

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176099-2

RECIBO OFICIAL DE CAJA : 10 - 16,826  
FECHA : MARZO 3 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-049473- -00006-0000

Fecha: 2010-03-09 15:50:59 Dep: 2020 DIR NUL VASOR  
Tra: 11 PATENTILYII Lve: 378 FASLNACIONALI  
Act: 444 RESPULSTARLQUL Folios: 9

\*\*\*\*\* CONSIGNACION \*\*\*\*\*

| DEPOSITANTE       | TIPO PAGO    | BANCO           | CUENTA    | No. PAGO  | FECHA PGO  | VAL. PAGO     |
|-------------------|--------------|-----------------|-----------|-----------|------------|---------------|
| CAVELIER ABOGADOS | CONSIGNACION | BANCO DE BOGOTA | 062754387 | 076773622 | 03/03/2010 | 17,745,000.00 |

\*\*\*\*\* DONDE ESTO \*\*\*\*\*

| CANT. ENTREGADO | CONCEPTO                             | TOTAL CONCEPTO |
|-----------------|--------------------------------------|----------------|
| 1 50000-01-00   | PRORROGA DE TERMINOS                 | 80,000.00      |
|                 | *** ADICION PRORROGA DE TERMINOS *** | 80,000.00      |
|                 | TOTAL :                              | 80,000.00      |

SON: OCHENTA Y TRES MIL PESOS

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

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. \_\_\_\_\_

COLO : 14033 - 841 - 024 - 8

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

VIT : 500176089-2

RECIBO OFICIAL DE CAJA : 10 - 16,032  
FECHA : MARZO 1 DE 2010

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-049473-00006-0000

Fecha: 2010-03-09 15:50:59 Dep: 2020 DIR NDI VASOR  
Tra: 11 PATENTILYII Lve: 378 PASLNASIONAL  
Act: 444 RLSPULSTARLGUL Folios: 9

CONSIGNACION

| DEPOSITANTE       | TIPO PAGO    | BANCO           | CUENTA    | No. PAGO  | FECHA PAGO | VAL. PAGO     |
|-------------------|--------------|-----------------|-----------|-----------|------------|---------------|
| CAVELIER ABOGADOS | CONSIGNACION | BANCO DE BOGOTA | 062754367 | 175544272 | 01/03/2010 | 23,049,000.00 |

CONCEPTO

| CANT. REENTISTADO | CONCEPTO                       | TOTAL CONCEPTO |
|-------------------|--------------------------------|----------------|
| 1 50005-01-03     | CAMBIO DE MODALIDAD Y MODIFICA |                |
|                   | 12 MARCAS Y LEMAS COMERCIALES  | 14,000.00      |
|                   | TOTAL :                        | 14,000.00      |

SON: DIECIO SATORCE MIL PESOS

RESPONSABLE :

TS

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. \_\_\_\_\_

COLO: 14033 - 841 - 024 - 8

\*US06514529B2\*

(12) **United States Patent**  
**Yamamoto et al.**(10) **Patent No:**  
(45) **Date of Patent:****US 6,514,529 B2**

Feb. 04, 2003 ✓

(54) **Oxazolidinone tablet formulation**(75) Inventors: **Ken Yamamoto**, Portage, Michigan (US); and **Homer Lin**, Oak Park, California (US)(73) Assignee: **Pharmacia & Upjohn Company**, Kalamazoo, MichiganType: **U.S.**

( \* ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/809,696**(22) Filed: **Mar. 15, 2001****Related U.S. Application Data**

(60) Provisional Application No. 60/190969 Filed on Mar. 22, 2000

Prior Publication No. 20010051647 Filed on Dec. 13, 2001

(51) **Int. Cl.**<sup>7</sup> **A61K 9/20**; A61K 9/42; A61K 9/14; A61K 9/16; A61K 9/50(52) **U.S. Cl.** **424/465**; 424/464; 424/476; 424/489; 424/490; 424/497; 424/499; 424/502(58) **Field of Search** 424/489; 424/490; 424/497; 424/499; 424/502; 424/464; 424/465; 424/476(56) **References Cited****U.S. PATENT DOCUMENTS**

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|-------------|---------|------|
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| WO/00/01378 | 1/2000  | (WO) |
| WO/00/73301 | 12/2000 | (WO) |

\* cited by examiner

(74) **Primary Examiner** — Thurman K. Page**Assistant Examiner** — Humera N. Sheikh**Attorney, Agent, or Firm** — John H. Engelmann; Bruce Stein**Exemplary claim number** — 1**Art Unit** — 1615(57) **ABSTRACT**

[00001] The present invention provides a compressed tablet of an antibacterial oxazolidinone agent which provides high drug load and excellent bioavailability. ✓

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## 19 Claims, 0 Drawing Sheets, and 0 Figures

## CROSS-REFERENCE TO RELATED APPLICATIONS

[00002] This application claims the benefit of the following provisional application: U.S. Ser. No: 60/190,969, filed Mar. 22, 2000, under 35 USC 119(e)(i).

