



- (51) **International Patent Classification:**
A61K 31/675 (2006.01)
- (21) **International Application Number:**
PCT/US201 1/062050
- (22) **International Filing Date:**
23 November 2011 (23.11.2011)
- (25) **Filing Language:** English
- (26) **Publication Language:** English
- (30) **Priority Data:**
61/458,514 24 November 2010 (24.11.2010) US
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- (81) **Designated States (unless otherwise indicated, for every kind of national protection available):** AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.
- (84) **Designated States (unless otherwise indicated, for every kind of regional protection available):** ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU,

[Continued on nextpage]

- (54) **Title:** NOVEL CRYSTALLINE FORMS

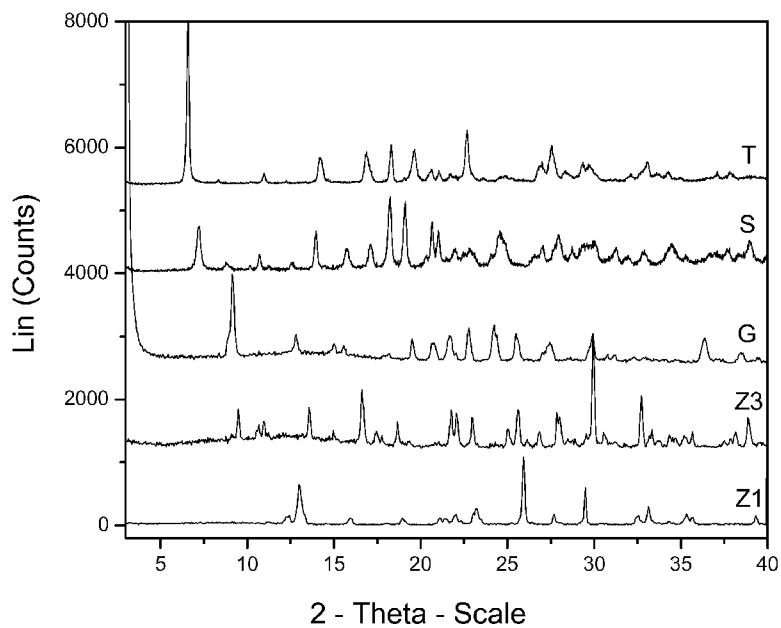


FIG. 1

- (57) **Abstract:** Preparation and characterization of novel forms of (1-hydroxy-2-imidazol-1-yl-1-phosphono-ethyl) phosphonic acid, suitable for pharmaceutical compositions in drug delivery systems for humans.

LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, Published:

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NOVEL CRYSTALLINE FORMS

CROSS REFERERNCCE TO RELATED APPLICATIONS

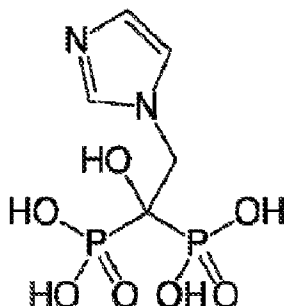
This application claims priority to U.S. Provisional Application 61/458,514, filed 24 November 2010, incorporated by reference in its entirety.

FIELD OF THE INVENTION

This disclosure pertains to generating novel crystalline forms of (1-hydroxy-2-imidazol-1-yl-1-phosphono-ethyl) phosphonic acid, in which such forms include but are not limited to cocrystals, salts, hydrates, solvates, solvates of salts, and mixtures thereof. Methods for the preparation and pharmaceutical compositions suitable for drug delivery systems that include one or more of these new forms are disclosed.

BACKGROUND OF THE INVENTION

Zoledronic acid, known as (1-hydroxy-2-imidazol-1-yl-1-phosphono-ethyl)phosphonic acid, is depicted by the following chemical structure:



