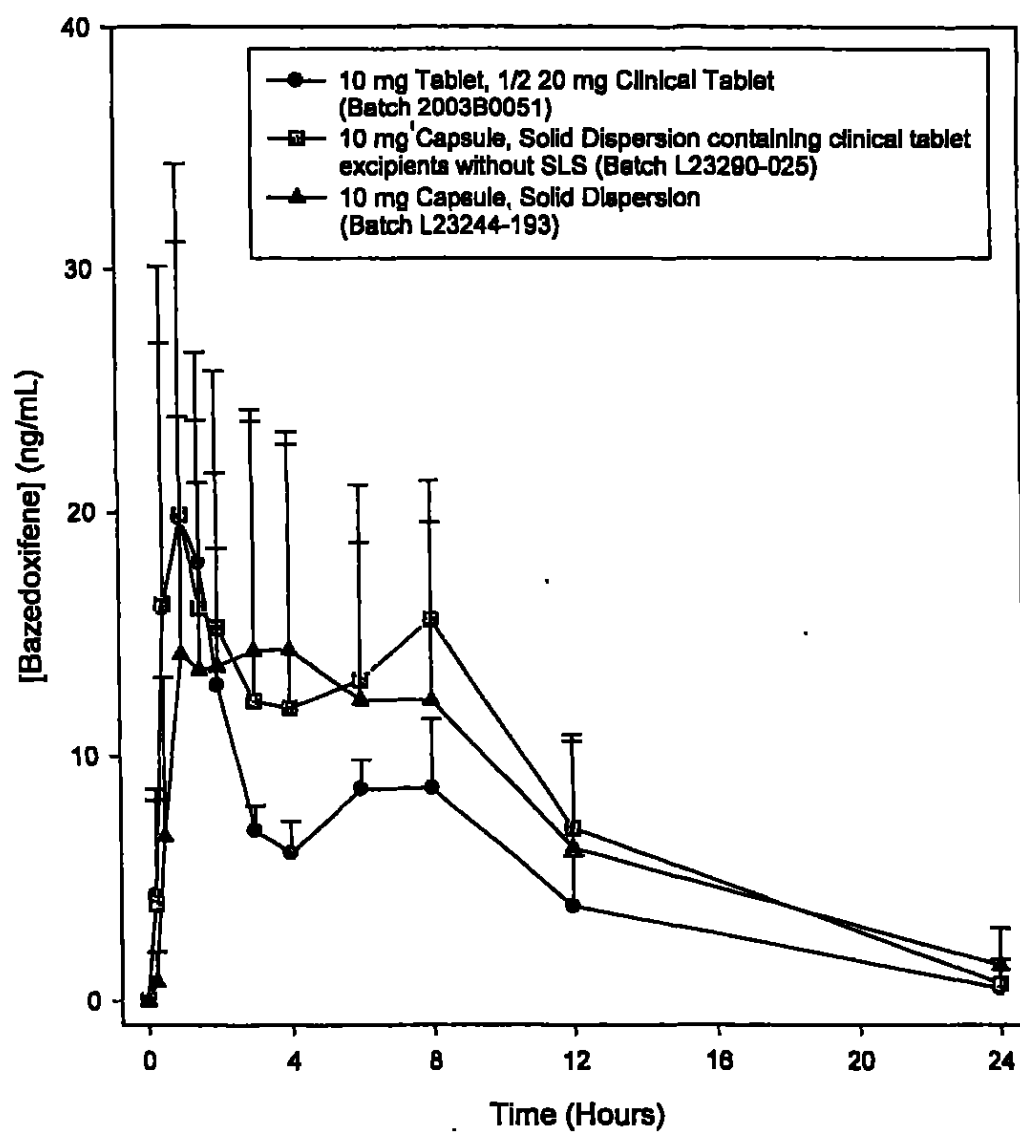


00003

22

FIGURE 2

Mean Plasma Bazedoxifene Levels in Dogs (n=6)
Following Oral Administration of 10 mg Bazedoxifene



