Packaging for Linezolid

Packaging comprising a) Linezolid or microcrystalline form of Linezolid and optionally Linezolid with pharmaceutically acceptable carrier or excipient.

Title: PACKAGING FOR LINEZOLID

Abstract: Provided is a stable microcrystalline form of Linezolid and a processes for preparation thereof. Also provided is a multiple packing and vacuum sealed pack comprising Linezolid, or stable microcrystalline form of Linezolid and optionally Linezolid - id with pharmaceutically acceptable carrier or excipient.
FIELD OF THE INVENTION

The present invention relates to stable microcrystalline form of Linezolid, which is stable to micronization, and processes for preparation thereof. Further the present invention also relates to a multiple packing and vacuum sealed pack comprising Linezolid, or stable microcrystalline form of Linezolid and optionally Linezolid with pharmaceutically acceptable carrier or excipient.

BACKGROUND OF THE INVENTION

Linezolid of formula I, has very valuable pharmacological and therapeutic properties, and is useful in many cardiovascular diseases such as angina pectoris, myocardial infarct and associated rhythm disturbances and is chemically known as N-[(5S)-3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl acetamide.

\[
\text{Formula I}
\]

Linezolid is chemically known as \( N-[(5S)-3-[3-\text{Fluoro}-4-(4-\text{mopholinyl})\text{phenyl}]-2-\text{oxo}-5-\text{oxazolidinyl}]\text{methyl} \) acetamide and marketed by Pfizer in US under brand name Zyvox. Linezolid is a synthetic antibacterial agent of the oxazolidinone class. It is used for the treatment of infections caused by multi-resistant bacteria including streptococci and methicillin-resistant Staphylococcus aureus. Linezolid was first disclosed in U.S. Pat. No. 5,688,792.
The compound stability is one of the most important criteria by most of the regulatory agencies. Therefore one need to demonstrate that even after the formulation the stability of the compound or its respective form is intact over a period of shelf life. The compound transformations can occur also in the different solid state, because of changes in humidity or temperature or oxidative degradation conditions.

The prior art discloses the importance of the production conditions of the medicinal products reported to undergo unwanted and undesirable transformations, if the process conditions are not opportunistically controlled. Consequently, a stable Linezolid would be a significant contribution to the technology, given changes paused to prepare a stable Linezolid.

Linezolid is known to occur in various particle size as well as crystalline forms as well as amorphous forms. However, Linezolid can be susceptible to oxidation, heat, light, moisture, low pH, and change to other crystalline forms. Linezolid during the process of micronization is where much susceptible to oxidation, heat, light, moisture, and change to other crystalline forms due to the process of micronization. Impurities generated upon degradation of active substances can reduce the therapeutic effects of an active substance and unnecessarily burden the body with degradation products. For examples, oxidative degradation of Linezolid can lead to impurities such as which are unwanted.

Linezolid solids are usually packed into various kinds of packing under normal conditions according to the prior art. These packing generally use LDPE, HDPE, plastic bags. Plastic bags find widespread use in the prior art.

Linezolid is known to occur in various crystalline forms as well as amorphous forms. However, Linezolid can be susceptible to oxidation, heat, light, moisture, low pH, and change to other crystalline forms. Impurities generated upon degradation of active substances can reduce the therapeutic effects of an active substance and unnecessarily burden the body with degradation products. For examples, oxidative degradation of Linezolid can lead to impurities such as which are unwanted.
There have been various attempts to stabilize the Linezolid. During our research on Linezolid it was observed that this class of compounds is not stable during stability tastings. Long term stability was performed at 25°C and 65% RH. Accelerated stability was performed at 30°C and 65 RH. The Linezolid have a tendency to change its polymorph and it appears that some different polymorph by-products are produced with time. The stability under nitrogen is known for Linezolid from the European Pharmacopoeia and the US Pharmacopoeia. It was observed that these conditions are not sufficient for Linezolid. In order to overcome this problem it was found that the packaging of Linezolid should be done in special conditions.

As used herein, the term "microcrystalline" is used to refer to a preparation of Linezolid having particle sizes that are less than 50 micron in diameter, on average. Since a micron is one-millionth of a meter (equal to one-thousandth of a millimeter).

The manufacturing processes disclosed herein offer a cost-effective way to create a stable microcrystalline form of Linezolid. Although it is presumed that these "microcrystalline" formulations will offer the highest possible bioavailability, for a Linezolid, it should be recognized that the final choice of a desired particle size range, for large-scale commercial quantities of Linezolid, will depend on highest possible bioavailability, regardless of cost. General rule is smaller particle size, higher is the bioavailability.

There is still a need for providing a packaging system for pharmaceutically active ingredient so as to enhance their stability. This can be provided by multiple packing and applying a vacuum, which provides additional benefits. Vacuum packed systems require a minimum of space (as compared to inflated bags produced by introduction of inert gases). Vacuum packaged systems are less prone to leakage and any leakage can be easily detected.
OBJECT OF THE INVENTION:

An object of the present invention relates to a stable microcrystalline form of Linezolid, which is stable to micronization, and processes for preparation thereof.

Yet another object of the present invention relates to a stable microcrystalline form of Linezolid and processes for preparation thereof.

Further object of the present invention relates to a stable microcrystalline form of Linezolid so as to enhance their stability.

Further object of the invention is to provide packaging system for Linezolid pharmaceutical compositions.

Further object of the invention to provide packaging system for pharmaceutically active ingredient so as to enhance their stability.

Further object of the invention is to provide a multiple packing and vacuum packed system comprising pharmaceutically active ingredient and at least one desiccant.

