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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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E. S. D.

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Solicitud de Patente de Invención titulada: "Formulaciones de dispersiones sólidas de acetato de bazedoxifeno"

Solicitante: Wyeth

RESPUESTA AL AUTO NOTIFICADO POR FIJACIÓN EN LISTA NO. 100**DEL 19 DE MARZO DE 2010, OFICIO NO. 3998 (EXAMEN DE FONDO)**

ÁLVARO CORREA ORDÓÑEZ, mayor de edad y vecino de Bogotá D.C., identificado tal como aparece al pie de mi firma, en mi carácter de apoderado de la sociedad en referencia, doy respuesta al auto emanado por ese Despacho dentro del término legal:

1. Objeciones del Examinador**1.1 Claridad de la solicitud**

Con relación a las reivindicaciones 14 a 16 el examinador establece que dichas reivindicaciones se caracterizan por su solubilidad en equilibrio en ácido acético o su AUC₀₋₂₄, C_{max}, t_{max}, lo cual es inaceptable ya que son resultados a esperar o ventajas, y no son las características esenciales de la dispersión.

Ahora bien, con relación a las reivindicaciones 8 a 12 su Despacho menciona que se reivindican relaciones de principio activo: agente de dispersión que no se han evaluado mediante ensayos, se requiere al solicitante restringir a lo que verdaderamente ha probado tener efectos ventajosos.

1.2 Excepción a la patentabilidad:

El examinador afirma que las reivindicaciones 35 a 41 se exceptúan de patentabilidad por referirse a métodos de tratamiento

1.3 Reivindicaciones relativas a un uso o a un segundo uso:

Su Despacho establece que la reivindicación 42 se refiere al uso de las dispersiones sólidas para la fabricación de medicamentos y este tipo de reivindicaciones están exceptuadas de patentabilidad.

1.4 Novedad

El Examinador plantea que, después de realizada la búsqueda de anterioridades, encontró que el documento EP 1336602 (D1) afecta la novedad de las reivindicaciones 1 a 16, 26 a 34 de la presente solicitud.

Particularmente, el Examinador considera que las características esenciales de la presente invención están incluidas en D1.

"Se observa que D1 enseña formulaciones de dispersión sólida entre las cuales están las que contienen el principio activo bazedoxifeno en forma amorfizada completa o parcial cuyo fin es mejorar la biodisponibilidad y la solubilidad, este principio activo se encuentra disuelto en un agente de dispersión como un alcohol y además contiene la polivinilpirrolidona como excipiente para resultar en formas farmacéuticas como tabletas o cápsulas".

1.5 Nivel Inventivo

Sobre el requisito del nivel inventivo, el Examinador establece que el documento D1 afecta el nivel inventivo de las reivindicaciones 17 a 25 ya que una persona del nivel técnico medio, versada en la materia, enfrentando al problema de lograr métodos alternativos para la preparación de dispersiones sólidas con bazedoxifeno y conociendo el estado de la técnica haría lo que dice en D1 ya que las técnicas de dispersión sólida ya eran conocidas a partir de dicha anterioridad, en donde se amortizan los compuestos mediante liofilización, amasamiento o preferiblemente secado en spray y comolienda. Por lo tanto, es una labor rutinaria para un experto medio en la materia preparar una dispersión sólida para mejorar la solubilidad y la biodisponibilidad, usando polímeros bien conocidos tales como PVP,

poloxamero o PEG en varias posibilidades de relaciones entre el principio activo y el polímero y de esta manera logra fácilmente lo reivindicado.

2. Argumentos a favor de la patentabilidad de la solicitud

2.1 Modificación a una solicitud en trámite:

De conformidad con el artículo 34 de la Decisión 486 que establece que el solicitante en cualquier momento del trámite puede presentar modificaciones a su solicitud siempre y cuando no se presente una ampliación de la invención originalmente presentada, me permito presentar un nuevo capítulo reivindicatorio conformado por 23 reivindicaciones.

En particular se presentan las siguientes modificaciones:

Se cancelaron las reivindicaciones 35 a 41 relacionadas con un método para tratar a un mamífero que tiene una enfermedad o síndrome relacionado con deficiencia de estrógenos o exceso de estrógenos.

Así mismo, se canceló la reivindicación 42 relacionada con el uso de una dispersión sólida en la elaboración de un medicamento.

2.1 Nivel inventivo.

Con el fin de agilizar el trámite y concesión de la presente solicitud de patente, mi representada cancela las reivindicaciones de método 17, 22 y 25.

2.2 Novedad

La novedad de una solicitud está legalmente definida en el Artículo 16 de la Decisión 486 así: *“una invención se considerará nueva, cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso de la prioridad reconocida...”*

En virtud de la anterior definición, consideramos que el documento D1 EP 1336602 no constituye documento del arte previo que afecte la novedad de la presente solicitud, por cuanto el nuevo pliego reivindicatorio se ha modificado de tal forma que se supera la observación de novedad.

En particular se modificó la reivindicación 1, de la siguiente forma:

"Una dispersión sólida que comprende acetato de bazedoxifeno disperso en un agente de dispersión, donde dicho acetato de bazedoxifeno en dicha dispersión sólida es amorfo y donde una forma de dosificación comprende aproximadamente 10 mg totales de acetato de bazedoxifeno en forma de dicha dispersión sólida caracterizada por una AUC_{0-24} superior a aproximadamente 140 ng.hr/ml cuando se administra oralmente a un mamífero".

Por lo tanto, si se efectúa la comparación elemento por elemento entre la reivindicación 1 de la presente invención y **D1** se puede concluir que dicho documento no contiene todas las características específicas reclamadas por el nuevo pliego reivindicatorio de la presente invención, y por lo tanto, la presente invención es novedosa con relación a **D1**.

Con relación a la observación del examinador en cuanto a que las reivindicaciones 8 a 12 reivindican relaciones de principio activo: agente de dispersión que no se han evaluado mediante ensayos. Se hace notar a su Despacho que las reivindicaciones 8 a 12 que ahora corresponden a las reivindicaciones 7 a 11 son dependientes de la nueva reivindicación 1, y por lo tanto, son susceptibles de patentabilidad.

Así mismo, las reivindicaciones 14 a 16 que ahora corresponden a las reivindicaciones 13 a 14 son también dependientes de la nueva reivindicación 1.

Teniendo en cuenta que la nueva reivindicación 1 es novedosa e inventiva las reivindicaciones dependientes también lo son.

Ahora bien, con relación a la observación de su Despacho en cuanto a que caracterizar una dispersión sólida por AUC_{0-24} , no corresponde a una característica esencial, se le informa a

su Despacho que en la página 40 del Manual Andino preparado por la OMPI¹ se menciona claramente:

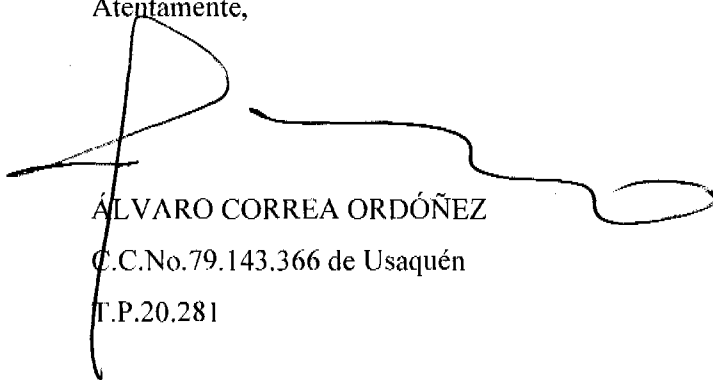
"Se pueden permitir características no esenciales cuando esté justificado y siempre y cuando permitan distinguir el estado de la técnica sin ambigüedad (novedad y nivel inventivo)".

En el presente caso, la nueva reivindicación 1 permite distinguir el estado de la técnica sin ambigüedad.

En este orden de ideas, tenemos que la invención propuesta por el solicitante si cumple con los requisitos de patentabilidad y de esta manera es susceptible de ostentar el título de patente de invención.

En virtud de lo anterior, solicito que se acepten las razones expuestas en el presente documento y en consecuencia, se otorgue el privilegio de patente de invención para el invento que se tramita en este expediente.

Atentamente,



ÁLVARO CORREA ORDÓÑEZ
C.C.No.79.143.366 de Usaquén
T.P.20.281

Anexos:

Capítulo reivindicatorio modificado

MGT/BOGDMS-#369715-V1-P2006_000206-0720.DOC

¹ MANUAL PARA EL EXAMEN DE SOLICITUDES DE PATENTES DE INVENCION EN LAS OFICINAS DE PROPIEDAD INDUSTRIAL DE LOS PAISES DE LA COMUNIDAD ANDINA, ECUADOR, 2004

REIVINDICACIONES

1.- Una dispersión sólida que comprende acetato de bazedoxifeno disperso en un agente de dispersión, donde dicho acetato de bazedoxifeno en dicha dispersión sólida es amorfo y donde una forma de dosificación comprende aproximadamente 10 mg totales de acetato de bazedoxifeno en forma de dicha dispersión sólida (caracterizada por una AUC_{0-24} superior a aproximadamente 140 ng.hr/ml cuando se administra oralmente a un mamífero.

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2.- La dispersión sólida de conformidad con la reivindicación 1, 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 polihidroxibutírico, mezclas de dos o más de los mismos o copolímeros de los mismos.