## BACKGROUND OF THE INVENTION

[00003] 1. Field of the Invention

[00004] The present invention is a novel tablet formulation which permits high drug load and does not use lactose. ✓

[00005] 2. Description of the Related Art

[00006] Oxazolidinones are well known to those skilled in the art as gram positive anti-bacterial agents, see, for example, U.S. Pat. Nos. 5,688,792, 5,529,998, 5,547,950, 5,627,181, 5,700,799, 5,843,967, 5,792,765, 5,684,023, 5,861,413, 5,827,857, 5,869,659, 5,698,574, 5,968,962 and 5,981,528.

[00007] Various tablet formulations are very well known to those skilled in the art which contain starch, microcrystalline cellulose, hydroxypropylcellulose and other ingredients. However, it is very difficult to get high drug load and blood levels similar to IV administration. ✓

## SUMMARY OF INVENTION

[00008] Disclosed is a compressed tablet containing the following ingredients:

[00009] antibacterial oxazolidinone, ✓

[00010] starch, ✓

[00011] microcrystalline cellulose, ✓

[00012] binder selected from the group consisting of hydroxypropylcellulose, hydroxypropylmethylcellulose, povidone and corn starch paste, ✓

[00013] disintegrants selected from the group consisting of sodium starch glycolate, croscarmellose sodium, crospovidone and low substituted hydroxypropylcellulose and ✓

[00014] lubricant selected from the group consisting of stearic acid, metallic salts of stearic acid, hydrogenated vegetable oil and talc.

[00015] Also disclosed is a method for providing blood levels of an antibacterial oxazolidinone by oral administration medically equivalent to the blood levels produced by IV administration of the same antibacterial oxazolidinone which comprises administration of a compressed tablet of the formulation:

[00016] antibacterial oxazolidinone,

[00017] starch,

[00018] microcrystalline cellulose,

[00019] binder selected from the group consisting of hydroxypropylcellulose, hydroxypropylmethylcellulose, povidone and corn starch paste,

[00020] hydroxypropylcellulose,

[00021] disintegrants selected from the group consisting of sodium starch glycolate, croscarmellose sodium, crospovidone and low substituted hydroxypropylcellulose and

[00022] lubricant selected from the group consisting of stearic acid, metallic salts of stearic acid, hydrogenated vegetable oil and talc.

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✓  
[00028] The preferred solid oral dosage form is a tablet. The composition of the tablets of the present invention can vary but includes the following essential features: ✓

[00029] antibacterial oxazolidinone, starch,

[00030] microcrystalline cellulose,

[00031] binder selected from the group consisting of hydroxypropylcellulose, hydroxypropylmethylcellulose, povidone and corn starch paste,

[00032] disintegrants selected from the group consisting of sodium starch glycolate, croscarmellose sodium, crospovidone and low substituted hydroxypropylcellulose and

[00033] lubricant selected from the group consisting of stearic acid, metallic salts of stearic acid, hydrogenated vegetable oil and talc.

[00034] It is preferred that the antibacterial oxazolidinone is selected from the group consisting of linezolid, eperezolid and (S)-N-[[3-[3-fluoro-4-(tetrahydro-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide S,S-dioxide. It is more preferred that the antibacterial oxazolidinone is linezolid. It is preferred that the linezolid is in crystal form II. It is preferred that the starch is corn starch. It is preferred that the binder is hydroxypropylcellulose and that the disintegrant is sodium starch glycolate. It is preferred that the lubricant is magnesium stearate. It is preferred that the tablet is film coated. It is also preferred that the tablet has a hardness range is from about 18 to about 30 Strong Cobb units; it is more preferred that the tablet has a hardness range is from about 20 to about 25 Strong Cobb units. ✓