Further object of the invention is to provide packaging system for Linezolid so as to enhance their stability.

SUMMARY OF THE INVENTION

In one of the aspect of present invention is to provide packaging system for pharmaceutically active ingredient so as to enhance their stability.

Another aspect of the invention is to provide a multiple packing and vacuum packed system comprising pharmaceutically active ingredient and at least one desiccant.
In another aspect, there is provided a vacuum sealed pack comprising a Linezolid and optionally pharmaceutically acceptable carrier or excipient.

In another aspect, there is provided a method of stabilizing Linezolid using a multiple sealed pack comprising Linezolid and optionally pharmaceutically acceptable carrier or excipient.

In another aspect, there is provided a method of stabilizing Linezolid using a vacuum sealed pack comprising, Linezolid and optionally pharmaceutically acceptable carrier or excipient.

In yet another aspect, there is provided a multiple sealed pack and vacuum sealed pack comprising an Linezolid and optionally pharmaceutically acceptable carrier or excipient and desiccant, wherein the Linezolid is packaged in a first impermeable bag under vacuum, the first impermeable bag and stabilizer are put into a second bag, then vacuum sealed. These bags may be then put into a rigid container.

In still another aspect, there is provided a vacuum sealed pack comprising a solid pharmaceutical composition comprising Linezolid wherein the pack comprises at least one pharmaceutically acceptable carrier or excipient selected from group of cellulose derivatives.

In yet a further aspect, there is provided a vacuum sealed pack comprising a solid pharmaceutical composition comprising an Linezolid wherein the pack comprises at least one pharmaceutically acceptable carrier or excipient and desiccant, wherein the composition are packaged in a first impermeable bag under vacuum, the first impermeable bag and stabilizer are put into a second bag, and then vacuum sealed. These bags may be then put into rigid container.
In yet a further aspect, invention relate to a stable microcrystalline form of Linezolid, which is stable after micronization, and processes for preparation thereof.

Yet another aspect of the present invention relates to a stable microcrystalline form of Linezolid and processes for preparation thereof.

Yet another aspect of the present invention relates provides packaging system for stable microcrystalline form of Linezolid so as to enhance their stability.

**BRIEF DESCRIPTION OF THE INVENTION**

Figure-1: PXRD graph of stable microcrystalline form of Linezolid.
Figure-2: FTIR (Nujol) of stable microcrystalline form of Linezolid.
Figure-3: DSC curve of stable microcrystalline form of Linezolid.
Figure-4: TGA curve of stable microcrystalline form of Linezolid.

**DETAILED DESCRIPTION OF THE INVENTION**

One of the embodiment of the present invention relate to a stable microcrystalline form of Linezolid, which is stable after micronization, and processes for preparation thereof.

In another embodiment of the present invention provide a stable microcrystalline form of Linezolid, which is stable to micronization, with a powder X-ray diffraction (PXRD) pattern having at about 7.3, 9.3, 13.5, 14.7, 16.8, 18.0, 18.7, 19.8, 21.0, 22.1, 25.3, 28.3, or 29.6 ± 0.2 degrees 2-theta.

In another embodiment of the present invention provide a stable microcrystalline form of Linezolid, which is stable to micronization, with a FTIR (Nujol) spectrum having main bands at about 3338, 2926, 2863, 1741, 1662, 1545, 1516, 1450, 1380, 1334, 1304, 1274,
In another embodiment of the present invention provides a stable microcrystalline form of Linezolid, which is stable to micronization, with any one or more of a powder X-ray diffraction (PXRD) pattern, a FTIR (Nujol), a thermogravimetric analysis (TGA) curve, and a differential scanning calorimetry (DSC) curve, substantially as illustrated by Figs. 1, 2, 3, and 4, respectively.

In another embodiment of the present application provides processes for the preparation of a stable microcrystalline form of Linezolid, which is stable to micronization, comprising:

i) providing a solution of Linezolid in a solvent;
ii) optionally, seeding the solution prepared in step a with crystals of Linezolid;
iii) isolating the Linezolid; and
iv) micronizing the Linezolid to stable microcrystalline form of Linezolid.

In another embodiment of the present application provides processes for the preparation of a microcrystalline stable microcrystalline form of Linezolid, comprising:

i) providing a slurry or suspension of Linezolid in a solvent;
ii) optionally, seeding the solution obtained in step a) with crystals of Linezolid;
iii) isolating the Linezolid; and
iv) micronizing the Linezolid to stable microcrystalline form of Linezolid.

The solution of Linezolid may be obtained by dissolving Linezolid in a solvent, or it may be obtained directly from a reaction mixture, in which the compound is formed in the course of synthesis of Linezolid. Any physical forms of Linezolid, such as crystalline, amorphous, or their mixtures may be utilized for preparing the solution of Linezolid in step i).
Solvents that may be employed for providing a solution of Linezolid in step i) include, but are not limited to: alcohol solvents, e.g., methanol, ethanol, 2-propanol, 1-propanol, 1-butanol, 2-butanol, or the like; ketonic solvents, e.g., acetone, ethyl methyl ketone, methyl isobutyl ketone, cyclohexanone, cyclopentanone, or the like; or mixtures thereof. The temperatures at which a solution may be obtained in step i) range from about 0°C to about the reflux temperature of the solvent that is used, or any other suitable temperatures.

Step ii) involves optionally seeding the solution obtained in step a) with crystals of the Linezolid. Crystals of the stable microcrystalline form that are used in step ii) may be obtained by any of the processes of the present application.