3.- La dispersión sólida de conformidad con la reivindicación 2, caracterizada además porque dicho agente de dispersión comprende polivinilpirrolidona, poloxámero o polietilenglicol.

4.- La dispersión sólida de conformidad con la reivindicación 3, caracterizada además porque dicho agente de dispersión comprende polivinilpirrolidona.

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5.- La dispersión sólida de conformidad con la reivindicación 3, caracterizada además porque dicho agente de dispersión comprende Poloxámero 188.

6.- La dispersión sólida de conformidad con la reivindicación 3, caracterizada además porque dicho agente de dispersión comprende PEG 1450.

7.- La dispersión sólida de conformidad con cualquiera de las reivindicaciones 1 a 6, caracterizada además porque la relación en peso de acetato de bazedoxifeno a agente de dispersión es aproximadamente 1:99 a aproximadamente 75:25.

8.- La dispersión sólida de conformidad con cualquiera de las reivindicaciones 1 a 6, caracterizada además porque la relación en peso de acetato de bazedoxifeno a agente de dispersión es aproximadamente 1:99 a aproximadamente 60:40.

9.- La dispersión sólida de conformidad con cualquiera de las reivindicaciones 1 a 6, caracterizada además porque la relación en peso de acetato de bazedoxifeno a agente de dispersión es aproximadamente 1:99 a aproximadamente 10:90.

10.- La dispersión sólida de conformidad con cualquiera de las reivindicaciones 1 a 6, caracterizada además porque la relación en peso de acetato de bazedoxifeno a agente de dispersión es aproximadamente 5:95.

11.- La dispersión sólida de conformidad con cualquiera de las reivindicaciones 1 a 6, caracterizada además porque la relación en peso de acetato de bazedoxifeno a agente de dispersión es aproximadamente 40:60 a aproximadamente 60:40.

12.- La dispersión sólida de conformidad con cualquiera de las reivindicaciones 1 a 6, caracterizada además porque la relación en peso de acetato de bazedoxifeno a agente de dispersión es aproximadamente 1:1.

5 13.- La dispersión sólida de conformidad con cualquiera de las reivindicaciones 1 a 6, caracterizada además porque tiene una solubilidad de equilibrio en ácido acético 0.0005 M a una temperatura de aproximadamente 20 a aproximadamente 26°C de por lo menos aproximadamente 8 mg/mL.

10 14.- La dispersión sólida de conformidad con cualquiera de las reivindicaciones 1 a 6, 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) 15 una C_{max} de aproximadamente 12 a aproximadamente 30 ng/mL; y c) un t_{max} de aproximadamente 1.0 a aproximadamente 3.5 horas; cuando se administra oralmente a un mamífero.

15.- Una composición que comprende la dispersión sólida de cualquiera de las 20 reivindicaciones 1 a 14 y un vehículo farmacéuticamente aceptable.

16.- La composición de conformidad con la reivindicación 15, caracterizada además porque comprende aproximadamente 1 a aproximadamente 99% en peso de dicha dispersión sólida.

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17.- La composición de conformidad con la reivindicación 15, caracterizada además porque comprende aproximadamente 1 a aproximadamente 50% en peso de dicha dispersión sólida.

18.- La composición de conformidad con la reivindicación 15, caracterizada además porque comprende aproximadamente 1 a aproximadamente 30% en peso de dicha dispersión sólida.

- 5 19.- La composición de conformidad con la reivindicación 15, caracterizada además porque comprende aproximadamente 1 a aproximadamente 20% en peso de dicha dispersión sólida.

- 20.- La composición de conformidad con la reivindicación 15, caracterizada
10 además porque comprende aproximadamente 1 a aproximadamente 10% en peso de dicha dispersión sólida.

21.- Una forma de dosificación que comprende la dispersión sólida de cualquiera de las reivindicaciones 1 a 14.

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22.- La forma de dosificación de conformidad con la reivindicación 21, caracterizada además porque dicha forma de dosificación es para administración oral, transdérmica o por implante.

- 20 23.- La forma de dosificación de conformidad con la reivindicación 21, caracterizada además porque dicha forma de dosificación es una tableta o cápsula.

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International Bureau144
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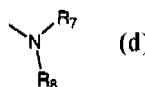
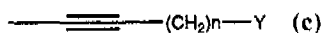
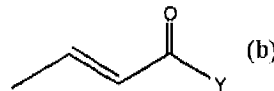
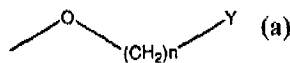
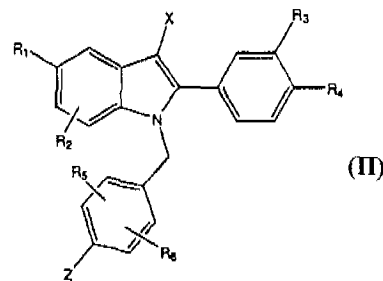
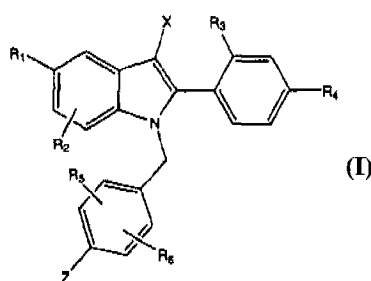
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[Continued on next page]

(54) Title: PHARMACEUTICAL COMPOSITIONS OF ESTROGENIC AGENTS



(57) Abstract: This invention comprises novel pharmaceutical carrier or excipient systems and oral pharmaceutical formulations comprising as an active ingredient raloxifene, amoxifen, droloxifene, arzoxifene, or CP 336156, or analogs thereof, or a compound of formulae (I) or (II), wherein Z is a moiety selected from the group of formulae (a, b or c), wherein: R₁ is selected from H, OH or the C₁-C₁₂ esters alkyl ethers thereof, benzyloxy, or halogen; or C₁-C₄ halogenated ethers; R₂, R₃, R₄, R₅, and R₆ are H, OH or C₁-C₁₂ esters or alkyl ethers thereof, halogens, or C₁-C₄ halogenated ethers, cyano, C₁-C₆ alkyl, or CF₃, with the proviso that, when R₁ is H, R₂ is not OH; Y is the moiety: formulae (d), wherein R₇ and R₈ are alkyl or concatenated together to form an optionally substituted, nitrogen-containing ring; or a pharmaceutically acceptable salt thereof; and excipients chosen from pharmaceutical fillers, glidants, lubricants, wetting agents and antioxidants.

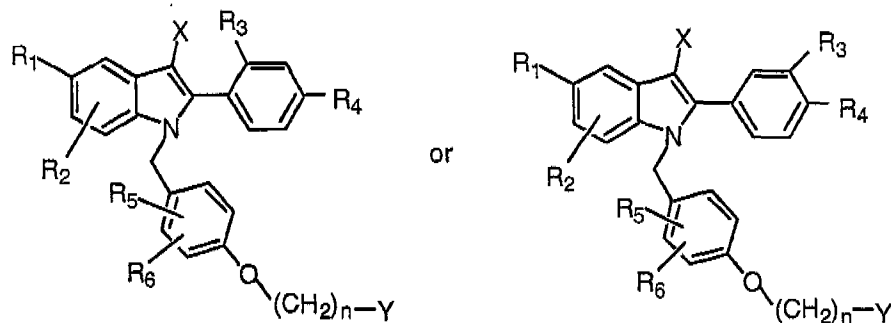
WO 02/03987 A2

PHARMACEUTICAL COMPOSITIONS OF ESTROGENIC AGENTS

This invention relates to pharmaceutical compositions utilizing compounds which have activity as estrogenic agents. This invention particularly relates to novel oral pharmaceutical compositions comprising one or more active pharmacological agents, such as TSE-424, ERA-923, raloxifene, tamoxifen, droloxifene, arzoxifene or CP 336156 and one or more pharmaceutically acceptable carriers or excipients.

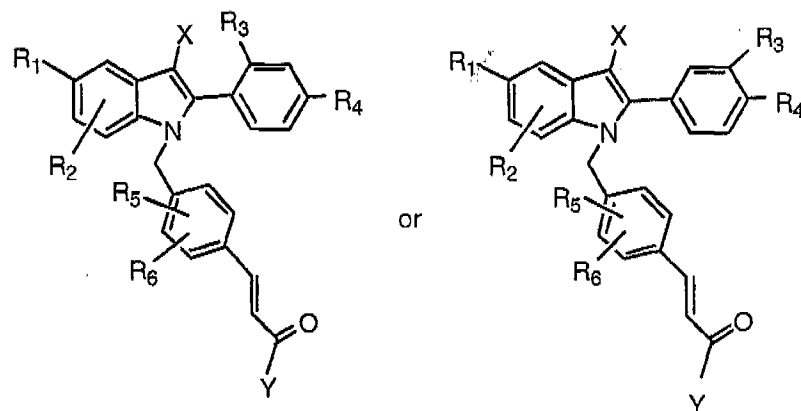
Background of the Invention

EP 0 802 183 A1 and U.S. Patent No. 5,780,497 describe substituted indole compounds of the formulae below:



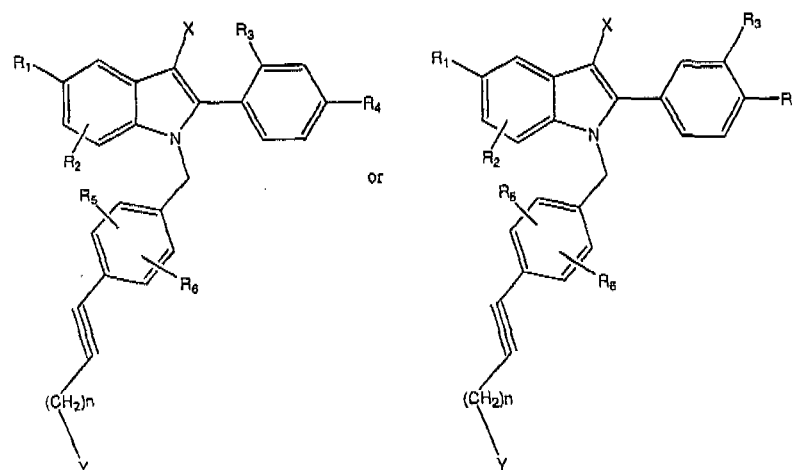
as well as their use as estrogenic agents, including the treatment of bone loss, cardiovascular disease, maladies associated with or resulting from the proliferation or abnormal development of endometrial or endometrial-like tissues, and disease states or syndromes associated with estrogen deficiency.