PATENT COOPERATION TREATY

WYTH0093-500 161212

MPS/CAG 53
QUART

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:
COZEN O'CONNOR
Attn. Goddard, Christine A.
1900 Market Street
Philadelphia, Pennsylvania 19103
UNITED STATES OF AMERICA

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

RECEIVED		Date of mailing (day/month/year) 12/07/2005
Applicant's or agent's file reference AM101417 PCT JUL 13 2005	FOR FURTHER ACTION See paragraphs 1 and 4 below	
International application No. DUE DATE 9-12-05 PCT/US2005/011678 10-12-05	International filing date (day/month/year) 07/04/2005	
Applicant WYETH 8-12-05 IDS due 10-12-05		

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 18:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 740.14.35
For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

Shortly after the expiration of 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within 18 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise, the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 18 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the PCT Applicant's Guide, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority  European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 851 epo nl, Fax: (+31-70) 340-3016	Authorized officer Eva Boháčová
--	---

Form PCT/ISA/220 (January 2004)

(See notes on accompanying sheet)

COPY SENT TO CLIENT

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purpose of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 25 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

A0006

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 48.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference AM101417 PCT	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, Item 5 below.	
International application No. PCT/US2005/011678	International filing date (day/month/year) 07/04/2005	(Earliest) Priority Date (day/month/year) 08/04/2004
Applicant WYETH		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. 1.

2. ☒ Certain claims were found unsearchable (See Box II).

3. ☐ Unity of invention is lacking (see Box III).

4. With regard to the title,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

BAZEDOXIFENE ACETATE SOLID DISPERSION FORMULATIONS

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,

a. the figure of the drawings to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☒ none of the figures is to be published with the abstract.

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/00 A61K9/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, Y	EP 1 336 602 A (SCARAMUZZINO, GIOVANNI) 20 August 2003 (2003-08-20) page 39, paragraph 46 page 142, paragraph 63-73 page 168; claim 1 page 192; claim 7 ----- -/-	1-42



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

I later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

B document member of the same patent family

Date of the actual completion of the international search

30 June 2005

Date of mailing of the international search report

12/07/2005

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel: (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Luangkhot, N

INTERNATIONAL SEARCH REPORT

national Application No

PCT/US2005/011678

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PCT/US2005/011678

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,Y	LEUNER CHRISTIAN ET AL: "Improving drug solubility for oral delivery using solid dispersions" EUROPEAN JOURNAL OF PHARMACEUTICS AND BIOPHARMACEUTICS, ELSEVIER SCIENCE PUBLISHERS B.V., AMSTERDAM, NL, vol. 50, no. 1, July 2000 (2000-07), pages 47-60, XP002155099 ISSN: 0939-6411 the whole document page 50, column 2, paragraph 3.1 - page 51, column 2, last paragraph page 52, column 1, paragraph 3.2 - page 54, column 2, paragraph 3.2.2.5	1-42
Y	PASSERINI NADIA ET AL: "Preparation and characterisation of ibuprofen-poloxamer 188 granules obtained by melt granulation." EUROPEAN JOURNAL OF PHARMACEUTICAL SCIENCES : OFFICIAL JOURNAL OF THE EUROPEAN FEDERATION FOR PHARMACEUTICAL SCIENCES. FEB 2002, vol. 15, no. 1, February 2002 (2002-02), pages 71-78, XP002334089 ISSN: 0928-0987 abstract	6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/011674 ~~44478~~**Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 35-41 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No	09071
PCT/US2005/011678	

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
EP 1336602	A	20-08-2003	EP	1336602 A1	20-08-2003

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)Applicant's or agent's file reference
see form PCT/ISA/220FOR FURTHER ACTION
See paragraph 2 belowInternational application No.
PCT/US2005/011678International filing date (day/month/year)
07.04.2005Priority date (day/month/year)
08.04.2004International Patent Classification (IPC) or both national classification and IPC
A61K31/00, A61K9/14Applicant
WYETH

