



No. 06-009536- -00003-0000

Fecha 2007-07-19 09 19 53 Dep 2020 NUECREACION
Tra 11 PATENTEIYII Eve 379 FASENACIONALI
Act 538 PETICION Folios 2

Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Ref: Expediente No. 06-009.536

Solicitud de patente de invención titulada: "PROCEDIMIENTOS DE SECADO POR PULVERIZACIÓN PARA LA FORMACIÓN DE DISPERSIONES SÓLIDAS AMORFAS DE FÁRMACOS Y PÓLIMEROS".

Solicitante: PFIZER PRODUCTS INC.

SOLICITUD DE EXAMEN DE PATENTABILIDAD SEGÚN
EL ARTÍCULO 44 DE LA DECISION 486, GACETA No. 577

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, D.C., identificado tal como aparece al pie de mi firma, en mi condición de apoderado del solicitante, respetuosamente me permito solicitar que se examine si la invención reúne los requisitos de patentabilidad previstos en la misma, dando cumplimiento a lo establecido en el artículo 44 de la Decisión 486 de la comisión de la Comunidad Andina de Naciones. Adjunto recibo por el monto de \$202.000 pesos para cubrir la tasa correspondiente, según la Resolución 36155 del año 2006.

Atentamente,

CARLOS R. OLARTE
C.C. 79.782.747 de Bogotá
T.P. 74.295

Anexo: Recibo por \$202.000 pesos

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 06-09536

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

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **577** DE

FECHA **29 DE JUNIO DE 2007** EL TÉRMINO HÁBIL SEÑALADO POR LA LEY

EXPIRA EL **27 DE SEPTIEMBRE DE 2007**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____

NO X

179

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

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
20 September 2001 (20.09.2001)

PCT

(10) International Publication Number
WO 01/68092 A2

(51) International Patent Classification⁷: **A61K 31/404**,
9/14, 9/16, 9/20

[CA/US]; Pfizer Global Research and Development,
Eastern Point Road, Groton, CT 06340 (US). **CREW,**
Marshall, D. [US/US]; 1986 Northeast Purser Lane, Bend,
OR 97701 (US).

(21) International Application Number: PCT/IB01/00389

(22) International Filing Date: 16 March 2001 (16.03.2001)

(74) Agents: **LUMB, J., Trevor** et al.; c/o Simpson, Alison,
Urquhart-Dykes & Lord, 30 Welbeck Street, London W1G
8ER (GB).

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/190,125 16 March 2000 (16.03.2000) US

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM,
HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK,
LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX,
MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL,
TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(71) Applicant (*for all designated States except US*): **PFIZER**
PRODUCTS INC. [US/US]; Eastern Point Road, Groton,
CT 06340 (US).

(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **BABCOCK, Wal-**
ter, C. [US/US]; 64815 Laidlaw Lane, Bend, OR 97701
(US). **FRIESEN, Dwayne, Thomas** [US/US]; 60779
Currant Way, Bend, OR 97702 (US). **LORENZ, Dou-**
glas, Alan [US/US]; 61332 King Jehu Way, Bend, OR
97702 (US). **MACRI, Christopher, A.** [US/US]; Pfizer
Global Research and Development, Eastern Point Road,
Groton, CT 06340 (US). **NIGHTINGALE, James, Alan,**
Schrivver [US/US]; 62900 Santa Cruz Avenue, Bend, OR
97701 (US). **SHANKER, Ravi, Mysore** [IN/US]; Pfizer
Global Research & Development, Eastern Point Road,
Groton, CT 06340 (US). **HANCOCK, Bruno, Caspar**

Published:

— without international search report and to be republished
upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.



WO 01/68092 A2

(54) Title: GLYCOGEN PHOSPHORYLASE INHIBITOR

(57) Abstract: Pharmaceutical compositions of a particularly effective sparingly soluble glycogen phosphorylase inhibitor are disclosed, as well as methods of making such compositions and dosage forms from such compositions.

enhance the concentration of Drug A. In addition, such polymers are conventionally used with crystalline drug while, for such polymers to provide concentration enhancement the drug must be in a concentration-enhanced form such as an amorphous state or an amorphous dispersion.