EP 0 802 184 A1, published October 22, 1997, describes comparable uses for substituted indole compounds of the formulae below.



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Analogous indole compounds having the general structures:



are described in U.S. Patent No. 5,880,137 (Miller et al.).

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U.S. Patent No. 5,811,120 (Gibson, L.L. et al), titled "Solid orally administerable raloxifene hydrochloride pharmaceutical formulation" (Eli Lilly and Company), describes a composition and process for raloxifene hydrochloride tablets including a surfactant being a sorbitan fatty acid ester or a polyoxyethylene sorbitan fatty acid ester, polyvinylpyrrolidone (PVP), and a water soluble diluent which is a polyol or sugar. Raloxifene has low water solubility. The Gibson et al. patented composition claims the inclusion of PVP and a water-soluble diluent to achieve adequate solubility of raloxifene.

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U.S. Patent No. 5,747,510 (Draper) teaches pharmaceutical formulations containing raloxifene in a dose range of from about 55 to about 150 mg. U.S. Patent No. 5,747,510 (Gibson et al.) provides raloxifene formulations utilizing a surfactant, polyvinylpyrrolidone and a water soluble diluent, particularly those in which the surfactant is a sorbitan fatty acid ester or a polyoxyethylene sorbitan fatty acid ester.

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U.S. Patent No. 5,510,358 (Palkowitz) and U.S. Patent No. 5,919,800 (Palkowitz) teach the synthesis and use of Arzoxifene, its analogs and salt forms, with or without combination with estrogen, for the treatment of osteoporosis, post-

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menopausal syndrome, cardiovascular-related pathological conditions and estrogen-dependent cancer.

U.S. 5,332,727 and U.S. 5,480,652 describe the use of antioxidants such as ascorbic acid in a solid pharmaceutical composition to stabilize the drug. In the case of NADH and NADPH formulations, the stabilizers added to the formulation include NaHCO_3 and PVP in addition to ascorbic acid and are not added to the formulation for an antioxidant effect per se. In the case of ibuprofen, the antioxidant must be in intimate contact with the active drug agent prior to its incorporation into the formulation in order to achieve its protective effect. This effect is only needed in the presence of alkaline carbonates in these effervescent formulations.

WO 96/21656 (Cameron et al.) teaches novel compounds, including CP 336156, and uses for treating or preventing obesity, breast cancer, osteoporosis, endometriosis, cardiovascular disease and prostatic disease.

Sawicka, J. "The influence of excipients and technological process on cholecalciferol stability and its liberation from tablets", *Pharmazie*, 46(1991), H. 7, pp. 519-521 describes the stabilization of cholecalciferol with various antioxidants in the solid state. The best antioxidant system described, however, yielded only 87.6% of the original content after 1 year of storage and the dissolution of the active material was also quite slow. Thus, improvements are required for stabilization of unstable solid drugs.

In light of the prior art, there is still a need to improve the solubility, stability and absorption qualities of poorly soluble pharmaceutical agents.

Description of the Invention

The present invention provides for orally administrable preparations that optimize the stability and enhance the dissolution of poorly soluble pharmaceutical agents, including estrogenic agents. Various formulations have been used to produce

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rapid dissolution of poorly soluble drugs, such as solubilization form (e.g. softgel capsules) or a high-energy form (e.g. solid dispersions). These techniques use specialized equipment and/or processes. The present invention provides pharmaceutically useful compositions which produce a rapid dissolution of poorly soluble drugs from a pharmaceutical solid dosage formulation via commonly used components and processes.

This invention comprises novel pharmaceutical carrier or excipient systems useful in the formulation of solid oral dosage forms for poorly soluble pharmacological agents, including estrogenic pharmacological agents including, but not limited to, those in the art known as TSE-424, ERA-923, raloxifene, tamoxifen, droloxifene, and arzoxifene, as well as their analogs and pharmaceutically acceptable salts. These carrier or excipient systems comprise:

a) a filler and disintegrant component comprising from about 5% to about 82% by weight (wght) of the total formulation, preferably between about 30% and about 80% of the formulation, of which from about 4% to about 40% by weight of the total formulation comprises one or more pharmaceutically acceptable disintegrants; and

b) a lubricant comprising from about 0.2% to about 10% of the composition (wght), such as selected from the group of 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 and sodium chloride.

It will be understood that the percentages listed above for the filler and disintegrant component and lubricant are percentages each will comprise of a final pharmaceutical composition. The remainder of the final composition will be comprised of the active pharmacological agent(s) and a pharmaceutically acceptable surface covering, such as a coating or capsule, as described herein. In preferred

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aspects of this invention, the active pharmacological agent(s) will comprise from about 0.5% to about 20%, by weight, of the final composition, more preferably from about 1% to about 5%, and the coating or capsule will comprise up to about 8%, by weight, of the formulation.

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Considering the filler and disintegrant component and lubricant component above, solely and without reference to an active pharmacological agent or coating, the carrier or excipient system would comprise:

10 a) from about 5.4% to about 89%, by weight, of a filler or disintegrant component, preferably from about 32.5% to about 87%; and

 b) from about 0.22% to about 10.9% of a lubricant component.

15 The carrier or excipient systems or compositions herein may also optionally utilize pharmaceutically acceptable wetting agents, glidants and antioxidants. Such systems or compositions comprise:

 a) a filler and disintegrant component comprising from about 5% to about
20 82% by weight (wght) of the total formulation, preferably between about 30% and about 80% of the formulation, of which from about 4% to about 40% by weight of the total formulation comprises one or more pharmaceutically acceptable disintegrants;

 b) optionally, a wetting agent comprising from about 0.2 to about 5% of
25 the composition (wght), such as selected from the group of sodium lauryl sulfate, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene alkyl ethers, sorbitan fatty acid esters, polyethylene glycols, polyoxyethylene castor oil derivatives, docusate sodium, quaternary ammonium compounds, sugar esters of fatty acids and glycerides of fatty acids;

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 c) a lubricant comprising from about 0.2% to about 10% of the composition (wght), such as selected from the group of magnesium stearate or other metallic stearates (e.g. calcium stearate or zinc stearate), fatty acid esters (e.g. sodium

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stearyl fumarate), fatty acids (e.g. stearic acid), fatty alcohols, glyceryl behenate, mineral oil, paraffins, hydrogenated vegetable oils, leucine, polyethylene glycols, metallic lauryl sulfates and sodium chloride; and

- 5 d) optionally, a glidant comprising from about 0.1% to about 10% (wght) of the composition, the glidant selected from those known in the art, including from the group of silicon dioxide, talc, metallic stearates, calcium silicate, or metallic lauryl sulfates.

- 10 This invention also comprises solid oral formulations or compositions of a pharmaceutically effective dose of an active pharmacological compound, or a pharmaceutically acceptable salt thereof, and a carrier or excipient system of this invention, as described above. Among the more preferred active pharmacological agents for use with these carrier or excipients systems are non-steroidal estrogenic
15 agents or tissues selective estrogenic agents. Examples of these compounds include, but are not limited to TSE-424, ERA-923, raloxifene, tamoxifen, droloxifene, arzoxifene or CP 336156, or a pharmaceutically acceptable salt of these compounds.

- While the formulations described herein may be used in an uncoated or non-
20 encapsulated solid form, preferably the final compositions are coated or encapsulated. The pharmacological compositions may be optionally coated with a film coating, preferably comprising from about 0.3% to about 8% by weight of the overall composition. 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
25 and a plasticizer. Additional ingredients such as wetting agents, sugars, flavors, oils and lubricants may 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.

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 The filler component listed above may utilize the filler or binder components known in the art for solid oral formulations. Pharmaceutically acceptable fillers or

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administration will be from about 10 mg/day to about 600 mg/day in a single dose or in two or more divided doses. More preferably, administration will be from about 1 mg/day to about 200 mg/day in a single dose or in two or more divided doses. It will also be understood that these methods and regimens may be completed either
5 remedially or prophylactically in the treatment, prohibition, inhibition or alleviation of the causes and symptoms of the maladies in question.

When the active ingredient in the formulations and methods of this invention is 1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol,
10 also known as TSE-424, or a pharmaceutically acceptable salt thereof, the preferred daily dosage for oral delivery is from about 0.1 to about 50 mg, preferably from about 2.5 to about 40 mg per day.