Zoledronic acid is a third generation bisphosphonate which far exceeds the previous generations in terms of efficacy and is used predominately for indications of osteoporosis, Paget's disease, hypercalcemia, and inhibition of bone metastasis. It was originally developed by Novartis and marketed as the monohydrate under the brand names Zometa® and Reclast®. Zoledronic acid was first approved in 2000 for the treatment of hypercalcemia in Canada. It was later approved for use in the US for hypercalcemia in 2001, for multiple myeloma and bone metastases from solid tumors in 2002, and for osteoporosis and Paget's disease in 2007. Clinical trials have also been conducted or are on-going exploring the use of zoledronic acid in neoadjuvant or adjuvant cancer

therapy, Coleman, et al., *British J Cancer* 2010;102(7):1099-1105, Gnant, et al., *New England J Medicine*. 2009, 360 (17):679-691 and Davies, et al. *J Clinical Oncology*, 2010, 28(7s): Abstract 8021. Zoledronic acid is administered as an intravenous (IV) dose of 4 mg over 15 minutes per month for hypercalcemia of malignancy, multiple myeloma, and bone metastases from solid tumors, while an IV dose of 5 mg over 15 minutes is used for osteoporosis and Paget's disease. Zoledronic acid is sparingly soluble in water and 0.1 N HCl solution but is freely soluble in 0.1 N NaOH. Zoledronic acid is practically insoluble in various organic solvents.

Much effort has been taken to generate novel oral formulations of zoledronic acid through crystallization and metal salt formation to improve its aqueous solubility, permeability, and subsequent oral bioavailability. A crystalline trihydrate was disclosed in the U.S. Patent application 2006/0178439 A1 and world patent application WO2007/032808. Seven hydrated forms, an amorphous form, three monosodium salts, and eleven disodium salts with varying degrees of hydration of zoledronic acid were also disclosed in the patent application WO2005/005447 A2. Zoledronate metal salts including Na⁺, Mg²⁺, Zn²⁺ were reported in the journal of *Drugs of the Future* (Sorbera et al, 25(3), *Drugs of the Future*, (2000)). Zoledronate, zoledronic, or zoledronic salt represents the ionic form of zoledronic acid. Patent application WO2008/064849 A1 from Novartis disclosed additional metal salts including two Ca²⁺ salts, two Zn²⁺ salts, one Mg²⁺ salt, as well as a monohydrate, a trihydrate, an amorphous form, and an anhydrous form.

According to the US Food and Drug Administration (FDA) Summary Basis of Approval (SBA) for zoledronic acid, the poor oral bioavailability (approximately 1%), is partially due to its poor permeability in the GI tract. It was also noted that insoluble metal complexes were formed in the upper intestines, most commonly with calcium. Zoledronic acid has also been shown to cause severe gastric and intestinal irritations. In some cases the irritations were so severe that medical treatment was required.

Due to the fact that zoledronic acid is only available as a parenteral dosage form there is a clear need to develop novel forms of zoledronic acid that can be included in an oral dosage form particularly as the use of orally administered drugs are becoming more wide spread in many therapeutic areas including the treatment of cancer. The upward trend in the use of oral drugs will continue especially in light of the goal to decrease the overall cost of healthcare. Thus, there is an opportunity to create oral dosage forms of IV drugs where oral dosage forms do not yet

exist due to their poor aqueous solubility and/or poor permeability providing a clear clinical benefit for patients.

Recent activity concerning the development of oral formulations has led to the use of medium chain fatty acids to enhance the drug's low permeability as disclosed in the US 2007/0134319 A 1 and US 2007/0196464 patent applications. Modified amino acid carriers, but not pure proteinogenic amino acids, have also been employed to improve the absorption of the drug as shown in the WO 2007/093226 A 1 application.

The development of oral forms of zoledronic acid has been problematic due to its poor aqueous solubility and permeability. By using pharmaceutically acceptable cocrystal formers to bond with pure zoledronic acid to create novel molecular complexes neutral and ionic (e.g. cocrystals, salts and solvates) which can improve solubility and/or permeability, the opportunity is therefore provided to tackle such problems and develop an oral dosage form.

All of the above attempts to improve the oral bioavailability of zoledronic acid were either focused on improving the aqueous solubility by generating novel solid forms, or by mixing the drug with an inactive ingredient that has enhanced GI tract permeability. The improvement of aqueous solubility failed to improve the bioavailability of zoledronic acid, since the formation of insoluble zoledronate calcium complexes is unlikely to be prevented. On the other hand, powder mixtures of the poorly permeable drug with inactive permeability enhancers improved the bioavailability of the drug. This approach of mixing different materials with different particle sizes and size distributions could result in poor blend/physical mixture uniformity. Constituents of the mixture could also segregate during transportation or with shaking and vibration. Additionally, the powder blends require that the ingredients are compatible and no potential for solid-solid interaction with or without atmospheric interferences exist thus impacting on their physical stability during storage or in a delivery system.