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[00043] The above tablet formulations are prepared by methods well known to those skilled in the art. It is preferred that the tablet formulations of the present invention be prepared as follows. The binder solution is prepared by adding part of the hydroxypropylcellulose to the purified water and mixing in an appropriate container until dissolved. The granulation is performed by adding the antibacterial oxazolidinone, corn starch, microcrystalline cellulose (intragranular, 24.0 mg), and the remaining hydroxypropylcellulose into a high shear mixer and mixing until adequately mixed. Then add the binder solution while mixing, and if needed, add an additional sufficient quantity of water while mixing, to form the granulation. Wet screen the granulation using appropriate equipment as is well known to those skilled in the art, for example, a Comil. Following granulation the granulation is dried using suitable equipment, such as a fluid bed dryer. After the granulation is dried, dry screen the granulation using appropriate equipment, such as a Comil. The lubrication portion is formed by mixing microcrystalline cellulose (extragranular, 93.6 mg) and sodium starch glycolate with the dry screened granulation in a suitable blender, such as a diffusion (tumble) type V-blender, until adequately blended. Next remove a portion of the blended material and combine with the magnesium stearate. Add the magnesium stearate mixture back into the blender, such as a diffusion (tumble) type V-blender, and mix until adequately blended. Finally, collect the lubricated powder mixture in appropriate containers.

[00044] Alternatively, no binder solution need be used. All the hydroxypropylcellulose can be added as powder. In that situation, the antibacterial oxazolidinone, starch and microcrystalline cellulose and hydroxypropylcellulose are combined, mixed and then the water is added. It is preferred that a binder solution be used.

[00045] The compressed tablets are formed using a suitable rotary compression machine and compression tooling. The lubricated powder mixture is compressed into tablets of proper weight, hardness, size and shape.

[00046] It is preferred to coat and wax the tablets. The Opadry White YS-1-18202-A and purified water are mixed to prepare the coating suspension. The coating mixture should be continuously stirred until the mixture is free of lumps and the Opadry is in suspension. Prior to using, the film coating suspension should be screened through an appropriate screen. The desired quantity of tablets is loaded into the appropriately sized perforated coating pans (such as an Accela-Cota or Glatt coating pan) equipped with baffles, spray guns and pumping system. The appropriate amount of aqueous film coating is sprayed on the moving tablets until tablets are evenly coated. After the coating is complete, the appropriate amount of carnauba wax is weighed and added to the bed of tablets to polish the film coated tablets.

[00047] It is preferred to print the tablets with identifying information as is known to those skilled in the art.

[00048] A flow chart of the manufacturing process is provided in CHART B.

[00049] The present invention also includes a method for providing blood levels of an antibacterial oxazolidinone by oral administration medically equivalent to the blood levels produced by IV administration of the same antibacterial oxazolidinone which comprises administration of a compressed tablet of the formulation:

[00050] antibacterial oxazolidinone,

[00051] starch,

[00052] microcrystalline cellulose,

[00053] binder selected from the group consisting of hydroxypropylcellulose, hydroxypropylmethylcellulose, povidone and corn starch paste,

[00054] disintegrants selected from the group consisting of sodium starch glycolate, croscarmellose sodium, crospovidone and low substituted hydroxypropylcellulose and

[00055] lubricant selected from the group consisting of stearic acid, metallic salts of stearic acid, hydrogenated vegetable oil and talc. All the preferences above with regard to the tablet formulation/composition are preferences for the method of providing blood levels of an antibacterial oxazolidinone by oral administration medically equivalent to the blood levels produced by IV administration of the same antibacterial oxazolidinone.

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[00063] Pharmaceutically acceptable refers to those properties and/or substances which are acceptable to the patient from a pharmacological/toxicological point of view and to the manufacturing pharmaceutical chemist from a physical/chemical point of view regarding composition, formulation, stability, patient acceptance and bioavailability.

[00064] When solvent pairs are used, the ratios of solvents used are volume/volume (v/v).

[00065] When the solubility of a solid in a solvent is used the ratio of the solid to the solvent is weight/volume (wt/v).

[00066] Opadry White refers to Colorcon's tablet coating product. The product code YS-1-18202-A refers to a specific tablet coating formula.

#### EXAMPLES

[00067] Without further elaboration, it is believed that one skilled in the art can, using the preceding description, practice the present invention to its fullest extent. The following detailed examples describe how to prepare the various compounds and/or perform the various processes of the invention and are to be construed as merely illustrative, and not limitations of the preceding disclosure in any way whatsoever. Those skilled in the art will promptly recognize appropriate variations from the procedures both as to reactants and as to reaction conditions and techniques.