When the active ingredient in the formulations and methods of this invention is 2-(4-hydroxy-phenyl)-3-methyl-1-(4-(2-piperidin-1-yl-ethoxy)-benzyl)-1H-indol-5-ol,
15 also known as ERA-923, or a pharmaceutically acceptable salt form thereof, the preferred daily dosage for oral delivery is from about 0.1 to about 200 mg, preferably from about 2.5 to about 100 mg per day.

20 Oral formulations containing the active compounds of this invention may comprise any conventionally used oral forms, including tablets, capsules, buccal forms, troches, lozenges and oral suspensions. Capsules may contain mixtures of the active compound(s) with inert fillers and/or diluents such as the pharmaceutically acceptable starches (e.g. corn, potato or tapioca starch), sugars, artificial sweetening
25 agents, powdered celluloses, such as crystalline and microcrystalline celluloses, flours, gelatins, gums, etc. Useful tablet formulations may be made by conventional compression, wet granulation or dry granulation methods and utilize pharmaceutically acceptable diluents, binding agents, lubricants, disintegrants, suspending or stabilizing agents, including, but not limited to, magnesium stearate, stearic acid, talc,
30 sodium lauryl sulfate, microcrystalline cellulose, carboxymethylcellulose calcium, polyvinylpyrrolidone, gelatin, alginic acid, acacia gum, xanthan gum, sodium citrate,

- 29 -

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 herein may utilize standard delay or time release formulations to alter the absorption of the active compound(s).

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Among the most preferred active pharmacological agents of this invention are 1-[4-(2-azepan-1-yl-ethoxy)-benzyl]-2-(4-hydroxy-phenyl)-3-methyl-1H-indol-5-ol, also known as TSE-424, and 2-(4-hydroxy-phenyl)-3-methyl-1-(4-(2-piperidin-1-yl-ethoxy)-benzyl)-1H-indol-5-ol, also known as ERA-923, or a pharmaceutically acceptable salt of TSE-424 or ERA-923.

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Among the formulations of this invention are pharmaceutical formulations containing a pharmaceutically effective amount of an active pharmacological agent and a carrier or excipient system comprising one or more, e.g. all, of the following features:

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- a) a filler and disintegrant component comprising between about 50% and about 87% of the formulation, with from about 4% to about 40% of the formulation comprising one or more disintegrant agents;
- 20 b) a wetting agent comprising between about 0.5% and about 2.7% of the formulation;
- c) a lubricant comprising between about 0.2% and about 5.5% of the formulation; and
- 25 d) a glidant comprising between about 0.1% and about 5.5% of the formulation.

The percentages listed in the formulations above indicate percentages by weight of the total weight of the components listed from a) to d). The formulations above also preferably contain an optional antioxidant component, preferably ascorbic acid, at a concentration of from about 0.5% to about 5.5% by weight of the

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Example 1. TSE-424 Acetate -Rapid Dissolution Formulations

Ingredient	without Ascorbic Acid	with Ascorbic Acid
TSE-424 acetate, micronized*	10.00	10.00
Lactose NF fast flow	33.10	31.60
Microcrystalline Cellulose, NF (Avicel PH101)	25.00	25.00
Starch 1500	20.00	20.00
Sodium Lauryl Sulfate NF	1.50	1.50
Sodium Starch Glycolate	10.00	10.00
Ascorbic Acid USP	--	1.5
Syloid 244 FP	0.15	0.15
Magnesium Stearate	0.25	0.25

* Amount in formula is adjusted for actual potency of TSE-424 as free base.

5 Corresponding adjustment made with Lactose.

The formulations given above in Table 1 were prepared by incorporating a portion of the excipients in the granulation and a portion is also added in the final blending steps as dry powders. A dissolution profile generated for the formulations demonstrated almost 90% release of the drug in 30 minutes. Thus, the unique combination of disintegrants and soluble diluents plus the incorporation of both granulated and powdered solids into the composition ensures the fastest release of drug.

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[54] PREPARATION OF SOLID PHARMACEUTICAL FORMS

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424/487, 467, 468

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[57] ABSTRACT

Process for the preparation of solid pharmaceutical forms by mixing one or more pharmaceutical active compounds with one or more fusible, pharmacologically tolerated binders and, if required, other conventional pharmaceutical auxiliaries, at from 50° to 180° C., and subjecting the mixture to injection molding or extrusion and shaping, wherein the fusible binder used is a NVP polymer which contains not less than 20% by weight of NVP as copolymerized units, and, where they are present, all of whose comonomers contain nitrogen and/or oxygen.

9 Claims, No Drawings

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D3

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PREPARATION OF SOLID PHARMACEUTICAL FORMS

The present invention relates to a process for the preparation of solid pharmaceutical forms which in an n-vinylpyrrolid-2-one (NVP) polymer as a binder, by injection molding or extrusion and shaping.

Conventional tableting machines operate by a cyclic process using punches and dies. The process requires thoroughly premixed and specially prepared tableting materials and the overall process is therefore a multi-stage one and is expensive. The production of solid pharmaceutical forms with controlled release of active compound is particularly expensive. This may require retardation measures on the one hand and measures for improving the absorption of active compounds on the other hand.

One possible method for improving the absorption of sparingly soluble active compounds is to use solid solutions of the active compounds in water-soluble polymers. The known solid solutions of this type in NVP polymers were prepared by dissolving the active compound and the polymer together in an organic solvent and removing the latter. As a rule, in order to dissolve both the hydrophobic compound and the hydrophilic polymer, chlorohydrocarbons were required. Complete removal of these solvents is very expensive. In order to avoid environmental pollution, the solvents must again be removed as completely as possible from the waste air, which in turn is very expensive. Processes of this type are described in, for example, U.S. Pat. No. 3,089,818; T. Tachibana and A. Nakamura, *Kolloid Zeitschrift und Zeitschrift für Polymere*, 203 (1965), 130; Japanese Patent No. 24,379; M. Mayersohn et al., *J. Pharm. Sci.* 55 (1966), 1323; DE-B-11 37 009; and W. Scholten, *Arzn. Forschung* 14 (1964), 469.

The extrusion of active compound/polymer mixtures has already been described (cf. for example DE-A No. 12 29 248; P. Speiser, *Pharmaceutica Acta Helv.*, 41 (1966), 340 and *ibid.* 46 (1971, 31). However, in no case were solvent-free NVP polymers melted, let alone extruded, without being mixed with other polymers or with water, and in no case is the formation of a solid solution of a sparingly water-soluble active compound in a water-soluble polymer described.

In R. Voigt, *Lehrbuch der pharmazeutischen Technologie*, 5th Edition, Verlag Chemie, Weinheim, 1984, pages 221-222, the preparation of solid pharmaceutical formulations by injection molding or extrusion shaping of active compound/thermoplastic mixtures is described in general form but without any specific information, in particular about the type of polymers which are suitable for this purpose. The polymers in question here were without a doubt not highly hydrophilic polymers, such as NVP polymers, since, in the pharmaceutical sector to date, these have been processed not via the dry melt but always as a base with solvents (as a rule water) (cf. for example, British Patent No. 1,388,786).

It is an object of the present invention to provide a simple process for the preparation of solid pharmaceutical forms, preferably with controlled release of active compound.

We have found that this object is achieved by a process for the preparation of solid pharmaceutical forms by mixing one or more pharmaceutical active compounds with one or more fusible, pharmacologically tolerated binders and, if required, other conventional

pharmaceutical auxiliaries, at from 50° to 180° C., preferably from 60° to 160° C., and subjecting the mixture to injection molding or extrusion and shaping, wherein the fusible binder used is a solvent-free NVP polymer which has a water content of not more than 3.5% by weight and contains not less than 20, preferably not less than 60, in particular 100, % by weight of NVP as copolymerized units, and, where they are present, all of whose comonomers contain nitrogen and/or oxygen, and, at least when the glass transition temperature of the mixture is above 120° C., an NVP polymer is used which is obtained by polymerization in an organic solvent or using an organic peroxide as an initiator in aqueous solution, and the mixture does not contain any thermoplastics which are sparingly soluble in gastric juice (less than 10% dissolving in 6 hours).

The NVP polymers should contain not less than 20, preferably not less than 60, in particular 100, % by weight of NVP as copolymerized units and have a Fikentscher K value (*Cellulose-Chemie* 13 (1932), 58-64 and 71-74) of from 10 to 70, preferably from 10 to 50, particularly preferably from 12 to 40, in particular from 12 to 35 and, in the case of NVP homopolymers, preferably from 12 to 35, in particular from 12 to 17.

