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(54) **Title:** HIGH OXAZOLIDINONE CONTENT SOLID DOSAGE FORMS

(57) **Abstract:** A high drug content oral solid dosage form is provided comprising about 50 mg to about 800 mg oxazolidinone or a pharmaceutically acceptable salt, hydrate or crystalline form thereof and a lactose-based water soluble excipient.

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HIGH OXAZOLIDINONE CONTENT SOLID DOSAGE FORMS

PRIORITY

[0001] This application claims the benefit under 35 U.S.C. §119 to U.S. Provisional Patent Application No. 60/819,040, filed on July 6, 2006, and entitled "HIGH DRUG CONTENT TABLETS" and to Indian Provisional Application No. 346/MUM/2006, filed on March 9, 2006, and entitled "HIGH DRUG CONTENT TABLETS", the contents of each of which are incorporated by reference herein.

BACKGROUND OF THE INVENTION

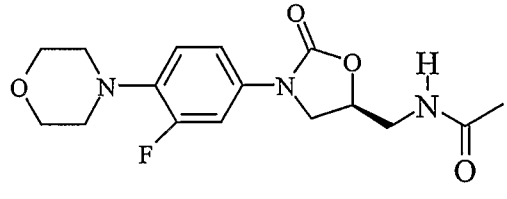
1. Technical Field

[0002] The present invention generally relates to high drug content solid dosage forms such as tablets.

2. Description of the Related Art

[0003] Oxazolidinones are well known to those skilled in the art as gram positive anti-bacterial agents. See, e.g., U.S. Patent 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. In clinical trials, the first member of the class, linezolid, demonstrated 100% bioavailability after oral dosing and achieved blood levels well in excess of the MIC_{90} for staphylococci, enterococci, and streptococci. The oxazolidinones are not cross-resistant with other antimicrobial classes and act by inhibiting the formation of the initiation complex in bacterial protein synthesis.

[0004] Linezolid, also known as (S)-N-[[3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide, is represented by the structure of Formula I



(I).

CONFIRMATION COPY

Linezolid has clinical utility in the treatment of infections caused by aerobic Gram-positive bacteria. The in vitro spectrum of activity of linezolid also includes certain Gram-negative bacteria and anaerobic bacteria. Linezolid inhibits bacterial protein synthesis through a mechanism of action different from that of other antibacterial agents, therefore, cross-resistance between linezolid and other classes of antibiotics is unlikely. Linezolid binds to a site on the bacterial 23S ribosomal RNA of the 50S subunit and prevents the formation of a functional 70S initiation complex, which is an essential component of the bacterial translation process. The results of time-kill studies have shown linezolid to be bacteriostatic against enterococci and staphylococci. For streptococci, linezolid was found to be bactericidal for the majority of strains. Linezolid is commercially sold under the trade name Zyvox®. See, e.g., The Merck Index, Thirteenth Edition, 2001, p. 986-87, monograph 5526; and Physician's Desk Reference, "Zyvox," 58th Edition, pp. 2808-2815 (2004). Zyvox® tablets for oral administration contain 400 mg or 600 mg linezolid as film-coated compressed tablets and also contain corn starch, microcrystalline cellulose, hydroxypropylcellulose, sodium starch glycolate, magnesium stearate, hypromellose, polyethylene glycol, titanium dioxide, and carnauba wax. The drug appears to inhibit the initiation of protein synthesis at the ribosomal level in susceptible bacteria.

[0005] Zyvox® injections (IV) are also available as a ready-to-use sterile isotonic solution for intravenous infusion. Linezolid can be administered both IV and orally every 12 hours, and must be used only when indicated to avoid the development of resistance against it. Potential side effects include thrombocytopenia, headache, nausea, and diarrhea. Other oxazolidinones are currently under investigation. However, it is very difficult to get high drug load and blood levels similar to IV administration.

[0006] Solid dosage forms such as a tablet or a capsule dosage form are the preferred dosage forms over other dosage forms due to several advantages, e.g., the ease of administration by the patient, ease of manufacturing and the cost. In the pharmaceutical industry, the formulation of tablets usually involves the mixing of the active pharmaceutical ingredient ("API") or drug with one or more excipients with or without a binder and finally compressing the blend into the tablet. The tablet suitably accommodates a mild or moderate dose of the API. A disadvantage of a tablet dosage form is the size of the tablet, especially when the quantity of active ingredient to be

presented in each tablet is relatively high. Under such circumstances, the swallowing of tablets becomes difficult due to the larger size of the tablet.