To the best of the inventors' knowledge, no attempt has been made prior to this invention towards a deliberate molecular design to create a molecular complex of the drug and additional component(s) (coformer(s)) in a single crystalline structure that is physically stable and is not influenced by the addition of excess coformer(s) in the formulation. The benefit of such design can lead to the elimination of all potential physical instability in the physical mix of the molecular complex and the coformer(s). Additionally, the resulting molecular complexes possess

very different physicochemical properties compared to the parent drug, coformer or their physical mixture. These properties include but are not limited to melting point, thermal and electrical conductivity, aqueous solubility, rate of dissolution and permeability across the GI tract membrane.

Orally administered drugs are becoming more preferred in various therapeutic areas including cancers. Clearly, there is an opportunity to create oral dosage forms of IV drugs where oral dosage forms do not yet exist due to their poor aqueous solubility and/or poor permeability providing a clear clinical benefit for patients. Given the fact that zoledronic acid is only approved for IV administration, there is a need to develop an oral dosage form of zoledronic acid. By using pharmaceutically acceptable and/or approved cofomers to hydrogen bond with zoledronic acid, novel molecular complexes (e.g. cocrystals, salts, solvates, and mixtures thereof) with improved solubility and/or permeability can be created. These novel molecular complexes could be used in the development of an oral dosage form for zoledronic acid.

SUMMARY OF THE INVENTION

The present disclosure is directed towards generating new forms of zoledronic acid, which have the therapeutic efficacy of zoledronic acid discussed above, with improved aqueous solubility, rate of dissolution, and/or improved permeability and thus enhanced bioavailability. One aspect of the present disclosure includes novel molecular complexes of zoledronic acid that includes cocrystals, salts, and solvates (e.g. hydrates and mixed solvates as well as solvates of salts), and mixtures containing such materials. In addition, the disclosure further includes methods for the preparation of such complexes.

The disclosure further includes compositions of molecular complexes of zoledronic acid suitable for incorporation in a pharmaceutical dosage form. Specific molecular complexes pertaining to the disclosure include, but are not limited to, complexes of zoledronic acid, DL-lysine. Obvious variants of the disclosed zoledronic acid forms in the disclosure, including those described by the drawings and examples, will be readily apparent to the person of ordinary skill in the art having the present disclosure and such variants are considered to be a part of the current invention.

In one aspect the invention provides for a crystalline form of zoledronic acid: DL-lysine.

In one embodiment the crystalline form is characterized by a powder X-ray diffraction pattern comprising a powder X-ray diffraction peak at about 6.6 ± 0.2 degrees 2-theta.

In one embodiment the crystalline form is characterized by a powder X-ray diffraction pattern comprising a powder X-ray diffraction peak at about 11.0 ± 0.2 degrees 2-theta.

In one embodiment the crystalline form is characterized by a powder X-ray diffraction pattern comprising a powder X-ray diffraction peak at about 14.2 ± 0.2 degrees 2-theta.

In one embodiment the crystalline form is characterized by a powder X-ray diffraction pattern comprising a powder X-ray diffraction peak at about 18.3 ± 0.2 degrees 2-theta.

In one embodiment the crystalline form is characterized by a powder X-ray diffraction pattern comprising a powder X-ray diffraction peak at about 19.7 ± 0.2 degrees 2-theta.

In one embodiment the crystalline form is characterized by a powder X-ray diffraction pattern comprising a powder X-ray diffraction peak at about 22.7 ± 0.2 degrees 2-theta.

In one embodiment the crystalline form is characterized by a powder X-ray diffraction pattern comprising a powder X-ray diffraction peak at about 27.6 ± 0.2 degrees 2-theta.

In one embodiment the crystalline form is characterized by a powder X-ray diffraction pattern comprising powder X-ray diffraction peaks at about 6.6 and 18.3 ± 0.2 degrees 2-theta.

In one embodiment the crystalline form is characterized by a powder X-ray diffraction pattern comprising powder X-ray diffraction peaks at about 6.6 and 19.7 ± 0.2 degrees 2-theta.