While specific polymers have been discussed as being suitable for use in the mixtures of the present invention, blends of such polymers may also be suitable. Thus the term "polymer" is intended to include blends of polymers in addition to a single species of polymer. For example, when it is desirable to combine two concentration-enhancing polymers such as PVP (a nonionic vinyl polymer that is highly water-soluble) and HPMCAS (an ionic cellulosic that has a high glass transition temperature (T_g) of 118°C), they can be combined in a wide variety of ways. For example, a solid amorphous dispersion of Drug A and both polymers can be combined such that they are as homogeneous as possible by, for example, dissolving all three materials in a solvent and then solidifying by precipitation in a non-solvent or by evaporation of the solvent. Alternatively, a dispersion may be formed from Drug A with a first concentration-enhancing polymer, followed by dry- or wet-blending a second concentration-enhancing polymer with the dispersion. The second concentration-enhancing polymer may also be added as a coating or as a wet-granulating material.

DISPERSIONS OF DRUG AND CONCENTRATION-ENHANCING POLYMER

A first aspect of this invention comprises solid amorphous dispersions of Drug A and one or more aqueous-soluble, concentration-enhancing polymers. Broadly, a major portion ($\geq 60\%$) of Drug A is in amorphous as opposed to crystalline, form. Preferably, Drug A in such dispersions is substantially amorphous in

the sense that at least 75% of Drug A is in a non-crystalline state (equivalent to 25% or less of Drug A being in a crystalline state). As previously mentioned, the amorphous nature of Drug A in the dispersion can be demonstrated, for example, by DSC or SEM analysis or by PXRD. Preferably, essentially all of Drug A is amorphous in the sense that less than 10% of Drug A in the dispersion is in the crystalline state.

Although, as discussed below, amorphous Drug A and the aqueous-soluble concentration-enhancing polymer can be a simple physical mixture, it is generally preferred that Drug A be at least partially dispersed in the concentration-enhancing polymer. Even more preferably, Drug A is as homogeneously dispersed as possible in the concentration-enhancing polymer. One method to determine whether Drug A is relatively homogeneously dispersed in the concentration-enhancing polymer is by DSC analysis. Generally, the observation of a single T_g for the dispersion that is between that of the polymer alone and that of Drug A alone is an indication of good homogeneity. Typically, for a non-homogeneous dispersion, such as a physical blend of amorphous Drug A and polymer, there will be two T_g s—one for Drug A and one for the polymer. Although dispersions may be prepared by any of the methods described below, some methods noted below are preferred in that they result in more homogeneous dispersions, and in a higher fraction of Drug A being in the amorphous state.

Methods of Forming Dispersion

The amorphous solid dispersion of drug may be prepared by any of the known ways for doing so, including, for example, by melt fusion, by melt congealing, by lyophilization, by extended mechanical processing such as by trituration, or in a twin-screw extruder or in a ball mill, or by solvent processing. When the dispersion is made by mechanical means such as

enhance the concentration of Drug A. In addition, such polymers are conventionally used with crystalline drug while, for such polymers to provide concentration enhancement the drug must be in a concentration-enhanced form such as an amorphous state or an amorphous dispersion.

While specific polymers have been discussed as being suitable for use in the mixtures of the present invention, blends of such polymers may also be suitable. Thus the term "polymer" is intended to include blends of polymers in addition to a single species of polymer. For example, when it is desirable to combine two concentration-enhancing polymers such as PVP (a nonionic vinyl polymer that is highly water-soluble) and HPMCAS (an ionic cellulosic that has a high glass transition temperature (T_g) of 118°C), they can be combined in a wide variety of ways. For example, a solid amorphous dispersion of Drug A and both polymers can be combined such that they are as homogeneous as possible by, for example, dissolving all three materials in a solvent and then solidifying by precipitation in a non-solvent or by evaporation of the solvent. Alternatively, a dispersion may be formed from Drug A with a first concentration-enhancing polymer, followed by dry- or wet-blending a second concentration-enhancing polymer with the dispersion. The second concentration-enhancing polymer may also be added as a coating or as a wet-granulating material.