[0007] While forming a tablet containing a mild or moderate dose of the drug, the excipient(s) tends to be the predominant portion of the tablet and compaction typically entails excipient selection, enhancing the excipient's properties, or improving the process to mix or formulate the tablet. However, when a high drug load is desired, selection and/or manipulation of the excipient and its quantities or the process to manufacture the tablet may not be enough to sufficiently compact the tablet. Furthermore, because of the high drug load, the mechanical properties (such as compactibility) of the API predominate. The impact of insufficient compaction may lead to larger size tablets or the need for a patient to take more tablets then would be required if compaction was insufficient to obtain the desired drug load.

[0008] U.S. Patent No. 6,514,529 ("the '529 patent") discloses tablets containing a high drug content of oxazolidinones such as linezolid,, wherein the oxazolidinone is compressed into a tablet using corn starch, microcrystalline cellulose, hydroxyl propyl cellulose, sodium starch glycolate and magnesium stearate as the excipients. The tablets thus produced provide blood levels of linezolid which are equivalent to the blood levels produced by IV administration of linezolid. The '529 patent further discloses that lactose is not used in formulating the high drug content tablet.

SUMMARY OF THE INVENTION

[0009] In accordance with one embodiment of the present invention, a high drug content oral solid dosage form is provided comprising about 50 mg to about 800 mg oxazolidinone or a pharmaceutically acceptable salt, hydrate or crystalline form thereof and a lactose-based water soluble excipient.

[0010] In accordance with a second embodiment of the present invention, a high drug content oral solid dosage form is provided comprising about 100 mg to about 700 mg oxazolidinone or a pharmaceutically acceptable salt, hydrate or crystalline form thereof and a lactose-based water soluble excipient.

[0011] In accordance with a third embodiment of the present invention, a high drug content oral solid dosage form is provided comprising about 400 mg to about 600 mg linezolid or a pharmaceutically acceptable salt, hydrate or crystalline form thereof and a lactose-based water soluble excipient.

[0012] In accordance with one embodiment of the present invention, a high drug content tablet is provided comprising about 50 mg to about 800 mg oxazolidinone or a pharmaceutically acceptable salt, hydrate or crystalline form thereof having a particle size distribution in which d(.9) is less than or equal to about 250 microns and a lactose-based water soluble excipient.

[0013] In accordance with a second embodiment of the present invention, a high drug content tablet is provided comprising about 100 mg to about 700 mg oxazolidinone or a pharmaceutically acceptable salt, hydrate or crystalline form thereof having a particle size distribution in which d(.9) is less than or equal to about 250 microns and a lactose-based water soluble excipient.

[0014] In accordance with a third embodiment of the present invention, a high drug content tablet is provided comprising about 400 mg to about 600 mg linezolid or a pharmaceutically acceptable salt, hydrate or crystalline form thereof having a particle size distribution in which d(.9) is less than or equal to about 250 microns and a lactose-based water soluble excipient.

[0015] The terms “drug”, “active agent”, “active ingredient” or “active pharmaceutical ingredient” have the same meaning herein and are used interchangeably.

[0016] The term "therapeutically effective amount" as used herein means the amount of a compound that, when administered to a mammal for treating a state, disorder or condition, is sufficient to effect such treatment. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, physical condition and responsiveness of the mammal to be treated.

[0017] By “pharmaceutically acceptable” is meant those salts and esters which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use. Representative acid additions salts include the hydrochloride, hydrobromide, sulphate,

bisulphate, acetate, oxalate, valerate, oleate, palmitate, stearate, laurate, borate, benzoate, lactate, phosphate, tosylate, mesylate, citrate, maleate, fumarate, succinate, tartrate, ascorbate, glucoheptonate, lactobionate, lauryl sulphate salts and the like. Representative alkali or alkaline earth metal salts include the sodium, calcium, potassium and magnesium salts, and the like.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0018] The present invention provides a high content oral solid dosage form of an oxazolidinone or a pharmaceutically acceptable salt, hydrate or crystalline form thereof and a lactose-based water soluble excipient. Oxazolidinones are known to those skilled in the art. Representative examples of oxazolidinones for use herein include linezolid, eperezolid, (S)-N-[[3-[3-fluoro-4-(tetrahydro-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl] acetamide and the like.