The polymeric binder must soften or melt in the total mixture of all components at from 50 to 180° C., preferably from 60° to 130° C., so that the melt can be extruded. The glass-transition temperature of the mixture must therefore in any case be less than 180° C., preferably less than 130° C. If necessary, it is reduced by conventional pharmacologically acceptable plasticizers, such as long-chain alcohols, ethylene glycol, propylene glycol, trimethylolpropane, triethylene glycol, butanediols, pentanols, hexanols, polyethylene glycols, aromatic carboxylates (eg. dialkyl phthalates, trimellitates, benzoates or terephthalates), aliphatic dicarboxylates (eg. dialkyl adipates, sebacates, azelaates, citrates or tartrates) or fatty acid esters. The plasticizer preferably accounts for no more than 20% by weight, based on the polymer. Particularly preferred NVP polymers are those which do not require additives of this type, ie. those which, as a mixture with the active ingredient and, if required, conventional pharmaceutical auxiliaries, melt or soften in the desired temperature range even without additives having a specific plasticizing effect. Melting or softening below a certain temperature may be necessary because of possible thermal and/or oxidative damage not only to the active ingredient but also to the NVP polymer. The latter may undergo yellowing on extrusion, and it is for this reason that NVP polymers have not usually been extruded to date. However, there is little danger at extrusion temperatures below 180° C., especially below 130° C., if the polymer has not been prepared in aqueous solution using hydrogen peroxide as an initiator, but has been obtained in an organic solvent or in water using an organic peroxide as an initiator, for example by the process according to German Patent application No. P 36 42 633.4 or by the process described in U.S. Pat. Nos. 4,520,179 and 4,520,180.

If the K value is greater than 17, in particular greater than 30 or even 40 (up to a maximum of 70), and no highly plasticizing component is present, the only suitable copolymers are those having a glass transition temperature T_g of less than 120° C., preferably less than 100° C., or the NVP polymer (including homopolymers) must not have been prepared in water containing H₂O₂ as an initiator. This would give rise to polymer

terminal groups which result in yellowing at elevated temperatures.

Suitable comonomers are unsaturated carboxylic acids, eg. methacrylic acid, crotonic acid, maleic acid and itaconic acid, and their esters with alcohols of 1 to 12, preferably 1 to 8, carbon atoms, as well as hydroxyethyl or hydroxypropyl acrylate and methacrylate, (meth) acrylamide, the anhydrides and half esters of maleic acid and itaconic acid (the half esters preferably not being formed until after the polymerization), N-vinylcaprolactam and vinyl propionate.

Preferred comonomers are acrylic acid and in particular vinyl acetate. Preferred NVP polymers are therefore those which either contain only NVP or vinyl acetate as the only comonomer or contain not less than 10, preferably not less than 30% by weight thereof as copolymerized units. Some or all of the vinyl acetate and vinyl propionate may be hydrolysed after the polymerization.

Solvent-free means that no organic solvent, in particular no chlorohydrocarbon, is added. Furthermore, thermoplastics which are poorly soluble in gastric juice should not be admixed, and the water content of the NVP polymer should not exceed 3.5% by weight. (This water content is due to spontaneous absorption of moisture from the air and not the intentional addition of water.) Higher water contents are harmful in that evaporation of the water after the polymer/active compound extrudate emerges from the die results in porous moldings or may even produce moldings possessing cracks in the surface.

The novel process is suitable, for example, for processing the following active compounds: betamethasone, thiotic acid, sotalol, salbutamol, norfenefrine, silymarin, dihydroergotamine, buflomedil, etofibrate, indometacin, oxazepam, β -acetyl-digoxin, piroxicam, haloperidol, ISMN, amitriptylin, diclofenac, nifedipine, verapamil, pyritinol, nitrendipin, doxycycline, bromhexine, methylprednisolone, clonidine, fenofibrate, allopurinol, pirenzepine, levothyroxin, tamoxifen, metildigoxin, o-(β -hydroxyethyl)-rutoside, propicillin, aciclovir mononitrate, paracetamol, naftidrofuryl, pentoxifylline, propafenone, acebutolol, L-thyroxin, tramadol, bromocriptine, loperamide, ketotifen, fenoterol, cadobelisate, propanolol, enalaprilhydrogen maleate, bezafibrate, ISDN, gallopamil, xantinol nicotinate, digitoxin, flunitrazepam, bencyclane, dexapanthenol, pindolol, lorazepam, diltiazem, piracetam, phenoxymethylpenicillin, furosemide, bromazepam, flunarizin, erythromycin, metoclopramide, acemetacin, ranitidin, biperiden, metamizole, doxepin, dipotassium chloroazepate, tetrazepam, estramustine phosphat, terbutaline, captopril, maprotiline, prazosin, atenolol, glibenclamide, cefaclor, etilefrine, cimetidine, theophylline, hydromorphone, ibuprofen, primidone, clobazam, oxaceprol, medroxyprogesterone, flecainid, mgpyridoxal 5-phosphate glutamate, hymechromone, etofylline clofibrate, vincamine, cinnarizine, diazepam, ketoprofen, flupentixol, molsimine, glibornuride, dimetinden, melperone, soquinolol, dihydrocodeine, clomethiazole, clemastine, glisoxepide, kallidinogenase, oxyfedrine, baclofen, carboxymethylcysteine, thioridazine, betahistine, L-tryptophan, myrtol, bromelaine, prenylamine, salazosulfapyridine, astemizol, sulpiride, benzerazide, dibenzepine, acetylsalicylic acid, miconazol, nystatin, ketoconazole, Na picosulfate, colestyramine, gemfibrocil, rifampicin, fluocortolone, mexiletin, amoxicillin, terfenadrin, mucopolysaccharide polysulfate, triazolam,

mianserin, tiaprofenic acid, amezinium metilsulfate, mefloquine, probucol, quinidine, carbamazepine, mg L-aspartate, penbutolol, piretanide, amitriptyline, cyproterone, Na valproinate, mebeverine, bisacodyl, 5-aminosalicylic acid, dihydralazine, magaldrate, phenprocoumon, amantadine, naproxen, carteolol, famotidine, methyl dopa, auranofine, estriol, nadolol, levomepromazine, doxorubicin, medofenoxate, azathioprine, flutamide, norfloxacin, fendiline, prajmalium bitartrate and aescin.

Solid solutions of the following active compounds are particularly preferred: acetaminophen (paracetamol), acetohexamide, acetyldigoxin, acetylsalicylic acid, acromycin, anipamil, benzocaine, β -carotene, chloramphenicol, chlordiazepoxide, chlormadinone acetate, chlorothiazide, cinnarizine, clonazepam, codeine, dexamethasone, diazepam, dicoumarol, digitoxin, digoxin, dihydroergotamine, drotaverine, flunitrazepam, furosemide, gramicidin, griseofulvin, hexobarbital, hydrochlorothiazide, hydrocortisone, hydrofluormethiazide, indomethacin, ketoprofen, lonetil, medazepam, mefruside, methandrostenolon e, methylprednisolone, methylsulfadiazine (sulfaperin), nalidixic acid, nifedipine, nitrazepam, nitrofurantoin, nystatin, estradiol, papaverine, phenacetin, pheno-barbital, phenylbutazone, phenytoin, prednisone, reserpine, spironolactone, streptomycin, sulfadimidine (sulfamethazine), sulfamethizole, sulfamethoxazole, sulfamethoxydiazine (sulfameter), sulfaperin, sulfathiazole, sulfoxazole, testosterone, tolazamide, tolbutamide, trimethoprim and tyrothricin.

The term solid solutions is familiar to the skilled worker, for example from the literature cited at the outset. In solid solutions of pharmaceutical active compounds in polymers, the active compound is present in the polymer in molecular disperse form.

The formation of solid solutions of the stated active compounds in NVP polymers was not to be foreseen and is all the more surprising since many active compounds which are sparingly soluble in water do not form (molecular disperse) solid solutions in other polymers but are incorporated in the particular polymer in the form of solid particles which can be detected under the electron microscope. In the case of crystalline active compounds, they also exhibit a Debye-Scherrer pattern, in contrast to the solid solutions.

If, in addition to the binders employed according to the invention, further water-soluble, fusible binders are used, the amount of the first-mentioned binders should be not less than 50, preferably not less than 70% by weight, based on all fusible binders used.

For the purposes of the present invention, solid pharmaceutical forms are, for example, tablets, tablet cores, granules and suppositories.

For the purposes of the present invention, pharmaceutical active compounds are all substances which have a pharmaceutical effect and have a very low level of side effects, provided that they do not decompose under the processing conditions. The amount of active compound per dosage unit and the concentration can vary within wide limits, depending on the activity and the rate of release. The only condition is that they are sufficient for achieving the desired effect. For example, the concentration of active compound may be from 0.1 to 95, preferably from 20 to 80, in particular from 30 to 70, % by weight. Combinations of active compounds may also be used. For the purposes of the present invention, vitamins too are active compounds. Active compounds which are sparingly soluble in water are those

whose absorption in the gastro intestinal tract is usually unsatisfactory owing to their low solubility.

The active compound or compounds can be mixed with the binders and, where relevant, other conventional pharmaceutical additives before or after melting of the polymeric binder, by a method conventionally used in industry. Mixing is preferably carried out in an extruder having a mixing zone, preferably a twin-screw extruder, or in the screw zone of an injection molding machine.

Shaping may be effected by injection molding or by extrusion followed by shaping of the plastic extrudate, for example by hotface cutting to give granules or molding to give tablets, for example by passing the extrudate between two rollers which are driven in opposite directions and have depressions opposite one another in the roller shell, the form of these depressions determining the tablet shape. Cold-face cutting is also suitable and may be followed by pressing of the granules to give tablets. For the purpose of the present invention, the extrusion includes injection molding.

By varying the type and amount of comonomer, the NVP polymer can, depending on the intended use, be made sufficiently strongly or weakly hydrophilic for the tablets prepared from it to dissolve (rapidly or with a delay) in the mouth (buccal tablets) or in the stomach or not until they reach the intestine, or to swell so that they release the active compound. They are sufficiently swellable when they absorb more than 10% by weight of water on storage at 90% relative humidity. If it is desirable for carboxyl-containing binders to release the active compound only when they reach the alkaline medium of the intestine, the above water absorption applies only to the neutralized form (salt form) of the polymer (in which some or all of the protons of the carboxyl groups have been replaced by ammonium, sodium or potassium ions).