DISPERSIONS OF DRUG AND CONCENTRATION-ENHANCING POLYMER

A first aspect of this invention comprises solid amorphous dispersions of Drug A and one or more aqueous-soluble, concentration-enhancing polymers. Broadly, a major portion ($\geq 60\%$) of Drug A is in amorphous, as opposed to crystalline, form. Preferably, Drug A in such dispersions is substantially amorphous in

by ball milling or extrusion, a major portion ($\geq 60\%$) of the drug is typically in an amorphous state, with the remaining portion in a crystalline state. However, in some cases mechanical processing may lead to larger fractions of Drug A being amorphous. When prepared by solvent processing, a major portion of the drug is in an amorphous state, usually substantially all ($>75\%$) is in an amorphous state, and often essentially all ($>90\%$) of the drug is in an amorphous state. By "amorphous state" is meant the drug may be present in the dispersion in any non-crystalline state such as any of the following three broad classes of forms: (a) in discrete, drug-rich domains; (b) homogeneously distributed therein, i.e., a solid solution; or (c) any state or combination of states between the extremes of (a) and (b).

In solvent processing, a homogeneous solution of solvent, drug and the concentration-enhancing polymer is formed, alone or along with other excipients that may or may not be dissolved, followed by solvent removal by precipitation or evaporation. Because solvent processing permits formation of homogeneous amorphous solid dispersions, it is the preferred class of fabrication methods for forming the amorphous solid dispersion of Drug A. All of the following forms of solvent processing are useful in forming the solid dispersion form of the pharmaceutical composition of the present invention: spray-drying, spray-coating, evaporation, rotovaporation, fluid bed drying, precipitation and combinations thereof. Precipitation is typically induced by contacting the drug/dispersion polymer solution with a non-solvent such as water, a liquid hydrocarbon or super-critical CO_2 .

A preferred method of forming the dispersion is by dissolving the drug and dispersion polymer in a common solvent, then removing the solvent by spray-drying or spray-coating. Spray-drying and spray-coating processes and equipment are described generally in Perry's Chemical Engineers' Handbook, pages 20-54 to 20-57 (6th Ed. 1984).

More details on spray-drying processes and equipment are reviewed by Marshal in 50 Chem. Eng. Prog. Monogr. series 2 (1954).

The terms "spray-drying" and "spray-coating" in connection with the present invention are used conventionally and broadly refer to processes involving breaking up liquid mixtures into small droplets (atomization) and rapidly removing solvent from the mixtures in a vessel such as a spray-drying apparatus or a fluidized bed- or pan-coater where there is a strong driving force for evaporation of solvent from the droplets. In the case of spray-coating, the droplets impinge on a particle, bead, pill, tablet, or capsule, resulting in a coating comprising the solid amorphous dispersion. Spray-coating may also be conducted on a metal, glass or plastic surface and the coated layer may subsequently be removed and milled to the desired particle size. In the case of spray-drying, the droplets generally dry prior to impinging on a surface, thus forming particles of solid amorphous dispersion on the order of 1 to 200 micrometers in diameter. The strong driving force for solvent evaporation is generally provided by maintaining the partial pressure of solvent in the spray-drying apparatus well below the vapor pressure of the solvent at the temperature of the drying droplets. This is accomplished by either (1) maintaining the pressure in the spray-drying apparatus at a partial vacuum (e.g., 0.01 to 0.50 atm); (2) mixing the liquid droplets with a warm drying gas; or (3) both (1) and (2). For example, a solution of drug and a dispersion polymer such as HPMCAS in acetone may be suitably spray-dried by spraying the solution at a temperature of 50°C (the vapor pressure of acetone at 50°C is about 0.8 atm) into a chamber held at 0.01 to 0.2 atm total pressure by connecting the outlet to a vacuum pump. Alternatively, such a solution may be sprayed into a chamber where it is

mixed with nitrogen gas at a temperature of 80°C to 250°C and pressure of 1.0 to 1.2 atm.