In one embodiment the crystalline form is characterized by a powder X-ray diffraction pattern comprising powder X-ray diffraction peaks at about 6.6 and 22.7 ± 0.2 degrees 2-theta.

In one embodiment the crystalline form is characterized by a powder X-ray diffraction pattern comprising powder X-ray diffraction peaks at about 6.6, 18.3 and 19.7 ± 0.2 degrees 2-theta.

In one embodiment the crystalline form is characterized by a powder X-ray diffraction pattern comprising powder X-ray diffraction peaks at about 18.3 and 19.7 ± 0.2 degrees 2-theta.

In one embodiment the crystalline form is characterized by a powder X-ray diffraction pattern comprising powder X-ray diffraction peaks at about 18.3, 19.7 and 27.6 ± 0.2 degrees 2-theta.

In one embodiment the crystalline form is characterized by a powder X-ray diffraction pattern comprising powder X-ray diffraction peaks at about 18.3 and 22.7 ± 0.2 degrees 2-theta.

In one embodiment the crystalline form is characterized by a powder X-ray diffraction pattern comprising powder X-ray diffraction peaks at about 6.6, 18.3 and 22.7 ± 0.2 degrees 2-theta.

In one embodiment the crystalline form is characterized by a powder X-ray diffraction pattern comprising powder X-ray diffraction peaks at about 19.7 and 22.7 ± 0.2 degrees 2-theta.

In one embodiment the crystalline form is characterized by a powder X-ray diffraction pattern comprising powder X-ray diffraction peaks at about 19.7, 22.7 and 27.6 ± 0.2 degrees 2-theta.

In one embodiment the crystalline form is characterized by a powder X-ray diffraction pattern comprising powder X-ray diffraction peaks at about 6.6, 19.7 and 22.7 ± 0.2 degrees 2-theta.

In one embodiment the crystalline form is characterized by a powder X-ray diffraction pattern comprising powder X-ray diffraction peaks at about 18.3, 19.7 and 22.7 ± 0.2 degrees 2-theta.

In one embodiment the crystalline form is characterized by a powder X-ray diffraction pattern comprising powder X-ray diffraction peaks at about 6.6, 18.3, 19.7 and 22.7 ± 0.2 degrees 2-theta.

In one embodiment the crystalline form is characterized by a powder X-ray diffraction pattern comprising powder X-ray diffraction peaks at about 14.2, 18.3, 19.7 and 22.7 ± 0.2 degrees 2-theta.

In one embodiment the crystalline form is characterized by a powder X-ray diffraction pattern comprising powder X-ray diffraction peaks at about 6.6, 14.2, 18.3, 19.7 and 22.7 ± 0.2 degrees 2-theta.

In one embodiment the crystalline form is characterized by a powder X-ray diffraction pattern comprising powder X-ray diffraction peaks at about 6.6, 14.2, 18.3, 19.7, 22.7 and 27.6 ± 0.2 degrees 2-theta.

In one embodiment the crystalline form is characterized by a powder X-ray diffraction pattern comprising powder X-ray diffraction peaks at about 6.6, 11.0, 14.2, 18.3, 19.7, 22.7 and 27.6 ± 0.2 degrees 2-theta.

In one embodiment the crystalline form is characterized by a powder X-ray diffraction pattern comprising a powder X-ray diffraction peak at about 7.2 ± 0.2 degrees 2-theta.

In one embodiment the crystalline form is characterized by a powder X-ray diffraction pattern comprising a powder X-ray diffraction peak at about 14.0 ± 0.2 degrees 2-theta.

In one embodiment the crystalline form is characterized by a powder X-ray diffraction pattern comprising a powder X-ray diffraction peak at about 18.3 ± 0.2 degrees 2-theta.

In one embodiment the crystalline form is characterized by a powder X-ray diffraction pattern comprising a powder X-ray diffraction peak at about 19.1 ± 0.2 degrees 2-theta.

In one embodiment the crystalline form is characterized by a powder X-ray diffraction pattern comprising a powder X-ray diffraction peak at about 20.7 ± 0.2 degrees 2-theta.

In one embodiment the crystalline form is characterized by a powder X-ray diffraction pattern comprising a powder X-ray diffraction peak at about 24.6 ± 0.2 degrees 2-theta.