Examples of conventional pharmaceutical auxiliaries, whose total amount may be up to 100% by weight, based on the polymer are extenders, such as silicates or silica, stearic acid or its salts with, for example, magnesium or calcium, methylcellulose, sodium carboxymethylcellulose, talc, sucrose, lactose, cereal or corn starch, potato flour or polyvinyl alcohol, as well as wetting agents, preservatives, disintegrating agents, adsorbents, colorants and flavorings (cf. for example H. Sucker et al., *Pharmazeutische Technologie*, Thieme-Verlag, Stuttgart 1978).

If desired, the solid pharmaceutical form may also be provided with a conventional coating to improve the appearance and/or the flavor (coated tablets) or additionally to delay the release of active compound. For oral tablets with sustained release of active compound, it may be advantageous to prepare the tablet by one of the known techniques in a closed-cell porous form so that it floats in the stomach and consequently remains there longer.

In the case of solid pharmaceutical forms with rapid release of active compound, the novel process permits substantially freer design of the pharmaceutical form than does the conventional tablet pressing technique. For example, the tablets can be engraved for designation, or virtually any shapes, which are clearly identifiable even by those with impaired vision, may be produced. Certain shapes, for example hemispheres may also be suitable for achieving certain characteristics of active compound release. By extrusion or hot or cold face cutting of the extrudate, it is possible to produce

very small-particled and uniformly shaped granules in a simple manner, for example for multiple-unit forms.

In the Examples which follow, parts and percentages are by weight. The active compound release time was determined by the half-change test method.

EXAMPLE 1

45 parts of a copolymer of 60% by weight of N-vinylpyrrolidone and 40% by weight of vinyl acetate, having a K value of 30, 5 parts of stearyl alcohol and 50 parts of theophylline were processed to tablet cores in an injection molding machine at 100° C. The tablet cores obtained were stable to mechanical effects and did not show any abrasion during transportation and packaging. In the half-change test (cf. for example R. Voigt, *Lehrbuch der pharmazeut. Technologie*, 5th Edition, Verl. Chemie. Weinheim; Deerfield Beach, Florida; Basel, 1984, page 627) in conjunction with the paddle method according to USP 21, the active compound was completely released in the course of from 6 to 8 hours.

EXAMPLE 2

50 parts of the copolymer of example 1 and 50 parts of theophylline were processed to oblong tablets having a length of 1 cm in an injection molding machine at 120° C. In this case too, the tablets thus obtained were stable to mechanical effects and released the active compound completely in the course of from 1 to 2 hours.

EXAMPLE 3

47.5 parts of a copolymer of 60% by weight of N-vinylpyrrolidone and 40% by weight of vinyl acetate, having a K value of 30, 2.5 parts of crosslinked polyvinylpyrrolidone (PVP) as a tablet disintegrator and 50 parts of theophylline were mixed and extruded in a twinscrew extruder. The temperature of each of the five shots was 120° C. The die was at 130° C. The still plastic extrudate was pressed to give oblong tablets with the aid of the apparatus described in the parallel German Application No. P 36 12 211.4. The tablets were stable to mechanical effects and the active compound was released in the course of from 30 to 45 minutes.

EXAMPLE 4

50 parts of a copolymer of 30% by weight of N-Weinheim; vinylpyrrolidone and 70% by weight of vinyl acetate, having a K value of 52, and 50 parts of theophylline were mixed and extruded in a twin-screw extruder. The temperatures of the five shots were 30, 60, 100, 100 and 120° C. The die was likewise heated to 120° C. The still plastic extrudate was pressed to give mechanically stable oblong tablets as described in Example 3. The active compound was completely released in the course of 8 hours.

EXAMPLE 5

47.5 parts of a copolymer of 60% by weight of N-vinylpyrrolidone and 40% by weight of vinyl acetate, having a K value of 30, 2.5 parts of stearyl alcohol and 50 parts of theophylline were melted in an injection molding machine at 100° C. and processed to tablet cores. The mold was left at room temperature. The tablet cores thus produced were stable to mechanical effects, and the active compound was completely released in the course of 6 hours.

In each of the Examples 6 to 11, a mixture of 50% by weight of an NVP homopolymer (PVP) having a Fikentscher K value of from 12 to 60 and 50% by weight

of theophylline was processed in a single-screw extruder at the following temperatures:

Example	K value	T [°C]					Die
		1st	2nd	3rd shot	4th	5th	
6	12	115	125	135	135	135	145
7	17	125	125	135	145	145	155
8	25	145	155	165	175	175	175
9	30	150	160	160	170	180	180
10	60	150	160	160	170	180	180
11	60	80	100	130	140	150	160

The active compound in the tablets thus obtained dissolved completely (in simulated gastric juice) in less than 30 minutes in the case of Examples 6 and 7, in the course of from 1 to 2 hours in the case of Examples 8 and 9, and after more than 2 hours in the case of Example 10. In Example 11, the PVP contained 10% by weight of stearyl alcohol. In this case, the time of release was 8 hours.

EXAMPLES 12 TO 14

36 parts of a copolymer of 60% by weight of N-vinylpyrrolidone and 40% by weight of vinyl acetate, having a K value of 30, 4 parts of stearyl alcohol, 40 parts of theophylline and 20 parts of starch in Example 12, lactose in Example 13 and sucrose in Example 14 were mixed in a 6-shot twin-screw extruder and shaped into tablets similarly to Example 1. The temperatures of the shots were 90°, 100°, 110°, 120°, 130° and 130° C., and the temperature of the die was 135° C. The active compound dissolved completely out of the tablets in the course of 6 hours.

EXAMPLE 15

50 parts of the copolymer of Examples 12 to 14 and 50 parts of lithium carbonate were processed to tablets on the same apparatus and at the same temperatures as in Examples 12 to 14. These tablets released the active compound (in simulated gastric juice) completely in the course of from 15 to 20 minutes.

EXAMPLE 16

50 parts of the copolymer of Examples 12 to 14 and 50 parts of verapamil were shaped into tablets as described in Examples 12 to 14. The active compound was released in this case in about 3 hours.

The copolymers used for the preparation of solid solutions had the following compositions and K values:

(A) 60% by weight of NVP and 40% by weight of vinyl acetate; K value about 33.

(B) 100% by weight of NVP; K value 30.

(C) 100% by weight of NVP; K value 12.

(D) 100% by weight of NVP; K value 12.

The polymers B, C and D were prepared according to German Patent Application P 36 42 633.4 in water using an organic peroxide as the initiator.

EXAMPLE 17

3 parts of copolymer A and 1.5 parts of benzocaine were premixed in a plowshare mixer and were extruded in a simple, 6-shot extruder, the individual shots having the following temperatures, proceeding toward the die: 30°, 30°, 40°, 50°, 60° and 70° C. The die temperature was likewise 70° C. The extrudate consisted of a solid solution, as was shown by the Debye-Scherrer photograph, which did not give the slightest indication of crystallinity. A similar procedure was used for the remaining Examples (cf. Table), and the same result was obtained.

Example no.	Active compound	Polymer	Active comp./polymer weight ratio	Active comp./polymer weight ratio						Die temp. °C.
				T1	T2	T3	T4	T5	T6	
17a	Benzocaine	A	1:3	20	30	40	40	50	50	50
18	Paracetamol	C	1:3	60	80	100	120	120	120	120
19	Phenytoin	C	1:3	60	80	100	120	120	120	120
20	Benzocaine	C	1:3	50	50	60	60	70	80	90
21	Indomethacin	A	1:3	50	60	70	80	80	80	80
22	Indomethacin	A	1:3	60	80	100	120	120	120	120
23	Anipamil	A	1:3	30	30	40	50	50	60	60
24	Anipamil	C	1:3	30	30	40	50	50	60	60
25	Benzocaine	A	1:1	30	30	40	500	50	60	60
26	Benzocaine	B	1:1	30	30	40	500	50	60	60
27	Benzocaine	C	1:1	30	30	40	50	50	60	60
28	Phenytoin	A	1:3	60	80	100	120	120	120	130
29	Paracetamol	A	1:3	60	80	100	120	120	120	130
30	Sulfathiazole	A	1:1	70	90	100	100	100	100	130
31	Benzocaine	A	1:3	50	50	60	60	70	80	90
32	Benzocaine	C	1:3	50	50	60	60	70	80	80
33	Sulfathiazole	C	1:3	70	90	100	100	100	100	120
34	Benzocaine	A	1:9	30	40	50	60	60	70	70
35	Benzocaine	A	1:6	50	60	70	80	85	85	85
36	Benzocaine	C	1:9	30	30	40	50	60	60	60
37	Benzocaine	C	1:6	30	40	60	60	70	70	70
38	Benzocaine	B	1:9	60	70	90	90	90	100	100
39	Benzocaine	B	1:6	60	80	80	100	120	120	120
40	Benzocaine	B	1:3	60	80	80	100	120	120	120
41	Benzocaine	B	1:1	60	80	95	100	120	135	140
42	Phenytoin	A	1:9	60	70	90	90	90	100	100
43	Phenytoin	A	1:6	60	70	90	100	100	100	100
44	Phenytoin	C	1:9	60	70	90	90	90	100	100
45	Phenytoin	C	1:6	60	70	90	100	100	100	100
46	Phenytoin	B	1:9	60	80	110	130	150	150	150
47	Phenytoin	B	1:6	60	80	110	130	150	160	160
48	Phenytoin	B	1:3	60	80	110	120	150	160	170

-continued

Example no.	Active compound	Polymer	Active comp./polymer Weight ratio	T1	T2	T3	T4	T5	T6	Die temp. °C.
49	Phenytoin	B	1:1	60	80	125	150	160	175	180

T1 to T6 are the temperatures of shots 1 to 6 in °C.