[0019] Linezolid is well known and can be obtained by any known technique. See, e.g., U.S. Patent Nos. 5,688,792; 5,837,870; 5,968,962; 6,444,813; 6,514,529 and 6,559,305; the contents of which are incorporated by reference herein. In one embodiment, crystalline Form II of linezolid is used in preparing the high drug content oral solid dosage forms of the present invention. Crystalline Form II of linezolid can be prepared as described in, e.g., U.S. Patent No. 6,514,529. For example, once linezolid is synthesized, crystalline Form II can be prepared by starting with linezolid of high enantiomeric purity, e.g., more than 98% enantiomerically pure, preferably more than 99% pure and more preferably 99.5% pure. The linezolid of greater than 98% enantiomeric purity to be used to form crystalline Form II can either be in solution or be a solid. The linezolid starting material, solid or solution, can be mixed with a solvent such as water, acetonitrile, chloroform, methylene chloride, R^1-OH wherein R^1 is a C_1-C_6 alkyl; R^1-C(O)-R^2 wherein R^1 is as defined above and R^2 is a C_1-C_6 alkyl; phenyl substituted with 1 thru 3 R^1 groups wherein R^1 is as defined above; R^1-C(O)-O- R^2 wherein R^1 and R^2 are as defined above; R^1-O-R^2 wherein R^1 and R^2 are defined above and the like. Preferably the solvent is one or more of water, ethyl acetate, methanol, ethanol, propanol, isopropanol, butanol, acetonitrile, acetone, methyl ethyl ketone, chloroform, methylene chloride, toluene, xylene, diethyl ether, and methyl-t-butyl ether. It is more preferred that the

solvent is ethyl acetate, acetone, acetonitrile, propanol, or isopropanol. It is most preferred that the solvent is ethyl acetate.

[0020] The mixture of linezolid in the solvent is agitated at a temperature below 80°C until crystals of Form II are formed and crystals of other solid forms, such as Form I, disappear. It is preferred to dissolve the linezolid in ethyl acetate at a temperature near the boiling point of the solvent. This mixture is then cooled to a temperature of about 70°C. The mixture may be seeded with crystals of Form II to facilitate crystallization. The solid product can then be cooled and agitated at a temperature between about 45°C and about 60°C until the solids consist only of Form II crystals. It is most preferred to maintain the slurry at a temperature of about 55°C. It is preferred to mix the linezolid and solvent for at least 10 minutes, it is even more preferred to mix the linezolid and solvent for at least 20 minutes and it is most preferred to mix the linezolid and solvent for at least 30 minutes. The time and temperature will vary depending on the solvent used. For example, when using ethyl acetate, it is preferable to mix for not less than 60 minutes. The crystalline slurry may be further cooled to improve yield, and the solid Form II product may be isolated. The mixture may be further cooled and agitated. Other measures which can be used to facilitate crystallization include, but are not limited to, cooling, concentration of the solution by evaporation or distillation, or through addition of other solvents. The crystals can then be isolated by procedures known to those skilled in the art.

[0021] Eperezolid, also known as (S)-N-[[3-[3-fluoro-4-[4-(hydroxyacetyl)-1-piperazinyl]-phenyl]-2-oxo-5-oxa zolidinyl]methyl]acetamide, is the compound of Example 8 of U.S. Patent No. 5,837,870.

[0022] (S)-N-[[3-[3-fluoro-4-(tetrahydro-2H-thiopyran-4-yl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide S,S-dioxide is the compound of Example 51 of U.S. Patent No. 5,968,962.

[0023] The term "high drug content solid dosage form" as used herein represents a solid dosage form, e.g., a tablet, wherein the quantity of the oxazolidinone or a pharmaceutically acceptable salt, hydrate or crystalline form thereof is equal to or greater than about 50 weight % of total weight of the solid dosage form. In one embodiment, the high drug content solid dosage form can range from about 50 to about 95 weight % of the

total weight of the solid dosage form and preferably from about 60 to about 80 weight % of the total weight of the solid dosage form.