#### EXAMPLE 1

[00068] Linezolid (400 mg) Tablet Formulation

[TABLE-US-00009]

| Ingredients                                 | Amount    |
|---------------------------------------------|-----------|
| Linezolid                                   | 400.0 mg  |
| Corn starch NF                              | 40.0 mg   |
| Microcrystalline cellulose NF               | 16.0 mg   |
| Hydroxypropylcellulose (intragranular) NF   | 5.92 mg   |
| Hydroxypropylcellulose (binder solution) NF | 2.08 mg   |
| Microcrystalline cellulose NF               | 62.4 mg   |
| Sodium starch glycolate NF                  | 28.0 mg   |
| Magnesium stearate NF                       | 5.6 mg    |
| Purified water USP 22.0% uncoated tablet wt |           |
| Film Coating Phase                          |           |
| Opadry White YS-1-18202-A                   | 16.8 mg   |
| Purified Water USP                          | 129.2 mg  |
| Polishing Phase                             |           |
| Carnauba Wax NF                             | 0.0224 mg |

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[00069] The binder solution is prepared by adding part of the hydroxypropylcellulose to the purified water and mixing in an appropriate container until dissolved. The granulation is performed by adding the antibacterial oxazolidinone, corn starch, microcrystalline cellulose (intragranular, 24.0 mg), and the remaining hydroxypropylcellulose into a high shear mixer and mixing until adequately mixed. Then add the binder solution while mixing, and if needed, add an additional sufficient quantity of water while mixing, to form the granulation. Wet screen the granulation using appropriate equipment as is well known to those skilled in the art, for example, a Comil. Following granulation the granulation is dried using suitable equipment, such as a fluid bed dryer. After the granulation is dried, dry screen the granulation using appropriate equipment, such as a Comil. The lubrication portion is formed by mixing microcrystalline cellulose (extragranular, 93.6 mg) and sodium starch glycolate with the dry screened granulation in a suitable blender, such as a diffusion (tumble) type V-blender, until adequately blended. Next remove a portion of the blended material and combine with the magnesium stearate. Add the magnesium stearate mixture back into the blender, such as a diffusion (tumble) type V-blender, and mix until adequately blended. Finally, collect the lubricated powder mixture in appropriate containers.

[00070] The compressed tablets are formed using a suitable rotary compression machine and compression tooling. The lubricated powder mixture is compressed into tablets of proper weight, hardness, size and shape.

[00071] It is preferred to coat and wax the tablets. The Opadry White YS-1-18202-A and purified water are mixed to prepare the coating suspension. The coating mixture should be continuously stirred until the mixture is free of lumps and the Opadry is in suspension. Prior to using, the film coating suspension should be screened through an appropriate screen. The desired quantity of tablets is loaded into the appropriately sized perforated coating pans (such as an Accela-Cota or Glatt coating pan) equipped with baffles, spray guns and pumping system. The appropriate amount of aqueous film coating is sprayed on the moving tablets until tablets are evenly coated. After the coating is complete, the appropriate amount of carnauba wax is weighed and added to the bed of

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tablets to polish the film coated tablets.

[00072] It is preferred to print the tablets with identifying information as is known to those skilled in the art.

[00073] A flow chart of the manufacturing process is provided in CHART B.

#### EXAMPLE 2

[00074] Linezolid (600 mg) Tablet Formulation

[TABLE-US-00010]

| Ingredients                                 | Amount    |
|---------------------------------------------|-----------|
| Linezolid                                   | 600.0 mg  |
| Corn starch NF                              | 60.0 mg   |
| Microcrystalline cellulose NF               | 24.0 mg   |
| Hydroxypropylcellulose (intragranular) NF   | 8.88 mg   |
| Hydroxypropylcellulose (binder solution) NF | 3.12 mg   |
| Microcrystalline cellulose NF               | 93.6 mg   |
| Sodium starch glycolate NF                  | 42.0 mg   |
| Magnesium stearate NF                       | 8.4 mg    |
| Purified water USP 22.0% uncoated tablet wt |           |
| Film Coating Phase                          |           |
| Opadry White YS-1-18202-A                   | 25.2 mg   |
| Purified Water USP                          | 193.9 mg  |
| Polishing Phase                             |           |
| Carnauba Wax NF                             | 0.0336 mg |