EXAMPLE 50

Examples 18, 19 and 20 were repeated on an injection molding machine at a die temperature of 130° C. Tablets consisting of solid solutions were obtained.

EXAMPLE 51

Vitamin C, as the active compound, was mixed in a weight ratio of 1:1 with the following NVP polymers in a twin-screw extruder, the mixture was extruded at the temperatures stated in the Table for shots 1 to 6 and for the die, and the extrudate was shaped into tablets via a calender, according to the parallel German application No. P 36 12 211.4.

(a) Copolymer of 60% by weight of NVP and 40% by weight of vinyl acetate; K value about 33.

(b) 90% by weight of copolymer (a) and 10% by weight of stearyl alcohol.

(c) Homopolymer of NVP; K value 17.

	T1	T2	T3	T4	T5	T6	Die
(a)	60	80	100	110	120	120	120° C.
(b)	60	80	80	100	100	110	110° C.
(c)	60	80	100	110	120	120	125° C.

In all three cases, the vitamin was liberated in water in the course of from 1 to 2 hours. During the processing described, it did not undergo any decomposition at all and, in this form, was protected from the effects of light and atmospheric oxygen when stored for a prolonged period.

We claim:

1. A process for the preparation of a solid pharmaceutical form by mixing one or more pharmaceutical active compounds with one or more fusible pharmacologically tolerated binders and subjecting the mixture to injection molding or extrusion and shaping at from 50° to 180° C., wherein the fusible binder used is a solvent-free N-vinylpyrrolidone polymer which has a water content of not more than 3.5% by weight and contains not less than 20% by weight of N-vinylpyrrolid-2-one (as copolymerized units, all copolymerized comonomers contain) nitrogen and/or oxygen and, at least when the glass transition temperature of the mixture is above 120° C., N-vinylpyrrolidone polymer is used which is obtained by polymerization in an organic solvent or using an organic peroxide as an initiator in aqueous solution, and the mixture does not contain any thermoplastics which are sparingly soluble in gastric juice.

2. A process as defined in claim 1, wherein the polymeric binder used contains not less than 60% by weight of N-vinylpyrrolidone as copolymerized units.

3. A process as defined in claim 1, wherein plasticizers are used in an amount of not more than 20% by weight, based on the N-vinylpyrrolidone polymer.

4. A process as defined in claim 1, wherein a polymeric binder used consists of N-vinylpyrrolidone or contains, in addition to N-vinylpyrrolidone, only vinyl acetate as copolymerized units.

5. A process as defined in claim 1, wherein a polymeric binder is used whose comonomers are selected from the following group: acrylic acid, methacrylic acid, crotonic acid, maleic acid, maleic anhydride, itaconic acid, itaconic anhydride and esters of the stated acids or half esters of the stated dicarboxylic acids with alcohols of 1 to 12 carbon atoms, and hydroxyethyl and hydroxypropyl acrylate and methacrylate, acrylamide, methacrylamide, N-vinylcaprolactam and vinyl propionate.

6. A process as defined in claim 1, wherein the active compound used is sparingly soluble in water, dissolves in the polymer melt without the addition of a solvent or water to give a molecular disperse solution, and forms a solid solution after the melt solidifies.

7. A process as defined in claim 1, wherein one or more active compounds from the following group are used: acetaminophen (paracetamol), acetohexamide, acetyldigoxin, acetylsalicylic acid, acromycin, anipamil, benzocaine, β -carotene, chloramphenicol, chlordiazepoxide, chlormadinone acetate, chlorothiazide, cinnarizine, clonazepam, codeine, dexamethasone, diazepam, dicoumarol, digitoxin, digoxin, dihydroergotamine, drotaverine, flunitrazepam, furosemide, gramicidin, griseofulvin, hexobarbital, hydrochlorothiazide, hydrocortisone, hydrofluormethiazide, indomethacin, ketoprofen, lonetil, medazepam, mefruside, methandrostenolone, methylprednisolone, methylsulfadiazine (sulfaperin), nalidixic acid, nifedipine, nitrazepam, nitrofurantoin, nystatin, estradiol, papaverine, phenacetin, phenobarbital, phenylbutazone, phenytoin, prednisone, reserpine, spironolactone, streptomycin, sulfadimidine (sulfamethazine), sulfamethizole, sulfamethoxazole, sulfamethoxydiazine (sulfameter), sulfaperin, sulfathiazole, sulfisoxazole, testosterone, tolazamide, tolbutamide, trimethoprim, tyrothricin.

8. A process as defined in claim 1, wherein a N-vinylpyrrolidone polymer having a Fikentscher K value of from 10 to 50 is used.

9. A process as defined in claim 1, wherein a N-vinylpyrrolidone polymer having a Fikentscher K value of from 12 to 35 is used.

* * * * *

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCION DE NUEVAS CREACIONES

2020
Bogotá, D.C.

Abogado
ÁLVARO CORREA ORDÓÑEZ

ASUNTO	Radicación	06-101178
	Trámite	011
	Evento	378
	Actuación	430
	Oficio	105-17
	Folios	022

Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional	☐		
Vía PCT (fase nacional)	☒	Cap. I	☒
		Cap. II	☐

No. Sol. Internacional	PCT/US2005/011678
Fecha de Presentación Internal.	07-04-2005

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

1. Documentos estudiados

Descripción:	Folios 18-43 y 49-52	como se radicó inicialmente
Reivindicaciones:	Folios 43-48	como se radicó inicialmente
	Folios 140-143	como se radicó el 16-06-2006
Prioridad:	Folio 1	US, 60/560.452, 08-04-2004
Respuesta del solicitante	Folio 135-139	como se radicó el 16-06-2006

2. Objeto de la invención

Título de la solicitud: FORMULACIONES DE DISPERSIONES SOLIDAS DE ACETATO DE BAZEDOXIFENO (folio 1)

El problema técnico planteado en esta solicitud esta relacionado con la necesidad de mejorar la biodisponibilidad de acetato de bazedoxifeno en composiciones farmacéuticas sólidas orales (folio 19; pág. 2).

Para solucionar este problema técnico la solicitud en estudio proporciona dispersiones solidas de acetato de bazedoxifeno en un medio de dispersión (por ej. celulosas, polisacáridos, poloxámeros, polivinilpirrolidonas, polietilenglicoles,

propilenglicoles, miglioles, entre otros, mezcla de los mismos o copolímeros de los mismos), composiciones y formas de dosificación sólida que contienen tal dispersión sólida de acetato de bazedoxifeno.

El objeto de la presente solicitud se cataloga en A61K31/55, A61K9/14, A61K47/10, de acuerdo con la Clasificación Internacional de Patentes (IPC).

3. De la solicitud de Patente

3.1. Reivindicaciones (artículo 30 D 486)

Existe falta de claridad en la reivindicación 1 (y dependiente 14), al señalar al mismo tiempo dos tipos de objeto "*una dispersión sólida que comprende... y una forma de dosificación que comprende...*"; no obstante lo anterior, se aclara que dado que el preámbulo de la reivindicación 1 (y dependientes 2-14) indica "*una dispersión sólida*", se toma en cuenta para el análisis la materia relacionada con la dispersión sólida que comprende acetato de bazedoxifeno (está en forma amorfa) en un agente de dispersión.

Al tiempo, se señala al solicitante que es necesario eliminar en la reivindicación 1 (y dependiente 14) la segunda parte que señala "*...y donde una forma de dosificación comprende...*", ya que la dispersión sólida sólo debe caracterizarse por los elementos que la comprenden como son al acetato de bazedoxifeno, el agente dispersante y la proporción si es necesario, de acuerdo con la materia que evidencia resolver el problema planteado.

Asimismo, se aclara que en las reivindicaciones 1, 13 y 14, no es apropiado caracterizar la dispersión sólida por los resultados de área bajo la curva AUC₀₋₂₄ y solubilidad en equilibrio, puesto que son resultados a alcanzar y el alcance de la reivindicación incluiría no sólo la solución propuesta en la solicitud, sino todas las alternativas presentes o futuras que lleguen a ese resultado. Por ende, se reitera que la dispersión sólida sólo debe caracterizarse por los elementos que la comprenden como son al acetato de bazedoxifeno, el agente dispersante y la proporción si es necesario, de acuerdo con la materia que evidencia resolver el problema planteado.

Por lo anterior, el capítulo reivindicatorio no cumple con el requisito de tener claridad, concisión y sustento de acuerdo con las exigencias de los artículos 30 de la Decisión 486.

4. Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente de la que se reivindica prioridad es 08-04-2004, se buscaron documentos del estado de la técnica relacionados, con fecha de publicación anterior a ésta.