Step iii) involves isolating the Linezolid. Isolation in step iii) may involve any methods, including removal of solvent, cooling, concentrating the mass, using an anti-solvent, extraction with a solvent, adding seed crystals to induce crystallization, or the like. Stirring or other alternate methods such as shaking, agitation, or the like, may also be employed for the isolation. Suitable temperatures for isolation may be less than about 60°C, less than about 40°C, less than about 20°C, less than about 10°C, less than about 5°C, less than about 0°C, less than about -10°C, less than about -20°C, or any other suitable temperatures.

The isolated solid may be recovered by any methods, including decantation, centrifugation, gravity filtration, suction filtration, or any other suitable techniques for the recovery of solids. The recovered solid may optionally be dried. Drying may be carried out in a tray dryer, vacuum oven, air oven, cone vacuum dryer, rotary vacuum dryer, fluidized bed dryer, spin flash dryer, flash dryer, or the like. The drying may be carried out at temperatures less than about 100°C, less than about 80°C, less than about 60°C, less than about 50°C, less than about 30°C, or any other suitable temperatures, at atmospheric pressure or under a reduced pressure, as long as the Linezolid is not
degraded in quality. The drying may be carried out for any desired times until the desired product quality is achieved.

Milling or micronization techniques that may be used for particle size reduction include, without limitation sifting, milling using mills, such as, for example, ball, roller and hammer mills, or jet mills, including, for example, air jet mills, or any other conventional techniques.

The resulting stable microcrystalline form of Linezolid is usually in the form of small particles. The mean size of the particles may be less than 500 µm in diameter, or less than 100 µm in diameter, or less than 50 µm in diameter, or less than 20 µm in diameter or less than 15 µm in diameter.

The particle sizes of a drug substance can influence biopharmaceutical properties of its pharmaceutical products. For example, the particle sizes of the drug substance affects drug product manufacturing and dissolution, and hence the bioavailability from formulated products. When drug substance particles are small, shorter periods of time are required to achieve high dissolved concentrations. From this perspective, smaller particles are preferred. In addition, smaller particle sizes tend to improve the homogeneity of powder blends, which may result in improved uniformity of the drug content in a pharmaceutical product.

Particle size distributions of a stable microcrystalline form of Linezolid, which is stable to micronization, particles may be measured using any techniques known in the art. For example, particle size distributions of Linezolid particles may be measured using microscopy or light scattering equipment, such as, for example, a Malvern Master Size 2000 from Malvern Instruments Limited, Malvern, Worcestershire, United Kingdom. The particle size distributions can be expressed, for example, in terms of d(90), d(50), and d(10) values, where the values (e.g., expressed in µm) are the maximum sizes for 90, 50, and 10 percent of the particles, respectively.
Another useful parameter is "Span," defined as Span = D(90) - D(10) - D(50), where D(50) is the diameter corresponding to the diameter of particles that make up 50% of the total volume of particles of equal or smaller diameter, D(90) is the diameter corresponding to the diameter of particles that make up 90% of the total volume of particles of equal or smaller diameter, and D(10) is the diameter corresponding to the diameter of particles that make up 10% of the total volume of particles of equal or smaller diameter. Span, sometimes referred to in the art as the Relative Span Factor or RSF, is a dimensionless parameter indicative of the uniformity of the particles size distribution. Generally, the lower the Span, the more narrow the size distribution, resulting in improved flow characteristics. Preferably, the Span of the particles produced by the process is less than about 3, more preferably less than about 2.5, and most preferably less than about 2.0.

"Particle," as used herein, refers to an aggregated physical unit of the Linezolid compound, i.e., a piece or a grain of Linezolid.

As used herein, the term "mean," when used in reference to the size of Linezolid particles, refers to the sum of the size measurements of all measurable particles measured divided by the total number of particles measured. For example, for five measurable particles which could be measured, and were determined to have diameters of 20 microns, 23 microns, 20 microns, 35 microns and 20 microns, the mean diameter would be 23.6 microns. As used herein, the term "diameter" is a volumetric measurement based on the presumed spherical shape of Linezolid particles.

As used herein, the term "median," when used in reference to the size of Linezolid particles, indicates that about 50% of all measurable particles measured have a particle size less than the defined median particle size value, and that about 50% of all measurable particles measured have a particle size greater than the defined median particle size value. For example, for the five particle values listed above, the median diameter would be 20 microns.
As used herein, the term "mode," when used in reference to the size of Linezolid particles, indicates the most frequently-occurring particle size value. For example, for the five particle values listed above, the mode diameter would be 20 microns.

As used herein, the term "percent cumulative," when used in reference to the size of Linezolid particles, refers to an aggregate of the individual percent values for all measurable particles measured at specified diameters.

As used herein, "about" means plus or minus approximately ten percent of the indicated value, such that "about 50 microns" indicates approximately 45 to 55 microns. The size of the particle can be determined, e.g., by the methods provided below, and by conventional methods known to those of skill in the art.

In another embodiment of the present application provides processes for the preparation of a microcrystalline stable microcrystalline form of Linezolid, comprising: micronizing a stable microcrystalline form of Linezolid, which is stable to micronization, having particle size distributions where particles having particle size distributions where D(90) is less than 50µm.

In another embodiment of the present application provides pharmaceutical compositions comprising a stable microcrystalline form of Linezolid, which is stable to micronization, together with at least one pharmaceutically acceptable excipient. In an aspect, the present application provides pharmaceutical compositions comprising a microcrystalline stable microcrystalline form of Linezolid, together with at least one pharmaceutically acceptable excipient.