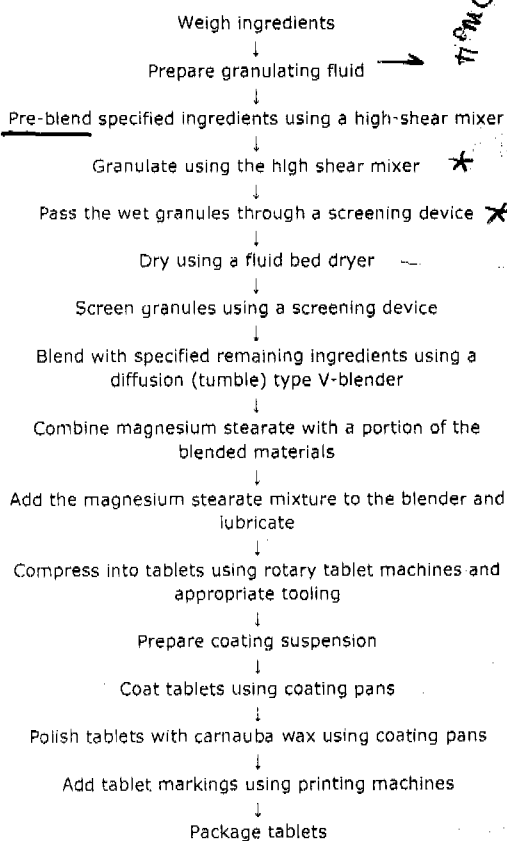
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[00075] Following the general procedure of EXAMPLE 1 and making non-critical variations but using the amounts of ingredients above Linezolid 600 mg tablets are produced.

00077] and an infrared (IR) spectrum (mineral oil mull) of 3364, 1748, 1675, 1537, 1517, 1445, 1410, 1401, 1358, 1329, 1287, 1274, 1253, 1237, 1221, 1145, 1130, 1123, 1116, 1078, 1066, 1049, 907, 852 and 758  $\text{cm}^{-1}$ .

[TABLE-US-00012]

#### Linezolid Tablet Manufacturing Flowchart



*Handwritten notes:*  
HPMC + LSH  
\*  
\*  
Carnauba  
Keto Thinner  
Wax  
Turbido

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D2

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(19) World Intellectual Property Organization  
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(43) International Publication Date  
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PCT

(10) International Publication Number  
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09/707,966 8 November 2000 (08.11.2000) US
- (71) Applicant (for all designated States except US): **AERO-MATIC-FIELDER AG** [CH/CH]; Hauptstrasse 145, CH-4416 Bubendorf (CH).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ (utility model), DE, DE (utility model), DK, DK (utility model), DM, DZ, EC, EE, EE (utility model), ES, FI, FI (utility model), 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, SK (utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

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**Published:**

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

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

- (72) Inventor; and
- (75) Inventor/Applicant (for US only): **HANSEN, Ove, Emil** [DK/DK]; Ravnsholtvej 22, DK-3450 Allerød (DK).
- (74) Agent: **INTERNATIONAL PATENT-BUREAU**; Høje Taastrup Boulevard 23, DK-2630 Taastrup (DK).



**WO 02/38126 A2**

(54) Title: A PROCESS FOR PRODUCTION OF PARTICLES FOR PHARMACEUTICAL COMPOSITIONS HAVING INCREASED BIOAVAILABILITY

(57) Abstract: A process for production of particles for a pharmaceutical composition having increased bioavailability is disclosed. the process involves spraying a core with a solution or dispersion comprising hydroxypropylmethylcellulose acetate succinate (HPMCAS) and a sparingly water-soluble pharmaceutical active compound in an evaporable liquid, evaporating the liquid to obtain a deposit of HPMCAS and the sparingly water-soluble pharmaceutical active compounds, and repeating the process until a predetermined particle size or weight is obtained.

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A PROCESS FOR PRODUCTION OF PARTICLES FOR PHARMA-  
CEUTICAL COMPOSITIONS HAVING INCREASED BIOAVAILABI-  
LITY

5 Field of the invention

The present invention relates to a process for  
production of particles for pharmaceutical compo-  
sitions having increased bioavailability and a par-  
ticle obtainable according to said process.

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Background of the invention

When a patient receives a dosis form, which may  
be a tablet, capsule or the like, the pharmaceutical  
active compound of the dosage form generally enters  
15 the blood through a mucosa or the gastro-intestinal  
channel. In most instances, it is not the entire  
administered amount of pharmaceutical active compound  
which is actually absorbed by the body. Various  
reasons may be the cause for this lack of absorption,  
20 including low solubility of the active compound in  
the relevant body fluid, the dosage form and the fed  
state of the patient. If the active compound has a  
poor solubility in the relevant body fluid, the  
bioavailability is low due to the fact that the  
25 active compound to cross the mucosa or the gastric-  
intestine channel generally has to be in a solubili-  
zed state.