[0024] In one embodiment, the oxazolidinone or pharmaceutically acceptable salt, hydrate or crystalline form thereof, e.g., linezolid, for use in the high drug content solid dosage forms of the present invention can have a D_{90} particle size of less than or equal to about 250 microns, preferably less than or equal to about 100 microns, more preferably less than or equal to about 75 microns, and most preferably less than or equal to about 55 microns. In one embodiment, the oxazolidinone or pharmaceutically acceptable salt, hydrate or crystalline form thereof can have a D_{90} particle size ranging from about 20 to about 55 microns. In another embodiment, the oxazolidinone or pharmaceutically acceptable salt, hydrate or crystalline form thereof can have a D_{50} particle size of less than or equal to about 20 microns. In another embodiment, the oxazolidinone or pharmaceutically acceptable salt, hydrate or crystalline form thereof can have a D_{10} particle size of less than or equal to about 10 microns. The particle size can be determined by such techniques as, for example, Malvern light scattering, a laser light scattering technique, etc. It is noted the notation D_x means that X% of the particles have a diameter less than a specified diameter D. Thus, a D_{90} of about 250 microns means that 90% of the particles in a oxazolidinone composition preferably have a diameter less than or equal to about 250 microns. The particle sizes can be obtained by, for example, any milling, grinding, micronizing or other particle size reduction method known in the art to bring the solid state oxazolidinone into any of the foregoing desired particle size range.

[0025] In the present invention, the high drug content solid dosage forms of the present invention will advantageously contain at least one lactose-based water soluble excipient. The lactose-based excipient for use herein includes, but is not limited to, lactose, anhydrous lactose, lactose monohydrate and the like and combinations thereof. In one embodiment, commercially available grades of lactose which are suitable for granulation are preferred such as Pharmatose 200M. Pharmatose 200M consists of 100% of the particles having a particle size less than 250 microns. The lactose-based excipient advantageously acts as a compression aid, having a sufficient hardness and without facing the problem of capping or lamination, particularly in the case where 90% of the particles of the oxazolidinone are not more than about 250 microns, preferably less than about 100

microns, more preferably less than about 75 microns, and most preferably less than about 50 microns. The lactose-based water soluble excipient will ordinarily be present in the high drug content solid dosage forms of the present invention in an amount ranging from about 5 to about 25% by weight, based on the total weight of the composition.

[0026] The solid dosage forms of the present invention can also contain one or more additional water soluble excipients. Suitable additional water soluble excipients include sugars and sugar alcohols such as, for example, mannitol, dextrose, sucrose, sorbitol and the like and mixtures thereof. Preferably, the additional water soluble excipient is mannitol. Mannitol is a naturally occurring sugar alcohol, 50% as sweet as sucrose. Mannitol is commercially available as Pearlitol SD 200 from Roquette. The water soluble excipients for use in the high drug content solid dosage forms of the present invention can be added as intragranular and/or extragranular. The water soluble sugars and sugar alcohols will ordinarily be present in the high drug content solid dosage forms of the present invention in an amount ranging from about 5 to about 25% by weight, based on the total weight of the composition.

[0027] The high drug content solid dosage forms of the present invention can further include one or more pharmaceutically acceptable excipients typically used in solid dosage forms. Suitable excipients and the amounts to use may be readily determined by the formulation scientist based upon experience and consideration of standard procedures and reference works in the field. Examples of pharmaceutically acceptable excipients include, but are not limited to, binders, disintegrants, lubricants and the like and mixtures thereof.

[0028] Suitable binders include, but are not limited to, polyvinyl pyrrolidone, acacia, carbomer (e.g. carbopol), carboxymethylcellulose sodium, dextrin, ethyl cellulose, gelatin, guar gum, hydrogenated vegetable oil, hydroxyethyl cellulose, hydroxypropyl cellulose (e.g. Klucel®), hydroxypropyl methyl cellulose (e.g. Methocel®), liquid glucose, magnesium aluminum silicate, maltodextrin, methylcellulose, polymethacrylates, pregelatinized starch, starch and mixtures thereof. The preferred binders are polyvinyl pyrrolidone and carboxymethylcellulose sodium.

[0029] Disintegrants include, but are not limited to, carboxymethylcellulose calcium, carboxymethylcellulose sodium (e.g. Ac-Di-Sol®) Primellose croscarmellose sodium, guar gum, magnesium aluminum silicate, methyl cellulose, microcrystalline cellulose, polacrilin potassium, powdered cellulose, pregelatinized starch, sodium alginate, sodium starch glycolate (e.g. Explotab®) and starch.