In another embodiment, a multiple packing and vacuum packed system comprising pharmaceutically active ingredient and at least one desiccant.

In another embodiment, a multiple packing and vacuum packed system for a solid pharmaceutical composition is obtained by
i) putting the composition into a first bag along with a desiccant;
ii) closing the bag by under vacuum of step i);
iii) putting the bag of step i) into second bag;
iv) vacuum sealing the second bag along with a desiccant under nitrogen gas purging;
v) putting the vacuum sealed bag of step iv) into a third bag with an desiccant, under nitrogen gas purging and vacuum sealing the third bag;
v) putting the bag of step ii) into a rigid container along with an desiccant; and
vii) sealing the rigid container using induction.

In another embodiment, a multiple packing and vacuum packed system for a solid pharmaceutical composition can be obtained by
i) putting the composition into a first LDPE bag along with an desiccant;
ii) vacuum sealing the bag of step i);
iii) putting the bag of step i) into second HMHDPE bag;
iv) vacuum sealing the second HMHDPE bag along with an desiccant under nitrogen gas purging;
v) putting the vacuum sealed bag of step iv) into a third bag triple laminated aluminum bag with an desiccant, under nitrogen gas purging and vacuum sealing the third bag;
v) putting the bag of step ii) into a rigid container along with an desiccant; and
vii) sealing the rigid container using induction.

A multiple sealed pack and vacuum sealed pack wherein the "pharmaceutically active ingredient" is selected from the group from comprising of analgesics, anti-inflammatory agents, anti-helminthics, anti-arrhythmic agents, anti-asthma agents, anti-bacterial agents, anti-viral agents, anti-coagulants, anti-dementia agents, antidepressants, anti-diabetics, anti-epileptics, anti-fungal agents, anti-gout agents, anti-hypertensive agents, anti-malarials, anti-migraine agents, anti-muscarinic agents, anti-neoplastic agents,
immunosuppressants, antiprotozoal agents, anti-thyroid agents, anti-tussives, anxiolytics, sedatives, hypnotics, neuroleptics, neuroprotective agents, β-blockers, cardiac inotropic agents, cell adhesion inhibitors, corticosteroids, cytokine receptor activity modulators, diuretics, antiparkinsonian agents, gastro-intestinal agents, histamine H-receptor antagonists, keratolytics, lipid regulating agents, muscle relaxants, nitrates and other anti-anginal agents, non-steroid anti-asthma agents, nutritional agents, opioid analgesics, sex hormones, stimulants and anti-erectile dysfunction agents, and combinations thereof.

In another embodiment, a multiple packing and vacuum packed system for stable microcrystalline form of Linezolid can be obtained by

i) putting the stable microcrystalline form of Linezolid into a bag;

ii) closing the bag by under vacuum;

iii) putting the bag of step i) into at-least more than one bag;

iv) optionally vacuum sealing the another bags along with an a desiccant under nitrogen gas purging;

v) putting the bag of step iv) into a rigid container; and

vi) sealing the rigid container using induction.

In another embodiment, a multiple packing and vacuum packed system for stable microcrystalline form of Linezolid can be obtained by

i) putting the stable microcrystalline form of Linezolid into a LDPE bag;

ii) vacuum sealing the bag of step i);

iii) putting the bag of step ii) into second HMHDPE bag;

iv) vacuum sealing the second HMHDPE bag along with an desiccant, under nitrogen gas purging;

v) putting the vacuum sealed bag of step iv) into a third bag Triple laminated aluminum bag with an desiccant, under nitrogen gas purging and vacuum sealing the third bag;

vi) putting the bag of step v) into a rigid container; and

vii) sealing the rigid container using induction.
In another embodiment of a multiple packing and vacuum packed system for Linezolid can be obtained by

i) putting the Linezolid into a bag;
ii) closing the bag by under vacuum;
iii) putting the bag of step i) into second bag;
iv) vacuum sealing the second bag along with an a desiccant under nitrogen gas purging;
v) putting the vacuum sealed bag of step iv) into a third bag with an desiccant
   and/or a desiccant, under nitrogen gas purging and vacuum sealing the third bag.
vi) putting the bag of step v) into a rigid container; and
vii) sealing the rigid container using induction.

In another embodiment, a multiple packing and vacuum packed system for Linezolid can be obtained by

i) putting the Linezolid into a bag;
ii) closing the bag by under vacuum;
iii) putting the bag of step i) into atleast more than one bag; and
iv) optionally vacuum sealing the another bags along with an a desiccant under nitrogen gas purging;
v) putting the bag of step iv) into a rigid container; and
vi) sealing the rigid container using induction.

In another embodiment, a multiple packing and vacuum packed system for Linezolid can be obtained by

i) putting the Linezolid into a LDPE bag;
ii) vacuum sealing the bag of step i);
iii) putting the bag of step ii) into second HMHDPE bag;
iv) vacuum sealing the second HMHDPE bag along with an desiccant, under nitrogen gas purging;
v) putting the vacuum sealed bag of step iv) into a third bag Triple laminated aluminum bag with a desiccant, under nitrogen gas purging and vacuum sealing the third bag;

vi) putting the bag of step v) into a rigid container; and

vii) sealing the rigid container using induction.

The term "desiccant" is a hygroscopic substance that induces or sustains a state of dryness (desiccation) in its local vicinity in a moderately well-sealed container. Commonly encountered pre-packaged desiccants are solids, and work through absorption or adsorption of water, or a combination of the two. Desiccants for specialized purposes may be in forms other than solid, and may work through other principles, such as chemical bonding of water molecules.