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
☐ Box No. II Priority
☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐ Box No. IV Lack of unity of invention
☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐ Box No. VI Certain documents cited
☒ Box No. VII Certain defects in the international application
☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Luangkhot, N

Telephone No. +49 89 2399-7857



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/US2005/011678

Box No. 1 Basis of the opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2005/011678

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
☒ claims Nos. 35-41 regarding industrial applicability

because:

- ☒ the said international application, or the said claims Nos. 35-41 regarding industrial applicability relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the whole application or for said claims Nos.
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
- the written form ☐ has not been furnished
☐ does not comply with the standard
- the computer readable form ☐ has not been furnished
☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
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Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	
	No: Claims	1-42
Inventive step (IS)	Yes: Claims	
	No: Claims	1-42
Industrial applicability (IA)	Yes: Claims	1-34,42
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2005/011678

Re Item I.

- 1) The documents cited in the International Search Report (ISR) were numbered respectively from D1-D3; this numbering results from the citation order in the ISR and will be used for the procedure. Unless otherwise specified, the cited passages of each document in the ISR will be considered.

D1: EP-A-1 336 602 (SCARAMUZZINO, GIOVANNI) 20 August 2003 (2003-08-20)

D2: LEUNER CHRISTIAN ET AL: "Improving drug solubility for oral delivery using solid dispersions" EUROPEAN JOURNAL OF PHARMACEUTICS AND BIOPHARMACEUTICS, ELSEVIER SCIENCE PUBLISHERS B.V., AMSTERDAM, NL, vol. 50, no. 1, July 2000 (2000-07), pages 47-60, XP002155099 ISSN: 0939-6411

D3: PASSERINI NADIA ET AL: "Preparation and characterisation of ibuprofen-poloxamer 188 granules obtained by melt granulation." EUROPEAN JOURNAL OF PHARMACEUTICAL SCIENCES : OFFICIAL JOURNAL OF THE EUROPEAN FEDERATION FOR PHARMACEUTICAL SCIENCES. FEB 2002, vol. 15, no. 1, February 2002 (2002-02), pages 71-78, XP002334089 ISSN: 0928-0987

Re Item III.

- 2) Claims 35-41 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V.

- 3) Novelty and inventive step according to Art.33(2) and 33(3) PCT
- 3a) The subject-matter of independent claim 1 is not novel in the light of D1 because this latter describes solid dispersion formulation (see §63-73 on page 142) of compounds of general formula (I), which can be bazedoxifene (see §46 on page 39), in a

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2005/011678

completely or partially amorphized form in order to improve their bioavailability and solubility.

The subject-matter of independent claim 1 is not inventive in the light of D1 taken alone, or combined with D2 or D3, because it is a matter of routine for the skilled man in the art to formulate any drugs in solid dispersion form.

In addition it should be noted that it is doubtful that the problem of providing a valuable solid dispersion of bazedoxifene acetate showing **good bioavailability** and solubility, could **indeed be solved over the full scope** of the invention since the applicant merely demonstrates the requested effects for some specific polymers at a specific ratio (active substance/polymer).

Therefore, the applicant is requested to support the present scope by providing experimental data for further tested polymers and ratio, or to restrict the scope of the claims to a **reasonable generalisation** (see the Guidelines, C-III, 6.1 and 6.2).

- 3b) Dependent claims 2-42 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step, see documents D2-D3 and the corresponding passages cited in the search report.
- 3c) Should the applicant renders the subject-matter of the present application novel by pointing out the importance a technical feature that is not described explicitly in prior art or by introducing into the claims the use of a **specific dispersing agent or a specific ratio** or whatever, inventive step may be recognized **only if he demonstrates that a surprising effect** is attributed to the distinguishing technical feature that the skilled man in the art will not be able to deduct from the prior art.