Several important pharmaceutical compounds have  
reduced bioavailability due to a low solubility in  
30 body fluids. To increase the bioavailability of such  
compounds several measures exist, among these the use  
of a solubility enhancer or the increment of the  
amorphisity. The amorphisity can be increased by  
35 dissolving the pharmaceutical active compound in a  
solvent and subsequently rapidly evaporate the sol-

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vent. The amorphisity can also be enhanced by providing the compound as an amorphous dispersion in a suitable solid carrier, such as a polysaccharide. The present invention is directed to the improvement of the bioavailability of a pharmaceutical active compound by providing the pharmaceutical active compound as a solid dispersion in a derivative of a polysaccharide. Especially, the present is directed to the dispersion of a pharmaceutical active compound in hydroxypropylmethylcellulose acetate succinate (HPMCAS).

US patent No. 4,983,593 discloses a solvate of the drug NZ-105 and HPMCAS. The solvate can be prepared into tablets, capsules, granules, and powders, which exhibit an enhanced bioavailability of the drug. As methods for preparation of the solid solvate, it is suggested to remove the solvent from a solution of NZ-105 and HPMCAS by means of vacuum-drying or freeze-drying. As an alternative, it is suggested to apply a coating on a core filler particle by spraying a solution of NZ-105 and HPMCAS onto the core by means of a fluidized bed granulation method, a centrifugal coating method or a pan coating method.

EP 0 901 786 A2 discloses a composition comprising a dispersion of a sparingly water-soluble drug in HPMCAS. The dispersion is prepared by spray drying a solution of the sparingly water-soluble drug and HPMCAS to form particles with an average diameter less than 100  $\mu$ m. The spray drying process involves atomizing a solution which comprises the sparingly water-soluble drug, HPMCAS and a suitable solvent into a plurality of small droplets and subsequent removing the solvent from said droplets. It is demonstrated that a supersaturation is obtained for a

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c) recovering the particles.

In a second aspect of the present invention a particle is provided which is obtainable in accordance with the above process. In a third aspect of the invention a particle is provided which comprises a core and a layer comprising a solid dispersion of a sparingly water-soluble pharmaceutical active compound in a matrix of hydroxypropylmethylcellulose acetate succinate (HPMCAS)

#### Detailed description of the invention

The pharmaceutical active compound may be any sparingly water-soluble compound having a pharmaceutical activity, i.e. compounds showing therapeutic and/or prophylactic properties when administered to a subject. The term sparingly water-soluble pharmaceutical compound refers herein to a compound which is essentially totally water-insoluble or poorly water-soluble. More specifically, a sparingly water-soluble pharmaceutical compound, as used herein, refers to a compound having a dosage to aqueous solubility greater than 100ml, preferably greater than 500ml, where the aqueous solubility is measured in unbuffered water.

The pure pharmaceutical active compound can be crystalline or amorphous at normal temperatures and pressures. However, the advantages of the present invention is predominantly obtained for compounds that tend to be crystalline at ambient temperatures and pressures.

The term HPMCAS generally refers to a family of cellulose derivatives that can have (1) two types of ether substituents, methyl and/or 2-hydroxypropyl or (2) two types of ester substituents, acetyl and/or

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Without wishing to be bound by theory, it is believed that the layering technique used in the present invention effects rapid solvent removal so that crystallization of the pharmaceutical active compound and HPMCAS is largely prevented or at least minimized relative to processes involving solvent removal in a less rapid fashion, such as rotary evaporation. Thus, the present invention provides a process in which the pharmaceutical active compound is efficiently dispersed in a matrix of HPMCAS. Preferably, the pharmaceutical active compound is molecularly dispersed in the HPMCAS matrix, however, a minor amount of local crystallization in the HPMCAS can be accepted.

The solution or dispersion comprising HPMCAS and the pharmaceutical compound may contain further components if so desired. For example, the solution can contain polymers other than HPMCAS that are soluble in the relevant body fluid. Such further polymers include matrix materials such as polyvinylpyrrolidone, hydroxypropylcellulose and hydroxypropylmethylcellulose. } ✓

A surfactant can also be included in the solution to increase the rate of dissolution of the resulting particle by facilitating wetting and also to inhibit crystallization or precipitation of the pharmaceutical active compound. Examples of surfactants which may be used are fatty acids, alkyl sulfonates, benzethonium chloride, polyoxyethylene sorbitan fatty acid esters (Tween), sodium taurocholic acid, 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine, lecithin, and other phospholipids and mono- and diglycerides.

It may also be suitable to include a pH modifier in the solution. pH modifiers can be acids, bases

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WO 02/38126

PCT/DK01/00715

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supplemented with a muffling gas which impedes the scattering effect of the atomizing gas. The entire disclosure of WO 00/40339 is included herein by reference.