Pre-packaged desiccant is most commonly used to remove excessive humidity that would normally degrade or even destroy products sensitive to moisture. Some commonly used desiccants are: silica gel, activated charcoal, calcium sulfate, calcium chloride, montmorillonite clay, and molecular sieves. Silica gel is often used in musical instrument cases.

A specific usage of a desiccant would be in insulated windows where it is placed inside the spacer between the air space and window edge. This prevents moisture condensation between the panes.

The desiccant includes activated carbon, silicas, zeolites, molecular sieves, hydrogels, calcium oxide and diatomaceous earth. The particular moisture-retaining materials used will depend upon the humidity level of the environment, for example, in a very low-humidity environment, a moisture-carrying material such as a hydrogel that partially binds water may be preferred. The desiccant can be supplied in the form of a sachet, cartridge or canister. A preferred form is a canister of silica gel, such as SorBit™ (commercially supplied by Sud-Chemie Corporation). Multisorb provides variety of
desiccant under trade name of Natrasorb M, Natrasorb S, Natrasorb C, and Hi-dry, which comprise diatomaceous earth, silica gel, calcium oxide and molecular sieve, respectively.

The size and number of desiccant can depend on the amount of residual moisture after vacuum has been applied, hence would mainly depend on package system such as HDPE bottle or permeable/impermeable bags. The desiccant may be in the form of packet, sachet, strips or canisters. The packet, sachet, strips or canisters may additionally comprise a moisture-indicating card.

The packaging material for package system refer to the substances (e.g., glass, Polyethylene (PE), bi-axially oriented polypropylene (BOPP), PET (polyethylene terpthalate), oriented polyamide (OPA), aluminum foil, resin, metal) used to manufacture a packaging component.

The packaging material for package system could comprise air as well as moisture-impermeable material so that vacuum created during packaging is maintained throughout the shelf life of the drug. It can be chosen from Polyethylene (PE), bi-axially oriented polypropylene (BOPP), PET (polyethylene terpthalate), oriented polyamide (OPA), aluminum foil, or a blend of these polymers or a laminated structure of these polymers. Possible structures of the laminate are PET/aluminum foil/PE, or OPA/PET/PE, and various other permutations and combinations are possible. The laminate structure would primarily depend on moisture/light or gas barrier required by the drug or the composition.

As the polyethylene-based resin, there can be enlisted but are not limited to linear low density polyethylene (LLDPE), high density polyethylene (HDPE), low density polyethylene (LDPE), High Molecular High Density Polyethylene (HMHDPE) polypropylene, acrylonitrile, polyamide, polyvinylidinefluoride (PVDF), ethylene acrylic acid, ethylene/methacrylic acid (E/MAA) copolymer, polypropylene lacquer, polyacetal and copolymers thereof or the like.
The rigid container as used herein include non-airtight/air-tight plastic/metal drums, corrugated shipper or fiberboard drum for drug packaging and HDPE (high density polyethylene), PP (polypropylene), LDPE (low density polyethylene), PET, PVC (polyvinyl chloride) bottle for composition packaging.

The following examples illustrate the invention further. It should be understood however, that the invention is not confined to the specific limitations set forth in the individual example but rather to the scope of the appended claims.

Example 1: Synthesis of Linezolid.
Reflux the Acetone (1020ml) and Linezolid crude (100g) at 55-60°C for the 30 minutes. Filter the hot turbid solution & wash it with hot (55-60°C) acetone (50ml). Cool the reaction mixture at -5 to 0°C for 1 hour, wash the solid with chilled (-5 to 0°C) acetone (50ml). After drying the Linezolid semi pure (77g) add n-Propanol (308ml) reflux it at 95-100°C for 30 min & filter it by hot solution through hyflo bed. Cool the mix to 0-5°C for 1 hour and wash the solid with chilled (0-5°C) n-Propanol (77ml). Dry the material at 55-60°C. Yield: 0.73.: Percentage 73%w/w.

Example 2: Synthesis of Linezolid.
Reflux n-propanol (400ml) and Linezolid (100g) at 95-100°C till all solid gets dissolved. Add activated charcoal (2.0g) and heat for 30 mins. Filter thro hyflo bed. Heat the filtrate and concentrate the solution by partially removing n-propanol. Cool to 0-5°C and filter the solid and dry it at 55-60°C under vacuum. Yield: 0.9.: Percentage 90%w/w.

Example 3
Linezolid drug substance was packaged for long term use or transporting according to various packaging options as described below:

1. Linezolid was packaged in a LDPE bag and flushed with nitrogen gas; the bag was twisted and tied; the bag was put into a double laminated bag along with desiccant and
flushed with nitrogen gas; vacuum was applied to the double laminated bag and heat sealed; the sealed double laminated bag was packaged into a triple laminated bag along with molecular sieve and flushed with nitrogen gas; vacuum was applied to the triple laminated bag and heat sealed.

2. Linezolid was packaged in a LDPE bag and flushed with nitrogen gas; the bag was twisted and tied; the bag was put into a double laminated bag along with desiccant and silica gel; vacuum was applied to the double laminated bag and heat sealed; sealed double laminated bag was packaged into a triple laminated bag along with molecular sieve; vacuum was applied to triple laminated bag and heat sealed.

3. Linezolid was packaged in a LDPE bag and flushed with nitrogen gas; the bag was twisted and tied; the bag was put into a double laminated bag along with two molecular sieve; vacuum was applied to the double laminated bag and heat sealed; sealed double laminated bag was packaged into a triple laminated bag along with two molecular sieve; vacuum was applied to triple laminated bag and heat sealed.