In the absence of a **surprising effect** directly attributed to the distinguishing feature or **evidence of a particular prejudice**, inventive step cannot be acknowledged because the introduced/distinguishing technical feature will be considered as an **obvious alternative** that the skilled man in the art will perform **routinely** in order not to interact with prior art.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

84428
International application No.

PCT/US2005/011678

It is indeed a matter of routine for the skilled man in the art (see also D2 and D3) to prepare a solid dispersion of any drugs, in order to enhance solubility and bioavailability, by using well-known polymers such as PVP, polaxamer or a PEG used at various ratio. The applicant should provide evidences that it was not obvious to select a specific polymer used at a specific ratio.

Re Item VII.

- 4) For the assessment of the present claims 35-41 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII.

- 5) It should be noted that the formulations in claims 14-16 "having an equilibrium solubility, an AUC etc..." do not delimit the scope of the protection to be sought and are rather to be construed as an attempt to define the invention by a result to be achieved, in particular they only amount to claiming the underlying technical problem.

Therefore these formulations will not be considered as distinguishing technical features and will be ignored while assessing novelty.

- 6) Any information the applicant may wish to submit concerning the subject-matter of the invention, for example further details of its advantages or of the problem it solves, and for which there is no basis in the application as filed, should be confined to the letter of reply and not be incorporated into the application.
- 7) The attention of the applicant is drawn to the fact that the application may not be amended in such a way that it contains subject-matter which extends beyond the content of the application as filed.

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/US2005/011678

In order to facilitate the examination of the conformity of the amended application with the requirements of Article 34(2)(b) PCT, the applicant is requested to clearly identify the amendments carried out, no matter whether they concern amendments by addition, replacement or deletion, and to indicate the passages of the application as filed on which these amendments are based (see also Rule 66.8(a) PCT). Preferably these indications should be submitted in handwritten form on a copy of the relevant parts of the application as filed.

- 8) The applicant is kindly requested to take account of the above objections and give convincing argumentations.

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

GODDARD, Christine, A.
Cozen O'Connor
1800 Market Street
Philadelphia, PA 19103
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COZEN IP DEPT.

JUN 06 2005

DUE DATE N/A
MAX DATE _____
DOCKETED BY W

Date of mailing (day/month/year) 30 May 2005 (30.05.2005)		
Applicant's or agent's file reference AM101417 PCT <u>WYTH0093-502</u>	IMPORTANT NOTIFICATION	
International application No. PCT/US05/011678	International filing date (day/month/year) 07 April 2005 (07.04.2005)	
International publication date (day/month/year)	Priority date (day/month/year) 08 April 2004 (08.04.2004)	
Applicant WYETH et al		

1. By means of this Form, which replaces any previously issued notification concerning submission or transmittal of priority documents, the applicant is hereby notified of the date of receipt by the International Bureau of the priority document(s) relating to all earlier application(s) whose priority is claimed. Unless otherwise indicated by the letters "NR", in the right-hand column or by an asterisk appearing next to a date of receipt, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
2. (If applicable) The letters "NR" appearing in the right-hand column denote a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
3. (If applicable) An asterisk (*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b) (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In cases such a copy is not accepted by the designated Office as the priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
08 April 2004 (08.04.2004)	60/560,452	US	12 May 2005 (12.05.2005)

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INDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE
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PATENTE DE INVENCION

[1]

MODELO DE UTILIDAD

[]

- ◆ Indicación de que se solicita la concesión de una patente [1]
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud [1]
- ◆ Descripción de la invención [1]
- ◆ Dibujos de ser estos pertinentes []
- ◆ Comprobante de pago de las tasas establecidas [1]

COMPLETA []

INCOMPLETA []

DISEÑO INDUSTRIAL []

- ◆ Indicación de que se solicita el registro de Diseño Industrial []
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud []
- ◆ Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño []
- ◆ Comprobante de pago de las tasas establecidas []

COMPLETA []

INCOMPLETA []

ESQUEMA DE TRAZADO []

- ◆ Indicación de que se solicita el registro de un Esquema de Trazado []
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud []
- ◆ Representación gráfica del esquema trazado []
- ◆ Comprobante de pago de las tasas establecidas []

COMPLETA []

INCOMPLETA []

Firma Responsable

Fecha

06 OCT. 2006

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