Generally, the temperature and flow rate of the drying gas is chosen so that dispersion polymer/drug
5 solution droplets are dry enough by the time they reach the wall of the apparatus that they are essentially solid, so that they form a fine powder and do not stick to the apparatus wall. The actual length of time to
10 achieve this level of dryness depends on the size of the droplets. Droplet sizes generally range from 1 to 500 μm in diameter, with 5 to 100 μm being more typical. The large surface-to-volume ratio for the droplets and the large driving force for evaporation of solvent generally leads to actual drying times of a few seconds or less,
15 and more typically substantially less than a second. For some mixtures of drug/dispersion polymer/solvent this rapid drying generally leads to a more uniform, homogeneous composition, as opposed to the generally less desirable separation into drug-rich and polymer-rich
20 phases. Such dispersions having a homogenous composition can be considered solid solutions and may be supersaturated in drug.

However, as described below, separation of Drug A from the dispersion polymer to form essentially a
25 physical blend of particles or domains of amorphous Drug A and the concentration-enhancing polymer can also have good performance and also forms a part of this invention. As a result, solidification times can be quite long—even in excess of an hour as might occur by
30 bulk evaporation of solvent from a stirred or agitated vessel. However, preferably, solidification times should be less than 100 seconds, preferably less than 20 seconds, and more preferably less than 1 second. In general, to achieve such rapid solidification of the
35 drug/dispersion polymer solution, it is preferred that the solution be spray-dried or spray-coated by the formation of droplets during the spray-drying or spray-

coating process that are less than 500 μm . The so-formed solid particles resulting from solidification of these droplets generally tend to be 1 to 200 μm in diameter.

Following solidification, the solid particles
5 may remain in the spray-drying chamber for additional time, evaporating more solvent. Generally, when the dispersion exits the spray-drying apparatus, its residual solvent content should be less than 10 wt% and preferably less than 2 wt%.

10 The solution spray-dried to form the solid amorphous dispersion can be quite simple, containing only Drug A, one or more concentration-enhancing polymers and one or more solvents. In such cases, the solids content of the spray-drying solution is generally in the range of
15 from 1 to 30 wt%, and more preferably from 5 to 20 wt%. Following spray-drying and, if required, a secondary drying step, the resulting dispersion is essentially free of solvent and thus consists primarily of Drug A and one or more concentration-enhancing polymers.

20 When the dispersion is the only source of concentration-enhancing polymer in the dosage form, the Drug A content of the dispersion is generally 5 to 75 wt%. Preferably, to limit the total mass of the dosage form, the Drug A content is at least 15 wt%,
25 although good relative bioavailability is generally expected at even very low drug loadings (Drug A content of 1 to 15 wt%). In addition, when concentration-enhancing polymer other than in the dispersion is included in the dosage form, rather surprisingly it has
30 been found that the Drug A content of the dispersion can be quite high, approaching 100%, since dispersions containing 99 wt% Drug A have shown marked enhancement of Drug A concentration.

When the concentration-enhancing polymer is
35 HPMCAS, typically 5 to 10 wt% Drug A and 5 to 10 wt% HPMCAS are dissolved either in pure acetone or acetone containing up to 10 wt% water. For example, to form a

dispersion of 50% Drug A and 50% HPMCAS, 6.5 wt% Drug A and 6.5 wt% HPMCAS are dissolved in a solvent composed of 95% acetone and 5% water. Thus, the solution composition is 6.5 wt% Drug A, 6.5 wt% HPMCAS, 82.65 wt% acetone and 4.35 wt% water. It was found that Drug A was stable in this solution for up to 7 days' storage at ambient temperatures in a stainless steel container. Solids contents in such solutions have been increased to up to 15 wt% and have been successfully spray-dried with good results.