5           The treatment of the layered particles in step b) continues until a predetermined particle size or weight is obtained. The determination of the desired particle size or weight can be conducted in accordance with known classification procedures. Alternatively, and preferred, a predetermined amount of cores  
10 is sprayed with a predetermined amount of solution to produce the particles with the desired particle size or weight.

          The particles produced in accordance with the  
15 process of the present invention can be formulated into a pharmaceutical composition using methods conventional within the art. Preferred dosage forms are for oral use. Examples of such dosage forms are tablets, capsules, powders, granulates, cachets, and  
20 pills. Various additives can be mixed, ground, or granulated with the particles produced according to the invention to form a material which is suitable for the production of the dosage form. Examples of additives are matrix materials, fillers and diluents  
25 such as lactose, mannitol, xylitol, microcrystalline cellulose, calcium diphosphate, and starch; surfactants such as lauryl sulfate, and polysorbate 80; complex binding agents or solubilizers such as polyethylene glycols, caffeine, xanthene, and cyclodextrins; disintegrating agents such as sodium starch  
30 glycolate, sodium alginate, carboxymethyl cellulose, and methyl cellulose; binders such as methyl cellulose, microcrystalline cellulose, starch, guar gum, and tragacant; lubricants such as magnesium stearate and  
35 calcium stearate; and pH modifiers such as acids

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

2020  
Bogotá, D.C.,

Abogado:  
**LUZ CLEMENCIA DE PAEZ**

ASUNTO:                      Radicación No.              06 049 473  
                                    Trámite                              002  
                                    Evento                              378  
                                    Actuación                      430  
                                    Oficio  
                                    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 19 a 35 como se radicó inicialmente.

Reivindicaciones:              Folios 36 a 38 como se radicó inicialmente.  
                                            Folios 82 a 83 como se radicó 09-03-2010

Prioridad:                      DE 10355461.0 (2003-11-27)

**Objeto de la Invención**

Título de la invención: "Procedimiento para la producción de una composición farmacéutica sólida de administración oral."

Problema Técnico Planteado: "Necesidad de disminuir la variación en la biodisponibilidad y en la tasa absorción debido a la deficiente hidrosolubilidad relativa del activo 5-cloro-N-((5S)-2-oxo-3-[4-(3-oxo-4-morfolinil)-fenil]1,3-oxazolidin-5-il)-metil)-2-tiofencarboxamida"

Solución: "Proporcionar un método para tratar la superficie del principio activo y de este modo producir un mejor comportamiento de absorción en le marco de la granulación húmeda."

IPC: A61K 009/020, A61K 031/537, A61P 007/002

Se acepta el nuevo capítulo reivindicatorio para su uso.

**Análisis de la Solicitud de Patente**

### Determinación del Estado de la Técnica

El Estado de la Técnica se determinó con base en la fecha de presentación 2003-11-27 y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

| Item | Documento      | Título                                                                                                        | Fecha de Publicación |
|------|----------------|---------------------------------------------------------------------------------------------------------------|----------------------|
| D1   | US 6514529     | <i>Oxazolidinone tablet formulation</i>                                                                       | Feb 4, 2003          |
| D2   | WO 2002/038126 | <i>A process for production of particles for pharmaceutical compositions having increased bioavailability</i> | May 16, 2002         |

### Análisis de Patentabilidad (Art 14 D486)

#### Nivel Inventivo (Art18 D486)

La reivindicación 1 dice: "1. Un procedimiento para la producción de una composición farmacéutica sólida de administración oral que contiene 5-cloro-N-(((5S)-2-oxo-3-[4-(3-oxo-4-morfolinil)-fenil]-1,3-oxazolidin-5-il)-metil)-2-tiofencarboxamida (I) en forma hidrofílica, caracterizado porque (a) en primer lugar se produce, mediante granulación húmeda, un granulado que contenga el principio activo (I) en forma hidrofílica (b) y luego, el granulado, dado el caso con adición de aditivos farmacéuticos adecuados, se transforma en la composición farmacéutica.

D1 revela la preparación de tabletas que contienen derivados de oxazolidinona (pár. 1, f.83), que permiten una carga alta de activo y lograr niveles altos del activo en sangre (pár.7, f.84), D1 enseña el procedimiento de producción de la composición, el cual comprende los pasos de: preparar un fluido de granulación; pre-mezclar el fluido con los excipientes; granular y tamizar la mezcla mojada; secar la mezcla en un lecho fluidizado; tamizar la mezcla seca obtenida; mezclar y adicionar otros materiales a la mezcla y tabletear (f.89, Pág.77, table-us-12; pár. 43-45, f.86). D1 enseña composiciones que contienen el activo en 65% y 56% (ej.1y2, pár.68 y 74, f.87 y 88). D1 revela que la formulación contiene un derivado de oxazolidinona, celulosa microcristalina, aglutinantes como hidroxipropilmetilcelulosa e hidroxipropilmetilcelulosa, (pár. 8-14). Afirma que la forma usada del activo preferiblemente es cristalina (pár. 34).