[0030] The preferred solid oral dosage form herein is a tablet. The tablets of the present invention can be prepared using any process well-known in the pharmaceutical art such as, for example, wet granulation, dry granulation, etc. For example, the tablet can be prepared by mixing the oxazolidinone uniformly with a lactose-based excipient, optionally one or more water soluble excipients such as mannitol, a disintegrant and optionally a binder. The dry blend is further granulated using a suitable aqueous or non aqueous solvent optionally containing a binder dissolved or dispersed. The wet mass thus obtained can then be dried and subsequently milled or sieved to obtain the appropriate granule size. The dried granules can be further lubricated and compressed into tablets.

[0031] The compressed tablets can be 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. For example, when a dosage form such as a tablet is made by the compaction of a powdered composition, the composition is typically subjected to pressure from a punch and dye. Some excipients and active ingredients have a tendency to adhere to the surface of the punch and dye, which can cause the product to have pitting and other surface irregularities. Accordingly, a lubricant may be added to the solid dosage form to reduce adhesion and ease the release of the product from the dye. Suitable lubricants include, but are not limited to, magnesium stearate, calcium stearate, glyceryl monostearate, glyceryl palmitostearate, hydrogenated castor oil, hydrogenated vegetable oil, mineral oil, polyethylene glycol, sodium benzoate, sodium lauryl sulfate, sodium stearyl fumarate, stearic acid, talc, zinc stearate and the like and mixtures thereof.

[0032] The solid dosage forms such as tablets of the present invention can be optionally film coated, using common film forming polymers such as a class of celluloses or methacrylates. For example, a film forming agent such as Opadry White YS-1-18202-A and purified water can be mixed to prepare a coating mixture. 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 can be screened through an appropriate screen. The desired quantity of tablets are loaded into the appropriately sized perforated coating pans (such as an Accela-Cota or Glatt coating pan) equipped with baffles, spray guns and a pumping system. The appropriate amount of aqueous film coating is sprayed on the moving tablets until the 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.

[0033] Based on the individual dose, the solid dosage forms of present invention can contain from about 50 to about 800 mg of oxazolidinone, preferably from about 100 to about 700 mg of oxazolidinone, and more preferably from about 400 to about 600 mg of oxazolidinone. Preferably, the solid dosage forms of present invention contain from about 400 to about 600 mg of linezolid.

[0034] The following examples are provided to enable one skilled in the art to practice the invention and are merely illustrative of the invention. The examples should not be read as limiting the scope of the invention as defined in the features and advantages.

EXAMPLE 1

[0035] The preparation of a linezolid (600 mg) tablet formulation of the present invention is set forth below in Table I.

TABLE I

Ingredients	mg/tablet
I. Granulation	
Linezolid	600
Lactose monohydrate (Pharmatose 200M)	58.4
Mannitol (Pearlitol SD 200)	68.6
Croscarmellose Sodium (Ac Di Sol)	29.4
Carboxymethylcellulose sodium Binder	16.8
Purified Water	q.s.
II. Lubrication	
Mannitol (Pearlitol SD 200)	50
Croscarmellose Sodium (Ac Di Sol)	12.6
Magnesium Stearate	4.2
Total	840
Coating	
Opadry Y -1-7000	16.8

[0036] Linezolid having a particle size distribution d(0.9) of 30-50 μm was mixed uniformly with Pharmatose 200M and Pearlitol SD 200 and crosscarmallose sodium. The dry blend was further granulated using water as a solvent. The wet mass thus obtained was dried and subsequently passed through an American Society for Testing and Materials (ASTM) mesh 30#. The dried granules were mixed with Pearlitol SD 200, crosscarmellose sodium and magnesium stearate. Finally the lubricated granules were compressed into tablets.

EXAMPLE 2

[0037] The preparation of a linezolid (600 mg) tablet formulation of the present invention is set forth below in Table II.