Other excipients may be added to the spray solution, either co-dissolved in the solvent along with the drug and dispersion polymer or suspended in the solution to form a slurry. Such excipients may include: acids, bases or buffers to modify the ionic state, stability or dissolution properties of the resulting dispersion; fillers, binders, disintegrants or other materials to improve the tableting process or final properties of the tablet such as tablet hardness or friability and the dissolution of the dispersion; antioxidants to improve the dispersion's stability; osmotic agents, including both osmotically effective solutes such as sugars, salts and polyols as well as surfactants, all of which affect the wetting or dissolution rate of the dispersion itself, as well as the dissolution rate of any granules, beads, tablets or capsules into which the dispersion has been incorporated.

In particular, it is desirable to add excipients to the spray solution that will improve the manner in which the dispersion wets, disperses, disintegrates and ultimately dissolves when introduced into an aqueous use environment.

Since Drug A is itself hydrophobic and a number of the concentration-enhancing polymers suitable for forming dispersions show a tendency to agglomerate to form "hydrogel"-type materials in aqueous solutions,

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

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
3 January 2003 (03.01.2003)

PCT

(10) International Publication Number
WO 03/000226 A2(51) International Patent Classification⁷: A61K 9/00

(21) International Application Number: PCT/IB02/02256

(22) International Filing Date: 17 June 2002 (17.06.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/300,259 22 June 2001 (22.06.2001) US(71) Applicant (for all designated States except US): **PFIZER PRODUCTS INC.** [US/US]; Eastern Point Road, Groton, CT 06340 (US).

(72) Inventors; and

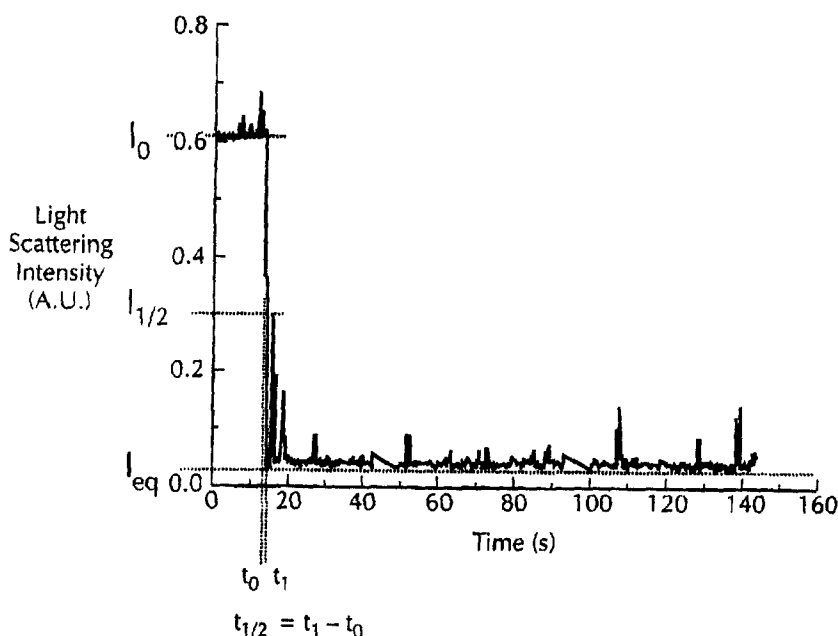
(75) Inventors/Applicants (for US only): **BABCOCK, Walter, Christian** [US/US]; Bend Research, Inc., 64550 Research Road, Bend, OR 97701 (US). **CREW, Marshall, David** [US/US]; Bend Research, Inc., 64550 Research Road, Bend, OR 97701 (US). **FRIESEN, Dwayne, Thomas** [US/US]; Bend Research, Inc., 64550 Research Road, Bend, OR 97701 (US). **RABENSTEIN, Mark, David**[US/US]; Bend Research, Inc., 64550 Research Road, Bend, OR 97701 (US). **SMITHEY, Daniel, Tod** [US/US]; Bend Research, Inc., 64550 Research Road, Bend, OR 97701 (US). **SHANKER, Ravi, Mysore** [IN/US]; Pfizer Global Research and Development, Eastern Point Road, Groton, CT 06340 (US).(74) Agents: **LUMB, Trevor, J.** et al.; c/o Simpson, Alison Urquhart-Dykes & Lord, 30 Welbeck Street, London W1G 8ER (GB).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent

[Continued on next page]

(54) Title: PHARMACEUTICAL COMPOSITIONS CONTAINING POLYMER AND DRUG ASSEMBLIES



(57) Abstract: Solutions containing polymer/drug assemblies of a low-solubility drug and polymer are disclosed. In addition, solid aggregated polymer/drug assemblies are disclosed comprising a low-solubility drug and polymer.