In one embodiment the crystalline form is characterized by a powder X-ray diffraction pattern comprising a powder X-ray diffraction peak at about 34.4 ± 0.2 degrees 2-theta.

In one embodiment the crystalline form is characterized by a powder X-ray diffraction pattern comprising powder X-ray diffraction peaks at about 7.2 and 18.3 ± 0.2 degrees 2-theta.

In one embodiment the crystalline form is characterized by a powder X-ray diffraction pattern comprising powder X-ray diffraction peaks at about 7.2 and 19.1 ± 0.2 degrees 2-theta.

In one embodiment the crystalline form is characterized by a powder X-ray diffraction pattern comprising powder X-ray diffraction peaks at about 7.2 and 20.7 ± 0.2 degrees 2-theta.

In one embodiment the crystalline form is characterized by a powder X-ray diffraction pattern comprising powder X-ray diffraction peaks at about 7.2, 18.3 and 19.1 ± 0.2 degrees 2-theta.

In one embodiment the crystalline form is characterized by a powder X-ray diffraction pattern comprising powder X-ray diffraction peaks at about 18.3 and 19.1 ± 0.2 degrees 2-theta.

In one embodiment the crystalline form is characterized by a powder X-ray diffraction pattern comprising powder X-ray diffraction peaks at about 18.3, 19.1 and 24.6 ± 0.2 degrees 2-theta.

In one embodiment the crystalline form is characterized by a powder X-ray diffraction pattern comprising powder X-ray diffraction peaks at about 18.3 and 20.7 ± 0.2 degrees 2-theta.

In one embodiment the crystalline form is characterized by a powder X-ray diffraction pattern comprising powder X-ray diffraction peaks at about 7.2, 18.3 and 20.7 ± 0.2 degrees 2-theta.

In one embodiment the crystalline form is characterized by a powder X-ray diffraction pattern comprising powder X-ray diffraction peaks at about 19.1 and 20.7 ± 0.2 degrees 2-theta.

In one embodiment the crystalline form is characterized by a powder X-ray diffraction pattern comprising powder X-ray diffraction peaks at about 19.1, 20.7 and 24.6 ± 0.2 degrees 2-theta.

In one embodiment the crystalline form is characterized by a powder X-ray diffraction pattern comprising powder X-ray diffraction peaks at about 7.2, 19.1 and 20.7 ± 0.2 degrees 2-theta.

In one embodiment the crystalline form is characterized by a powder X-ray diffraction pattern comprising powder X-ray diffraction peaks at about 18.3, 19.1 and 20.7 ± 0.2 degrees 2-theta.

In one embodiment the crystalline form is characterized by a powder X-ray diffraction pattern comprising powder X-ray diffraction peaks at about 7.2, 18.3, 19.1 and 20.7 ± 0.2 degrees 2-theta.

In one embodiment the crystalline form is characterized by a powder X-ray diffraction pattern comprising powder X-ray diffraction peaks at about 14.0, 18.3, 19.1 and 20.7 ± 0.2 degrees 2-theta.

In one embodiment the crystalline form is characterized by a powder X-ray diffraction pattern comprising powder X-ray diffraction peaks at about 7.2, 14.0, 18.3, 19.1 and 20.7 ± 0.2 degrees 2-theta.

In one embodiment the crystalline form is characterized by a powder X-ray diffraction pattern comprising powder X-ray diffraction peaks at about 7.2, 14.0, 18.3, 19.1, 20.7 and 24.6 ± 0.2 degrees 2-theta.

In one embodiment the crystalline form is characterized by a powder X-ray diffraction pattern comprising powder X-ray diffraction peaks at about 7.2, 14.0, 18.3, 19.1, 20.7, 24.6 and 34.4 ± 0.2 degrees 2-theta.

The foregoing and other features and advantages of the disclosed technology will become more apparent from the following detailed description, which proceeds with reference to the accompanying drawings. Such description is meant to be illustrative, but not limiting, of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 PXRD diffractograms of: (T= zoledronic:DL-lysine complex, S= zoledronic:DL-lysine complex,), (G = DL-lysine), (Z1 = Zoledronic acid monohydrate), and (Z3 = Zoledronic acid trihydrate).