4. Linezolid was packaged in a LDPE bag and flushed with nitrogen gas; the bag was vacuum sealed; the bag was put into a double laminated bag along with desiccant; vacuum was applied to the double laminated bag and heat sealed; sealed double laminated bag was packaged into a triple laminated bag along with molecular sieve and nitrogen flushed; vacuum was applied to triple laminated bag and heat sealed.
We Claim,

1. A stable microcrystalline form of Linezolid.

2. The stable microcrystalline form of Linezolid of claim 1, with a powder X-ray diffraction (PXRD) pattern having at about 7.3, 9.3, 13.5, 14.7, 16.8, 18.0, 18.7, 19.8, 21.0, 22.1, 25.3, 28.3, or 29.6 ± 0.2 degrees 2-theta.

3. The stable microcrystalline form of Linezolid of claim 1, with a FTIR (Nujol) spectrum having main bands at about 3338, 2926, 2863, 1741, 1662, 1545, 1516, 1450, 1380, 1334, 1304, 1274, 1256, 1228, 1213, 1198, 1177, 1146, 1117, 1081, 1050, 971, 936, 923, 903, 870, 824, 755, 661 cm⁻¹.

4. The stable microcrystalline form of Linezolid of claim 1 with powder X-ray diffraction (PXRD) pattern, substantially as illustrated by Figs. 1.

5. The stable microcrystalline form of Linezolid of claim 1 with FTIR (Nujol), substantially as illustrated by Figs. 2.

6. The stable microcrystalline form of Linezolid of claim 1 with thermogravimetric analysis (TGA) curve, substantially as illustrated by Figs. 3.

7. The stable microcrystalline form of Linezolid of claim 1 with differential scanning calorimetry (DSC) curve, substantially as illustrated by Figs. 4.

8. A process for the preparation of a stable microcrystalline form of Linezolid, comprising:
   i) providing a solution of Linezolid in a solvent;
   ii) optionally, seeding the solution prepared in step a with crystals of Linezolid;
   iii) isolating the Linezolid; and
iv) micronizing the Linezolid to stable microcrystalline form of Linezolid.

9. A process for the preparation of stable microcrystalline form of Linezolid, comprising:
   i) providing a slurry or suspension of Linezolid in a solvent;
   ii) optionally, seeding the solution obtained in step a) with crystals of Linezolid;
   iii) isolating the Linezolid; and
   iv) micronizing the Linezolid to stable microcrystalline form of Linezolid.

10. The process for the preparation of stable microcrystalline form of Linezolid according to claim 8 and 9 wherein solvent selected from the group comprising of methanol, ethanol, 2-propanol, 1-propanol, 1-butanol, 2-butanol, or the like; or acetone, ethyl methyl ketone, methyl isobutyl ketone, cyclohexanone, cyclopentanone, or the like; or mixtures thereof.

11. The process for the preparation of stable microcrystalline form of Linezolid according to claim 8 and 9 wherein micronizing techniques that may be used for particle size reduction include, sifting, milling using mills, such as, ball mill, roller mill, or hammer mills, or jet mills.

12. A stable microcrystalline form of Linezolid which is stable to micronization.

13. The stable microcrystalline form of Linezolid which is stable to micronization of claim 12, with a powder X-ray diffraction (PXRD) pattern having at about 7.3, 9.3, 13.5, 14.7, 16.8, 18.0, 18.7, 19.8, 21.0, 22.1, 25.3, 28.3, or 29.6 ± 0.2 degrees 2-theta.

14. A multiple sealed pack and vacuum sealed pack comprising pharmaceutically active ingredient and at least one desiccant.
15. A multiple sealed pack and vacuum sealed pack of claim 14 wherein the pharmaceutically active ingredient is selected from the group comprising of analgesics, anti-inflammatory agents, anti-helminths, anti-arrhythmic agents, anti-asthma agents, anti-bacterial agents, anti-viral agents, anti-coagulants, anti-dementia agents, antidepressants, anti-diabetics, anti-epileptics, anti-fungal agents, anti-gout agents, anti-hypertensive agents, anti-malarials, anti-migraine agents, anti-muscarinic agents, anti-neoplastic agents, immunosuppressants, antiprotocoal agents, anti-thyroid agents, anti-tussives, anxiolytics, sedatives, hypnotics, neuroleptics, neuroprotective agents, β-blockers, cardic inotropic agents, celt adhesion inhibitors, corticosteroids, cytokine receptor activity modulators, diuretics, antiparkinsonian agents, gastro-intestinal agents, histamine H-receptor antagonists, keratolyses, lipid regulating agents, muscle relaxants, nitrates and other anti-anginal agents, non-steroid anti-asthma agents, nutritional agents, opioid analgesics, sex hormones, stimulants and anti-erectile dysfunction agents, and combinations thereof.

16. A multiple sealed pack and vacuum sealed pack comprising Linezolid and at least one desiccant.

17. A multiple sealed pack and vacuum sealed pack comprising a solid pharmaceutical composition comprising Linezolid wherein the pack comprises at least desiccant.

18. The multiple sealed pack and vacuum sealed pack according to claim 17 wherein the pharmaceutical composition is tablet, capsule, pills, dry powder, dragees or granulate.

19. The multiple sealed pack and vacuum sealed pack according to claim 16 or 17 wherein the Linezolid is stable microcrystalline or unmicronized.
The multiple sealed pack and vacuum sealed pack according to claim 16 or 17 wherein the desiccant is selected from the group consisting of activated carbon, silicas, zeolites, molecular sieves, hydrogels, calcium oxide and diatomaceous earth.