WO 03/000226 A2

PHARMACEUTICAL COMPOSITIONS CONTAINING
POLYMER AND DRUG ASSEMBLIES

5 This application claims the benefit of priority of
provisional Patent Application Serial No. 60/300,259 filed
June 22, 2001.

BACKGROUND OF THE INVENTION

10 The present invention relates to pharmaceutical
compositions containing drug and polymer assemblies, and in
particular to compositions of low-solubility drugs which
provide improved drug concentrations.

 Several methods have been described to utilize
15 polymers to increase the concentration of low-solubility
drugs. One conventional method attempts to mix a polymer with
the drug to enhance the dissolution rate of the drug. For
example, Martin et al., U.S. Patent No. 4,344,934 mixed
poorly-soluble drugs with polymers such as hydroxypropyl
20 methyl cellulose (HPMC) and added an aqueous surfactant
solution to the drug-polymer mixture. While this results in
improved dissolution, there is only slight enhancement of drug
concentration relative to the equilibrium concentration.
Piergiorgio et al., U.S. Patent No. 4,880,623 used solvent
25 processing to co-precipitate nifedipine with PEG and adsorbed
this onto polymers such as HPMC, or onto other excipients.
While increased drug bioavailability was observed, no
comparison was made between different drug forms. Uedo
et al., U.S. Patent No. 5,093,372 mixed the sparingly-soluble
30 drug exifone with polymers such as HPMC to increase
bioavailability. However, this did not result in any enhanced
drug concentration of the drug/polymer mixture relative to the
bulk crystalline form of the drug.

 Utilizing solubility-improved forms of drugs such as
35 more soluble salt forms, more soluble polymorphs, or amorphous
drug forms may result in a temporary improvement in the
concentration of the drug in the solution, where the

Table 13

Example No.	DLS Mean Particle Size (nm)
26 (Drug 1/VAVAC-20%)	20
27 (Drug 1/VAVAC-12%)	574
28 (Drug 1/VAVAC-2%)	885
C5 (VAVAC-20%)	12
C6 (VAVAC-12%)	5

When no drug is present (Controls 5 and 6), small particles about 10 nm in size were present due to aggregation of the polymer, likely as a result of its amphiphilicity. For solutions containing Drug 1 (formed from the dispersions of Examples 26-28), larger particles were present. This demonstrates the formation of polymer/drug assemblies in solution.

Examples 30 and 31

These examples demonstrate polymer/drug assemblies formed by dissolution of dispersions of a second drug in polymer. Amorphous solid dispersions of 4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl-amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (Drug 2) and HPMCAS-MF were made by first mixing Drug 2 in a solvent together with HPMCAS-MF to form a spray solution. For Example 30, the spray solution comprised 1 wt% Drug 2, 9 wt% HPMCAS, and 90 wt% acetone. For Example 31, the spray solution comprised 2.5 wt% Drug 2, 7.5 wt% HPMCAS, and 90 wt% acetone. These spray solutions were then spray-dried by directing an atomizing spray using a two-fluid external-mix spray nozzle at 2.7 bar at a feed rate of 150 g/min into the stainless-steel chamber of a Niro spray-dryer. Nitrogen drying gas at a temperature of 155°C and about 1900 gm/min was

introduced to the dryer; drying gas and evaporated solvent exited the dryer at a temperature of 70°C.

The resulting solid dispersions were collected via a cyclone and then dried in a Gruenberg solvent tray-dryer at 40°C for at least 8 hours. After drying, the dispersions of Example 30 contained 10 wt% Drug 2, and the dispersions of Example 31 contained 25 wt% Drug 2.