FIG. 2 PXRD diffractograms of: (T= zoledronic:DL-lysine complex scaled up, T= zoledronic:DL-lysine complex, (G = DL-lysine), (Z1 = Zoledronic acid monohydrate), and (Z3 = Zoledronic acid trihydrate).

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

In general, active pharmaceutical ingredients (APIs) in the pharmaceutical compositions can be prepared in a variety of different forms including prodrugs, amorphous forms, solvates, hydrates, cocrystals, salts and polymorphs. The discovery of novel API forms may provide an opportunity to improve the performance characteristics of a pharmaceutical product. Additionally, discovery

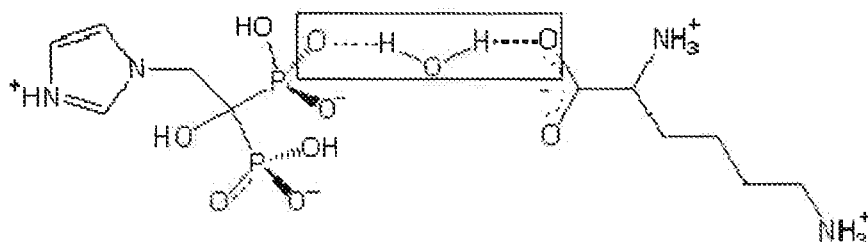
of novel drug forms expands the array of resources available for designing pharmaceutical dosage forms with targeted release profiles or other desired characteristics.

A specific characteristic that can be targeted includes the novel crystal form of an API and its subsequent new physicochemical properties. The alteration of the crystal form of a given API could result in the modification of the physical properties of the target molecule. For example, various polymorphs of a given API exhibit different aqueous solubility where the thermodynamically stable polymorph would exhibit a lower solubility than the meta-stable polymorph. In addition, pharmaceutical polymorphs can also differ in properties such as rate of dissolution, shelf life, bioavailability, morphology, vapor pressure, density, color, and compressibility. Accordingly, it is desirable to enhance the properties of an API by forming molecular complexes such as a cocrystal, salt, solvate or hydrate with respect to aqueous solubility, rate of dissolution, bioavailability, C_{max}, T_{max}, physicochemical stability, downstream processibility (e.g. flowability compressibility, degree of brittleness, particle size manipulation), decrease in polymorphic form diversity, toxicity, taste, production costs, and manufacturing methods.

In the development of orally delivered drugs, it is often advantageous to have novel crystal forms of such drugs that possess improved properties, including increased aqueous solubility and stability. In many cases, the dissolution rate increase of drugs is desired as it would potentially increase their bioavailability. This also applies to the development of novel forms of zoledronic acid which, when administered orally to a subject, could achieve a greater or similar bioavailability and PK profile when compared to an IV or other formulations on a dose-for-dose basis.

Cocrystals, salts, solvates and hydrates of zoledronic acid of the present invention could give rise to improved properties of zoledronic acid. For example, a new form of zoledronic acid is particularly advantageous if it can improve the bioavailability of orally delivered zoledronic acid. Of particular interest are molecular complexes the zoledronic acid and the standard amino acids such as lysine. A schematic diagram for zoledronic acid:lysine complex is shown below. The diagram shows a molecular structure of the complex and possible interactions between the constituents of the complex which is different from the physical mix of the constituents.

Zoledronic acid: lysine complex



These represent one of the arrangements that molecules of the drug and the standard amino acids cofomers could interact to form a stable complex that even when stressed thermally at elevated relative humidity (RH) environment have not displayed any signs of deterioration or disintegration to its original constituents. Such stability can be attributed to the hydrogen bonding (dashed line in the box) in these molecular complexes. When packing in a crystal structure these complexes have very different morphologies to that of its constituents or their physical mix as indicated by their powder X-ray diffraction (PXRD) patterns and therefore would possess different, unpredictable physicochemical properties.

The present invention provides a new crystal form of zoledronic acid in the form of a zoledronic DL-lysine complex (Form S), characterized by an PXRD pattern having strong peaks at about 7.2, 14.0, 18.3, 19.1, 20.7, 24.6 and 34.4 ± 0.2 degrees two-theta.