TABLE II

Ingredients	mg/tablet
I. Granulation	
Linezolid	600
Lactose monohydrate (Pharmatose 200M)	58.4
Mannitol (Pearlitol SD 200)	68.6
Croscarmellose Sodium (Ac Di Sol)	29.4
Polyvinyl pyrrolidone	16.8
Purified Water	q.s.
II. Lubrication	
Mannitol (Pearlitol SD 200)	50
Croscarmellose Sodium (Ac Di Sol)	12.6
Magnesium Stearate	4.2
Total	840
Coating	
Opadry Y -1-7000	16.8

[0038] Linezolid having a particle size distribution d(0.9) of 30-50 μm was mixed uniformly with Pharmatose 200M and Pearlitol SD 200 and crosscarmallose sodium. The dry blend was further granulated using water as a solvent. The wet mass thus obtained was dried and subsequently passed through an ASTM mesh 30#. The dried granules were mixed with Pearlitol SD 200, crosscarmellose sodium and magnesium stearate. Finally, the lubricated granules were compressed into tablets.

EXAMPLE 3

[0039] The preparation of a linezolid (600 mg) tablet formulation of the present invention is set forth below in Table III.

TABLE III

Ingredients	mg/tablet
I. Granulation	
Linezolid	600
Lactose monohydrate (Pharmatose 200M)	111
Povidone (Plasdone K 30)	35
Croscarmellose Sodium (Ac Di Sol)	30
Purified Water	q.s.
II. Lubrication	
Lactose monohydrate (Pharmatose DCL 11)	45
Croscarmellose Sodium (Ac Di Sol)	15
Magnesium Stearate	4
Total	840
Coating	
Opadry Y -1-7000	15

[0040] Linezolid having a particle size distribution d(0.9) of 30-50 μm was mixed uniformly with Pharmatose 200M and Pearlitol SD 200 and crosscarmallose sodium. The dry blend was further granulated using water as a solvent. The wet mass thus obtained was dried and subsequently passed through an ASTM mesh 20#. The dried granules were mixed with Pharmatose DCL 11, crosscarmellose sodium and magnesium stearate. Finally the lubricated granules were compressed into tablets.

[0041] It will be understood that various modifications may be made to the embodiments disclosed herein. Therefore the above description should not be construed as limiting, but merely as exemplifications of preferred embodiments. For example, the functions described above and implemented as the best mode for operating the present invention are for illustration purposes only. Other arrangements and methods may be implemented by those skilled in the art without departing from the scope and spirit of this invention. Moreover, those skilled in the art will envision other modifications within the scope and spirit of the features and advantages appended hereto.

WHAT IS CLAIMED IS:

1. A high drug content solid dosage form comprising about 50 mg to about 800 mg oxazolidinone or a pharmaceutically acceptable salt, hydrate or crystalline form thereof and a lactose-based water soluble excipient.

2. The high drug content solid dosage form of Claim 1, wherein the 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.

3. The high drug content solid dosage form of Claim 1, wherein the oxazolidinone is linezolid.

4. The high drug content solid dosage form of Claim 3, wherein the linezolid is in crystalline Form II.

5. The high drug content solid dosage form of Claims 1-4, wherein the oxazolidinone is present in about 100 mg to about 700 mg.

6. The high drug content solid dosage form of Claims 1-4, wherein the oxazolidinone is present in about 400 mg to about 600 mg.

7. The high drug content solid dosage form of Claims 1-6, wherein the amount of oxazolidinone or a pharmaceutically acceptable salt, hydrate or crystalline form thereof is greater than about 50 weight % of the total weight of the high drug content solid dosage form.

8. The high drug content solid dosage form of Claims 1-6, wherein the amount of oxazolidinone or a pharmaceutically acceptable salt, hydrate or crystalline form thereof is about 50 to about 95 weight % of the total weight of the high drug content solid dosage form.

9. The high drug content solid dosage form of Claims 1-6, wherein the amount of oxazolidinone or a pharmaceutically acceptable salt, hydrate or crystalline form thereof is about 60 to about 80 weight % of the total weight of the high drug content solid dosage form.

10. The high drug content solid dosage form of Claims 1-9, wherein the oxazolidinone or a pharmaceutically acceptable salt, hydrate or crystalline form thereof has a particle size distribution in which d(.9) is less than or equal to about 250 microns.

11. The high drug content solid dosage form of Claims 1-9, wherein the oxazolidinone or a pharmaceutically acceptable salt, hydrate or crystalline form thereof has a particle size distribution in which d(.9) is less than or equal to about 100 microns.