Example 32

The solutions formed from solid dispersions of Examples 30 and 31 were evaluated using light-scattering methods to demonstrate the formation of polymer/drug assemblies in solution. For DLS analysis, 500 mg of the dispersions of Example 30 or 200 mg of Example 31 were each added to 50 mL PBS equilibrated to 37°C for two hours. In both of these experiments, the total amount of active Drug 2 in PBS would have been 1000 µg/mL, if all of the drug had dissolved. Light-scattering was measured using a PSS-NICOMP 380 Submicron Particle Sizer as described in Example 3. The mean particle sizes (hydrodynamic radius) for the bulk of particles in solution are shown in Table 14.

For static light scattering (StLS) analysis, the solid dispersions of Examples 30 and 31 were each added to PBS equilibrated to 37°C for two hours. After centrifuging for 1 minute at 13,000 G, light-scattering was measured using a Horiba LA-910 as described in Example 3. The particle size distribution (radius of gyration) for StLS is calculated and results are shown below in Table 14.

5. A pharmaceutical composition comprising solid aggregated polymer/drug assemblies, said solid aggregated polymer/drug assemblies comprising a low-solubility drug and an amphiphilic polymer, said solid aggregated polymer/drug assemblies being formed by a process comprising forming a solution containing polymer/drug assemblies, wherein a substantial portion of said polymer/drug assemblies in said solution have a diameter of from 20 nm to 5000 nm, and isolating said solid aggregated polymer/drug assemblies from said solution.

6. The composition of any one of claims 3-5 wherein said amphiphilic polymer is selected from the group consisting of hydroxypropyl cellulose acetate succinate, hydroxypropyl methyl cellulose acetate, hydroxypropyl methyl cellulose succinate, hydroxypropyl methyl cellulose acetate succinate, hydroxypropyl methyl cellulose phthalate, hydroxypropyl methyl cellulose acetate phthalate, hydroxyethyl methyl cellulose, hydroxyethyl methyl cellulose succinate, hydroxyethyl cellulose acetate succinate, hydroxyethyl methyl cellulose acetate succinate, hydroxyethyl methyl cellulose acetate phthalate, hydroxyethyl cellulose acetate, hydroxyethyl ethyl cellulose, hydroxypropyl methyl cellulose, carboxymethyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate, methyl cellulose acetate phthalate, ethyl cellulose acetate phthalate, hydroxypropyl cellulose acetate phthalate succinate, cellulose propionate phthalate, hydroxypropyl cellulose butyrate phthalate, cellulose acetate trimellitate, methyl cellulose acetate trimellitate, ethyl cellulose acetate trimellitate, hydroxypropyl cellulose acetate trimellitate, hydroxypropyl methyl cellulose acetate trimellitate, hydroxypropyl cellulose

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

2020
Bogotá, D.C.,

Abogado:
CARLOS OLARTE

ASUNTO:	Radicación No.	06 00 9536
	Trámite	002
	Evento	378
	Actuación	430
	Oficio	548
	Folios	

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 comunica:

Documentos estudiados:

Descripción:	Folios 45 a 128 como fue presentada en fase Internacional.
Reivindicaciones:	Folios 129 a 133 como fue presentada en fase Internacional.
Prioridad:	US 60/492.407 (2003-08-04), US 60/568.989 (2004-05-07)

Objeto de la Invención

Título de la invención: "Procedimientos de secado por pulverización para la formación de dispersiones solidas amorfas de fármacos y polímeros"

Problema Técnico Planteado: "Necesidad de un procedimiento de secado por pulverización para preparar composiciones farmacéuticas de dispersiones solidas amorfas que comprende fármacos de solubilidad baja y polímeros que sea capaz de proporcionar grandes cantidades de dispersiones solidas amorfas secadas por pulverización que sean homogéneas, densas y presenten bajo contenido en disolvente residual"

Solución: "Se proporciona un procedimiento para la formación de una dispersión sólida amorfa que comprende un fármaco y un polímero."