The multiple sealed pack and vacuum sealed pack according to claim 16 or 17 wherein the Linezolid is packaged in impermeable package.

The vacuum sealed pack according to claim 20 wherein the package is bag.

The multiple sealed pack and vacuum sealed pack according to claim 22 wherein the package is made up of material selected from Polyethylene (PE), low density polyethylene (LLDPE), high density polyethylene (HDPE), low density polyethylene (LDPE), High Molecular High Density Polyethylene (HMHDPE) polypropylene, acrylonitrile, polyamide, polyvinylidinefluoride (PVDF), ethylene acrylic acid, ethylene/methacrylic acid (E/MAA) copolymer, polypropylene lacquer, polyacetal and copolymers thereof or bi-axially oriented polypropylene (BOPP) or PET (polyethylene terephthalate) or oriented polyamide (OPA) or aluminum foil, or a blend of thereof or a laminated structure of these polymers.

The multiple sealed pack and vacuum sealed pack according to claim 22 wherein the package is vacuum sealed in another package.

The multiple sealed pack and vacuum sealed pack according to any of the preceding claim wherein the Linezolid or composition and the stabilizer are packaged in first impermeable bag under vacuum, the first impermeable bag and the desiccant is put in second bag and vacuum sealed.

The multiple sealed pack and vacuum sealed pack according to claim 25 wherein the second bag and the desiccant is put in third bag and vacuum sealed.
27. The multiple sealed pack and vacuum sealed pack according to claim 26 wherein the third bag is triple laminated aluminum bag with desiccant.

28. The multiple sealed pack and vacuum sealed pack according to claim 28 wherein the third bag is put in rigid container and sealed.

29. The multiple sealed pack and vacuum sealed pack according to claim 28 wherein the rigid container is non-airtight/air-tight plastic/metal drums, corrugated shipper or fiberboard drum for amorphous statin and HDPE (high density polyethylene), PP (polypropylene), LDPE (low density polyethylene), PET, PVC (polyvinyl chloride) bottle for composition.

30. A multiple packing and vacuum packed system for pharmaceutically active ingredient comprising:
   i) putting the stable microcrystalline form of Linezolid into a bag;
   ii) closing the bag by under vacuum;
   iii) putting the bag of step i) into at least more than one bag;
   iv) optionally vacuum sealing the another bags along with an a desiccant under nitrogen gas purging;
   v) putting the bag of step iv) into a rigid container; and
   vi) sealing the rigid container using induction.

31. A multiple packing and vacuum packed system for pharmaceutically active ingredient comprising:
   i) putting the pharmaceutically active ingredient into a LDPE bag;
   ii) vacuum sealing the bag of step i);
   iii) putting the bag of step ii) into second HMHDPE bag;
   iv) vacuum sealing the second HMHDPE bag along with a desiccant, under nitrogen gas purging;
v) putting the vacuum sealed bag of step iv) into a third bag Triple laminated aluminum bag with a desiccant, under nitrogen gas purging and vacuum sealing the third bag;

vi) putting the bag of step v) into a rigid container; and

vii) sealing the rigid container using induction.

32. A multiple sealed pack and vacuum sealed pack of claim 30 and 31 wherein the pharmaceutically active ingredient is selected from the group from comprising of analgesics, anti-inflammatory agents, anti-helminthics, anti-arrhythmic agents, anti-asthma agents, anti-bacterial agents, anti-viral agents, anti-coagulants, anti-dementia agents, antidepressants, anti-diabetics, anti-epileptics, anti-fungal agents, anti-gout agents, anti-hypertensive agents, anti-malarials, anti-migraine agents, anti-muscarinic agents, anti-neoplastic agents, immunosuppressants, antiprotozoal agents, anti-thyroid agents, anti-tussives, anxiolytics, sedatives, hypnotics, neuroleptics, neuroprotective agents, β-blockers, cardie inotropic agents, celt adhesion inhibitors, corticosteroids, cytokine receptor activity modulators, diuretics, antiparkinsonian agents, gastro-intestinal agents, histamine H-receptor antagonists, keratolyses, lipid regulating agents, muscle relaxants, nitrates and other anti-anginal agents, non-steroid anti-asthma agents, nutritional agents, opioid analgesics, sex hormones, stimulants and anti-erectile dysfunction agents, and combinations thereof.

33. A multiple packing and vacuum packed system for stable microcrystalline form of Linezolid comprising:
   i) putting the pharmaceutically active ingredient into a bag;
   ii) closing the bag by under vacuum;
   iii) putting the bag of step i) into at least more than one bag;
   iv) optionally vacuum sealing the another bags along with an a desiccant under nitrogen gas purging;
   v) putting the bag of step iv) into a rigid container; and
   vi) sealing the rigid container using induction.
34. A multiple packing and vacuum packed system for stable microcrystalline form of Linezolid comprising:
   i) putting the stable microcrystalline form of Linezolid into a LDPE bag;
   ii) vacuum sealing the bag of step i);
   iii) putting the bag of step ii) into second HMHDPE bag;
   iv) vacuum sealing the second HMHDPE bag along with an desiccant, under nitrogen gas purging;
   v) putting the vacuum sealed bag of step iv) into a third bag Triple laminated aluminum bag with an desiccant, under nitrogen gas purging and vacuum sealing the third bag;
   vi) putting the bag of step v) into a rigid container; and
   vii) sealing the rigid container using induction.