La solicitud se diferencia de la reivindicación 1 en el derivado de oxazolidinona empleado y la forma hidrofílica incluida.

El Efecto Técnico que logra la diferencia es proporcionar un método de producción que permita obtener de comprimidos con baja variación en la biodisponibilidad y en la tasa absorción del activo 5-cloro-N-(((5S)-2-oxo-3-[4-(3-oxo-4-morfolinil)-fenil]-1,3-oxazolidin-5-il)-metil)-2-tiofencarboxamida.

El Problema Técnico Objetivo de esta solicitud es proporcionar un método de producción que permita obtener de comprimidos con baja variación en la biodisponibilidad y en la tasa absorción del activo 5-cloro-N-(((5S)-2-oxo-3-[4-(3-oxo-4-morfolinil)-fenil]-1,3-oxazolidin-5-il)-metil)-2-tiofencarboxamida.

D2 revela un proceso para la producción de partículas para composiciones de fármacos insolubles con una biodisponibilidad mejorada (portada, f.89). D2 revela estas composiciones para activos poco solubles en agua (p.1, ln.19-22;

f.90). D2 revela formas para aumentar la baja solubilidad de los compuestos insolubles como agregar un agente solubilizante a la composición o aumentar el grado de amorfismo de la molécula (p.1, ln. 30-35, f.90). D2 describe un proceso que consiste en dispersar el activo en una matriz de polímeros, (p.6, ln.15-23, f.93) en donde dicha matriz contiene un surfactante para incrementar la velocidad de disolución de las partículas, las cuales son formuladas dentro de una composición farmacéutica. D2 sugiere el uso de surfactantes como laurilsulfato en el procedimiento (p.12, ln.14-35).

El experto en la materia habría recurrido a D1 para formular composiciones con una oxazolidinona como la de la presente solicitud y para optimizar la solubilidad de este compuesto activo insoluble, habría recurrido a enseñanzas del estado de arte como la presentada por D2, en donde se enseña la producción de composiciones que contienen un activo insoluble, en donde se sugiere el uso de surfactantes que hidrofilizan la partícula que contiene el activo. El experto habría encontrado que justo después de la granulación y el secado de los gránulos, la adición de un surfactante, como laurilsulfato de sodio, ayudaría a mejorar de forma importante la biodisponibilidad del compuesto.

Por otro lado, al observar los datos de liberación *in vitro* no se observa una diferencia significativa con las tabletas que no han sido hidrofilizadas con laurilsulfato, de la misma manera no se observa que el tiempo máximo tenga una diferencia importante entre las dos tabletas, y la concentración máxima tampoco muestra datos que demuestren un efecto sorprendente o inesperado frente a lo revelado por el estado de la técnica.

Se concluye que las reivindicaciones 1-18 carecen de nivel inventivo.

### Conclusión

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

| Nº | Documento      | Reivindicaciones afectadas | Requisito que afecta |
|----|----------------|----------------------------|----------------------|
| D1 | US 6514529     | 1-18                       | Nivel inventivo      |
| D2 | WO 2002/038126 | 1-18                       | Nivel inventivo      |

### Respuesta a los argumentos del solicitante

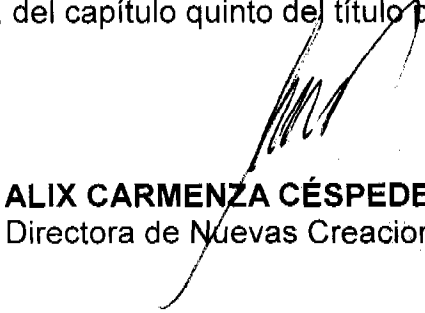
Se consideran superadas las objeciones relacionadas con las excepciones de patentabilidad y de usos.

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.

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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 \_\_\_\_\_ 15 de mayo 2007

|                                  |                                     |
|----------------------------------|-------------------------------------|
| CONCEPTO TÉCNICO<br>NUMERO: 2801 | EXAMINADOR TÉCNICO<br>Código:202092 |
|----------------------------------|-------------------------------------|

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