IPC: A61K 009/016, A61K 031/166, A61K 031/470, A61P 003/000

Determinación del Estado de la Técnica

El Estado de la Técnica se determinó con base en la fecha de presentación 2003-08-04 y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Item	Documento	Título	Fecha de Publicación
D1	WO0168092	<i>Glycogen phosphorylase inhibitor</i>	20.09.2001
D2	WO03000226	<i>Pharmaceutical compositions containing polymer and drug assemblies</i>	03.01.2003

Análisis de Patentabilidad (Art 14 D486)

Nivel Inventivo (Art18 D486)

La reivindicación 1 dice: Un procedimiento para formar una composición que comprende una dispersión sólida amorfa con un fármaco y un polímero, que comprende: (a) proporcionar un aparato de secado con un atomizador conectado a una cámara de secado; (b) formar una solución para pulverizar mediante disolución de dicho fármaco de solubilidad baja y dicho polímero en un disolvente; (c) pulverizar dicha solución a través del atomizador en la cámara para formar gotas que presentan un tamaño medio de volumen de menos de 500 μm ; (d) inyectar el gas de secado a través de la entrada a un caudal y a una temperatura T_{in} tal que dichas gotas solidifican en menos de aproximadamente 20 segundos; (e) ...la velocidad de alimentación de dicha solución para pulverizar es al menos 10 kg/hr, y la T_{in} de dicho gas de secado se controlan de forma que dicho gas de secado a dicha salida presenta una temperatura T_{out} , y dicha T_{out} es inferior que dicho punto de ebullición de dicho disolvente."

La reivindicación 15 dice: "El producto del procedimiento de cualquiera de las reivindicaciones 1-14"

D1 revela dispersiones amorfas de medicamento y uno o más polímeros mejoradores de la solubilidad, en donde el medicamento tiene una forma amorfa y además presenta un método para formar una dispersión sólida de por diversos medios como trituración o fundición (página 19), un método para formar la dispersión es disolver el medicamento y la dispersión del polímero en el solvente, para luego remover el solvente por spray-drying o spray-coating. Revela que la solución puede ser atomizada dentro de una cámara donde esta se mezcla con un gas a una temperatura entre 80 y 250°C con una presión de 1 a 2 atm (página 22). Revela que el tamaño de las partículas puede variar de 1 a 500 μm (página 23).

La solicitud se diferencia de D1 en los polímeros mencionados y en la velocidad de entrada.

El Efecto Técnico que logra la diferencia es la obtención de composiciones farmacéuticas de dispersiones solidas amorfas homogéneas, densas y presenten bajo contenido de disolvente residual.

El Problema Técnico Objetivo de esta solicitud es proveer un método de obtención de composiciones farmacéuticas de dispersiones solidas amorfas homogéneas, densas y presenten bajo contenido de disolvente residual.

D2 revela soluciones y agregados que comprenden una mezcla medicamento/polímero, en donde el medicamento posee baja solubilidad (portada), en la parte experimental revela la formación de una solución que contiene un solvente, un medicamento y un polímero derivado de celulosa, tal como la hidroxipropilcelulosa (página 214 y 247). Estas soluciones fueron

secadas por aspersión en donde el nitrógeno se empleó para secar las partículas a una temperatura de 155 °C, y se evaporó el solvente a una temperatura de 70° C, en donde la velocidad de alimentación de esta cámara es de 150 g / min (9 kg/hr).

El experto en la materia habría sido motivado por D2 a utilizar una velocidad de alimentación cercana a 9 kg/h y a emplear otro tipo de polímeros para llegar a la solución planteada por la presente solicitud.

Se concluye que las reivindicaciones independientes 1 sus dependientes y 15 carecen de nivel inventivo.

Conclusión

Los requisitos de Patentabilidad de la presente Solicitud se encuentran afectados así:

N°	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	WO0168092	1-15	Nivel inventivo
D2	WO03000226	1-15	Nivel inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de 60 días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

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

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

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

22 ene. 2010

CONCEPTO TECNICO
NUMERO: 4364

EXAMINADOR TÉCNICO
Código:202092