35. A multiple packing and vacuum packed system for Linezolid can be obtained by
   i) putting the Linezolid into a bag;
   ii) closing the bag by under vacuum;
   iii) putting the bag of step i) into second bag;
   iv) vacuum sealing the second bag along with an a desiccant under nitrogen gas purging;
   v) putting the vacuum sealed bag of step iv) into a third bag with an desiccant and/or a desiccant, under nitrogen gas purging and vacuum sealing the third bag.
   vi) putting the bag of step v) into a rigid container along with an desiccant; and
   vii) sealing the rigid container using induction.

36. A multiple packing and vacuum packed system for Linezolid comprising:
   i) putting the Linezolid into a bag;
   ii) closing the bag by under vacuum;
   iii) putting the bag of step i) into at least more than one bag;
iv) optionally vacuum sealing the another bags along with an a desiccant under nitrogen gas purging;

v) putting the bag of step iv) into a rigid container; and

vi) sealing the rigid container using induction.

37. a multiple packing and vacuum packed system for Linezolid can be obtained by
i) putting the Linezolid into a LDPE bag;
ii) vacuum sealing the bag of step i);
iii) putting the bag of step ii) into second HMHDPE bag;
iv) vacuum sealing the second HMHDPE bag along with an desiccant, under nitrogen gas purging;

v) putting the vacuum sealed bag of step iv) into a third bag Triple laminated aluminum bag with an desiccant, under nitrogen gas purging and vacuum sealing the third bag;

vi) putting the bag of step v) into a rigid container; and

vii) sealing the rigid container using induction.

38. a multiple packing and vacuum packed system for a solid pharmaceutical composition is obtained by
i) putting the composition into a first bag along with an a desiccant;
ii) closing the bag by under vacuum of step i);
iii) putting the bag of step i) into second bag;
iv) vacuum sealing the second bag along with an a desiccant under nitrogen gas purging;

v) putting the vacuum sealed bag of step iv) into a third bag with an desiccant, under nitrogen gas purging and vacuum sealing the third bag;

vi) putting the bag of step v) into a rigid container along with an oxygen a desiccant; and

vii) sealing the rigid container using induction.
39. a multiple packing and vacuum packed system for a solid pharmaceutical composition can be obtained by
   i) putting the composition into a first LDPE bag along with an a desiccant;
   ii) vacuum sealing the bag of step i);
   iii) putting the bag of step i) into second HMHDPE bag;
   iv) vacuum sealing the second HMHDPE bag along with an a desiccant under nitrogen gas purging; and
   v) putting the vacuum sealed bag of step iv) into a third bag Triple laminated aluminum bag with an desiccant, under nitrogen gas purging and vacuum sealing the third bag;
   vi) putting the bag of step v) into a rigid container along with an desiccant; and
   vii) sealing the rigid container using induction.

40. The multiple sealed pack and vacuum sealed pack comprising Linezolid according to any of the preceding claim, wherein a space between two containers is provided with an inert gas, and a desiccant.

41. The multiple sealed pack and vacuum sealed pack comprising Linezolid according to any of the preceding claim, wherein a space between two containers is provided with desiccant.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: C07D263/; B65D77/; A61L2/-

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>CN 2603785Y (SHANDONG REYOUNG PHARM. CO., LTD.), 18 Feb. 2004 (18.02.2004), see abstract, claims 1-3, pages 1-2</td>
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Further documents are listed in the continuation of Box C. See patent family annex.

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search

3 May 2013 (03.05.2013)

Date of mailing of the international search report

23 May 2013 (23.05.2013)

Name and mailing address of the ISA/CN

The State Intellectual Property Office, the P.R.China

6 Xinzheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088

Facsimile No. 86-10-62019451

Authorized officer

ZHANG, Hengjun

Telephone No. (86-10)82246670

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Form PCT/ISA /210 (patent family annex) (July 2009)
**INTERNATIONAL SEARCH REPORT**

**Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

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

2. ☐ Claims Nos.:
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

- See extra sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☑ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on protest**

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

- ☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (July 2009)
INTERNATIONAL SEARCH REPORT

Box No. Ill (Continuation). Observations where unity of invention is lacking

This Authority considers that there are 8 inventions covered by the claims indicated as follows:

I: Claims 1-7 and 12-13 directed to a stable microcrystalline form of Linezolid.

II: Claims 8-11 directed to a process for the preparation of a stable microcrystalline form of Linezolid.

III: Claims 14-15 directed to a multiple sealed pack and vacuum sealed pack comprising pharmaceutically active ingredient.

IV: Claims 16-27 and 40-41 directed to a multiple sealed pack and vacuum sealed pack comprising Linezolid.

V: Claims 30, 32 (part) and 33-34 directed to a multiple packing and vacuum packed system for a stable microcrystalline form of Linezolid.

V: Claims 31 and 32 (part) directed to a multiple packing and vacuum packed system for pharmaceutically active ingredient.

VI: Claims 35-37 directed to a multiple packing and vacuum packed system for Linezolid.

VI: Claims 38-39 directed to a multiple packing and vacuum packed system for solid pharmaceutical composition.

The reasons for which the inventions are not so linked as to form a single general inventive concept, as required by Rule 13.1 PCT, are as follows:

These claims above do not have special technical feature of make a contribution over the prior art. Hence the invention does not meet the requirements of unity of invention as defined in Rule 13.1 PCT.

A (Continuation). CLASSIFICATION OF SUBJECT MATTER

C07D263/20 (2006.1) i
B65D77/04 (2006.1) i
A61J1/00 (2006.1) i