N°	Documento	Título	Fecha de Publicación
D2	WO0203987	Pharmaceutical compositions of estrogenic agents	17-01-2002
D3	US4801460	Preparation of solid pharmaceutical forms	31-01-1989

Anterioridad D2 en folios 144-153, D3 en folios 154-159.

D2 está relacionado con composiciones farmacéuticas de compuestos con actividad como agentes estrogénicos, tal como TSE-424 (*bazedoxifeno*), ERA-923, raloxifeno, tamoxifeno, entre otros y uno o mas vehículos o excipientes farmacéuticamente aceptables (folio 145; pág. 1).

D3 está relacionado con la preparación de formas farmacéuticas solidas por mezcla de uno o más compuestos activos con uno o más aglutinantes fundibles, el cual es un polímero de NVP (n-vinilpirrolidon-2-ona) (folio 154; portada).

5. **Análisis de patentabilidad (artículo 14 D486)**

5.1. Nivel inventivo (artículo 18 D486)

Se solicita en las reivindicaciones 1-14 una dispersión sólida que comprende acetato de bazedoxifeno disperso en un agente de dispersión, en las 15-20 una composición que comprende tal dispersión solida y un vehículo farmacéuticamente aceptable y en las 21-23 una forma de dosificación que comprende tal dispersión solida.

SOLICITUD	D2	D3
Dispersión solida de	Dispersión solida de	Dispersión solida (soluciones solidas) de
acetato de bazedoxifeno	un fármaco poco soluble en agua	un fármaco poco soluble en agua
estando el activo en forma amorfa	√ como <u>acetato de bazedoxifeno</u> (acetato de TSE-424), tamoxifeno, entre otros (folios 148, 153; pág. 4, 35).	-- como tamoxifeno, entre otros (folio 156; col. 3)
en agente de dispersión	--	√ el fármaco esta en forma molecular dispersa en el polímero (<i>es decir amorfa</i>) (folio 156; col 4); ya que las dispersiones solidas no muestran indicación de cristalinidad (folio 158; col 8).
EFEECTO: aumentar la velocidad de disolución del activo poco soluble en medio acuoso y mejorar su biodisponibilidad (folio	aumentar la velocidad de disolución de fármacos pobremente solubles en agua, (folios 147-148; pág. 3-4)	√ en polímeros de NVP (n-vinilpirrrolidin-2-ona) como una polivinilpirrolidona (folio 155, 156, col.1, 4)
		aumentar la velocidad de disolución y mejorar la absorción del compuesto activo poco soluble (folio 155,157; col.1, 5)

El estado de la técnica más cercano es D2 que señala la técnica de formación de dispersiones solidas de compuestos pobremente solubles en agua (incluidos los agentes estrogénicos como tamoxifeno y el TSE-424 ó *bazedoxifeno* y sus sales farmacéuticamente aceptables como el acetato de bazedoxifeno) que permiten lograr una rápida disolución del fármaco, desde composiciones farmacéuticas solidas, tal como se señala en la tabla comparativa.

La diferencia de la solicitud con D2 es que señala específicamente una dispersión solida de acetato de bazedoxifeno en un agente de dispersión donde el fármaco esta en forma amorfa (siendo un agente dispersante el PVP -polivinilpirrolidona- acorde con lo soportado en folios 36, 40-42; pág. 19, 23- 25).

El efecto técnico que logra tal diferencia es que la dispersión sólida de acetato de bazedoxifeno permite aumentar la velocidad de disolución del activo en medio acuoso y mejorar su biodisponibilidad al ser comparado con formulaciones donde el acetato de bazedoxifeno no está en dispersión sólida (folios 40-42, 51-52; pág. 23-25, fig. 1 y 2).

Así, el Problema Técnico Objetivo está relacionado con la necesidad de obtener una dispersión sólida del acetato de bazedoxifeno, que permita aumentar la velocidad de disolución del activo en medio acuoso y mejorar su biodisponibilidad.

Sin embargo, se encuentra que D3 enseña la formación de dispersiones sólidas de compuestos activos escasamente solubles en agua (como tamoxifeno *otro modulador estrogénico como el bazedoxifeno de la solicitud*) con polímeros de NVP (n-vinilpirrolidina-2-ona) como una polivinilpirrolidona, donde el fármaco está en forma molecular dispersa en el polímero (*es decir amorfa*), ya que las dispersiones sólidas no muestran indicación de cristalinidad; siendo las dispersiones sólidas adecuadas para aumentar la velocidad de disolución y mejorar la absorción del compuesto activo, desde formas farmacéuticas sólidas, como se señala en la tabla comparativa.

En consecuencia, se considera que para un experto en la materia, la dispersión sólida de acetato de bazedoxifeno reclamada es obvia a las divulgaciones y enseñanzas de D2 y D3 para resolver el problema planteado; por tanto, la materia reclamada (dispersión de acetato de bazedoxifeno, composiciones y formas farmacéuticas que la contienen) no tiene nivel inventivo.

6. Respuesta al solicitante

- El solicitante anexa un nuevo capítulo reivindicatorio (folio 140-143), en el que ha eliminado las reivindicaciones que reclamaban usos, métodos de tratamiento, y métodos de preparar una dispersión sólida (afectadas por nivel inventivo); así mismo, ha modificado la reivindicación 1; capítulo que es aceptado por esta Oficina.

No obstante, se aclara que la reivindicación 1 presenta problemas de claridad al señalar al mismo tiempo dos tipos de objeto "una dispersión sólida que comprende... y una forma de dosificación que comprende...", tal como se explica en el respectivo numeral.

- En cuanto a las objeciones de las reivindicaciones, el solicitante menciona que:
 - De la observación del examinador de que no todas las relaciones de principio activo: agente de dispersión se han evaluado mediante ensayos, "*...se hace notar a su despacho que las reivindicaciones 8-12 que ahora corresponden a las reivindicaciones 7-11 son dependientes de la nueva reivindicación 1, y por lo tanto, son susceptibles de patentabilidad*" (folio 138; pág. 4 de respuesta).

En referencia, se aclara que la objeción no es por errores de dependencia, sino porque de acuerdo con la descripción, la materia que presenta el efecto técnico de aumentar la velocidad de disolución del activo en medio acuoso y mejorar su biodisponibilidad (folios 40-42, 51-52; pág. 23-25, fig. 1 y 2), es la dispersión sólida es la de acetato de bazedoxifeno en PVP en relación 1:1 y no existen datos de tal efecto para otras relaciones del activo y PVP.

- De la observación del Despacho de que caracterizar una dispersión solida por AUC₀₋₂₄ no corresponde a una característica esencial, *"...se le informa a su Despacho que en la pág. 40 del Manual andino...se menciona que se pueden permitir características no esenciales cuando esté justificado y siempre y cuando permitan distinguir el estado de la técnica son ambigüedad..."* (folios 138-139; pág. 4-5 de respuesta).

Al respecto, se aclara que al caracterizar la dispersión solida por el resultado del área bajo la curva (AUC₀₋₂₄), se esta caracterizando por un resultado a alcanzar, lo que no es admisible (Manual Andino, pág. 41, numeral 4.6.6), porque el alcance de la reivindicación incluiría no solo la solución propuesta en la solicitud, sino todas las alternativas presentes o futuras que lleguen a ese resultado.

Por tanto, la dispersión solida sólo debe caracterizarse por lo elementos que la comprenden como son acetato de bazedoxifeno, agente dispersante y proporciones si es necesario.

- En cuanto a la falta de novedad, el solicitante señala que al comparar elemento por elemento la materia de la reivindicación 1 y D1 *"...se puede concluir que dicho documento no contienen todas las características específicas reclamadas en el nuevo pliego reivindicatorio...por tanto, la presente invención es novedosa frente a D1"* (folio 138; pág.4 de respuesta).

Frente a esta observación, se señala primero que la reivindicación 1 tiene un problema de claridad, como se explica en el numeral de reivindicaciones, porque contiene a la vez dos tipos de objeto (una dispersión solida y una forma de dosificación); no obstante lo anterior, se aclara que dado que el preámbulo de la reivindicación 1 (y dependientes 2-14) señala "una dispersión solida", se toma en cuenta la materia relacionada con la dispersión solida que comprende acetato de bazedoxifeno en un agente de dispersión.

Segundo, se aclara que D1 enseña es una dispersión solida de un compuesto de formula (I): $F-(X)q$, donde **F** puede ser bazedoxifeno, **q** es un entero de 1-5 y **X** es un grupo que tiene incluido un grupo de nitrato o nitrito (folio 98, 99, 103; pág. 39, 142, 169), es decir que la formula (I) no enseña el bazedoxifeno acetato; por tanto tal documento no afecta la novedad de la solicitud.

Tercero, dado lo anterior, se ha revisado el estado de la tecnica y se han encontrado los documentos D2 y D3 que afectan el nivel inventivo de la materia reclamada, tal como se enseña en el respectivo numeral.

7. Conclusión

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

N°	Documento N°	Reivindicaciones Afectadas	Requisito que Afecta
D2	WO0203987	1-23	Nivel inventivo
D3	US4801460	1-23	Nivel inventivo

245/65

159

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el artículo 8 de la resolución reglamentaria No. 00210 del 15 de enero de 2001, advirtiéndole que contra él no procede recurso alguno en la vía gubernativa.



JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha
78 MAR. 2017

CONCEPTO TECNICO No.665	EXAMINADOR TECNICO Código No. 202079
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