12. The high drug content solid dosage form of Claims 1-9, wherein the oxazolidinone or a pharmaceutically acceptable salt, hydrate or crystalline form thereof has a particle size distribution in which d(.9) is less than or equal to about 55 microns.

13. The high drug content solid dosage form of Claims 1-9, wherein the oxazolidinone or a pharmaceutically acceptable salt, hydrate or crystalline form thereof has a particle size distribution in which d(.9) of about 20 to about 55 microns.

14. The high drug content solid dosage form of Claims 1-9, wherein the oxazolidinone or a pharmaceutically acceptable salt, hydrate or crystalline form thereof has a particle size distribution in which d(.5) is less than or equal to about 20 microns.

15. The high drug content solid dosage form of Claims 1-9, wherein the oxazolidinone or a pharmaceutically acceptable salt, hydrate or crystalline form thereof has a particle size distribution in which d(.1) is less than or equal to about 10 microns.

16. The high drug content solid dosage form of Claims 1-15, wherein the lactose-based water soluble excipient is selected from the group consisting of lactose, anhydrous lactose, lactose monohydrate and combinations thereof.

17. The high drug content solid dosage form of Claims 1-16, wherein the lactose-based water soluble excipient is present in the tablet in an amount of about 5 to about 25% by weight, based on the total weight of the tablet.

18. The high drug content solid dosage form of Claims 1-17, further comprising one or more additional water-soluble excipients.

19. The high drug content solid dosage form of Claim 18, wherein the additional water soluble excipient is selected from the group consisting of mannitol, dextrose, sucrose, sorbitol and mixtures thereof.

20. The high drug content solid dosage form of Claims 1-17, further comprising mannitol.

21. The high drug content solid dosage form of Claims 18-20, wherein the additional water soluble excipient is present in the tablet in an amount of about 5 to about 25% by weight, based on the total weight of the tablet.

22. The high drug content solid dosage form of Claims 1-21, further comprising one or more pharmaceutically acceptable excipients.

23. The high drug content oral solid dosage form of Claim 22, wherein the pharmaceutically acceptable excipient is selected from the group consisting of a diluent, binder, disintegrant, lubricant and mixtures thereof.

24. The high drug content solid dosage form of Claims 1-23, wherein the high drug content solid dosage form is film coated.

25. The high drug content solid dosage form of Claims 1-23, in the form of a tablet.

26. The high drug content solid dosage form of Claim 25, wherein the tablet is film coated.

27. A high drug content tablet comprising:

	mg/tablet
Linezolid	600
Lactose monohydrate (Pharmatose 200M)	58.4
Mannitol (Pearlitol SD 200)	68.6
Croscarmellose Sodium (Ac Di Sol)	29.4
Carboxymethylcellulose sodium Binder	16.8
Mannitol (Pearlitol SD 200)	50
Croscarmellose Sodium (Ac Di Sol)	12.6
Magnesium Stearate	4.2
Total	840
Coating	
Opadry Y -1-7000	16.8

28. A high drug content tablet comprising:

	mg/tablet
Linezolid	600
Lactose monohydrate (Pharmatose 200M)	58.4
Mannitol (Pearlitol SD 200)	68.6
Croscarmellose Sodium (Ac Di Sol)	29.4
Polyvinyl pyrrolidone	16.8
Mannitol (Pearlitol SD 200)	50
Croscarmellose Sodium (Ac Di Sol)	12.6
Magnesium Stearate	4.2
Total	840
Coating	
Opadry Y -1-7000	16.8

29. A high drug content tablet comprising:

	mg/tablet
Linezolid	600
Lactose monohydrate (Pharmatose 200M)	111
Povidone (Plasdone K 30)	35
Croscarmellose Sodium (Ac Di Sol)	30
Lactose monohydrate (Pharmatose DCL 11)	45
Croscarmellose Sodium (Ac Di Sol)	15
Magnesium Stearate	4
Total	840
Coating	
Opadry Y -1-7000	15

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2007/000573

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/5377 A61K9/32 A61K9/26 A61K9/16

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	example 140	27-29
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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"P" document published prior to the international filing date but later than the priority date claimed

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 July 2007	30/07/2007

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	GIMENEZ MIRALLES, J

INTERNATIONAL SEARCH REPORT

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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