The present invention provides a new crystal form of zoledronic acid in the form a zoledronic acid DL-lysine complex (Form T), characterized by a PXRD pattern having strong peaks at about $T = 6.6, 11.0, 14.2, 18.3, 19.7, 22.7, 27.6 \pm 0.2$ degrees two-theta.

Accordingly, in a first aspect, the present invention includes complexes of zoledronic acid DL-lysine, which are capable of complexing in the solid-state, for example, through dry or solvent-drop grinding (liquid assisted grinding), heating or solvent evaporation of their solution in single or mixed solvent systems, slurry suspension, supercritical fluids or other techniques known to a person skilled in the art.

Another aspect of the invention provides novel complexes of zoledronic acid and DL-lysine that have been observed by their PXRD patterns which are different from all the previous molecular complexes prepared.

Another aspect of the invention provides complexes of zoledronic acid and DL-lysine, suitable for a pharmaceutical formulation than can be delivered orally to the human body. The pharmaceutical formulation contains a therapeutically effective amount of at least one of the novel molecular complexes of zoledronic acid according to the invention and at least one pharmaceutically acceptable carrier, (also known in the art as a pharmaceutically acceptable excipient). The novel molecular complexes of zoledronic acid are therapeutically useful for the treatment and/or prevention of disease states associated with osteoporosis, hypercalcemia (TIH), cancer induced bone metastasis, Paget's disease or adjuvant or neoadjuvant therapies discussed above.

The invention also relates to methods of treatment using novel molecular complexes of zoledronic acid of the invention or a pharmaceutical formulation containing them. A pharmaceutical formulation of the invention may be in any pharmaceutical form which contains a novel molecular complex of zoledronic acid according to the invention. The pharmaceutical formulation may be, for example, a tablet, capsule, liquid suspension, injectable, suppository, topical, or transdermal. The pharmaceutical formulations generally contain about 1% to about 99% by weight of at least one novel molecular complex of zoledronic acid of the invention and 99% to 1% by weight of a suitable pharmaceutical excipient.

Another aspect of the invention provides the addition of excess cocrystal formers to the zoledronic acid complexes.

Another aspect of the invention provides a method where the excess cocrystal formers consist of standard amino acids.

The techniques and approaches set forth in the present disclosure can further be used by the person of ordinary skill in the art to prepare variants thereof, said variants are considered to be part of the inventive disclosure.

EXAMPLES

The following examples illustrate the invention without intending to limit the scope of the invention.

Zoledronic acid as a starting material used in all experiments in this disclosure was supplied by Farmkemi Limited (Wuhan Pharma Chemical Co.), China with purity of ca. 98% and was purified further via recrystallization from water. All other pure chemicals (Analytical Grade) were supplied by Sigma-Aldrich and Fisher and used without further purification.

Solid phase characterization

Analytical techniques used to observe the crystalline forms include PXRD. The particular methodology used in such analytical techniques should be viewed as illustrative, and not limiting in the context of data collection. For example, the particular instrumentation used to collect data may vary; routine operator error or calibration standards may vary; sample preparation method may vary.

Powder X-Ray Diffraction (PXRD): All zoledronic acid molecular complex products were observed by a D-8 Bruker X-ray Powder Diffractometer using Cu K α ($\lambda = 1.540562 \text{ \AA}$), 40kV, 40mA. The data were collected over an angular range of 3° to 45° 2 Θ in continuous scan mode at room temperature using a step size of 0.03 and 0.05° 2 Θ and a scan speed of 6.17 7min.

Example 1: Preparation of zoledronic acid (ZA) DL-Lysine complex form S methods

- A. Approximately 20-30 mg of Zoledronic acid (ZA) DL-lysine water molecular complex prepared as in previous applications; Example 12 in PCT US1123427 and in Example 13 in US 12847568 was dissolved in acetic acid (0.6 mL) at 90 °C in a 7-mL glass vial. The hot solution was polish-filtered through a syringe filter to a clean pre-heated vial. Anti-solvent was added until the solution turned turbid. The resulting hot solution was stored in a refrigerator (4 °C) for 15 hours to achieve a rapid cooling and induce particle formation. The particulate material was isolated by filtration and dried at ambient temperature under vacuum (30 in Hg) for 15 hours. This novel form can be obtained using a variety of anti-solvents such as dioxane, N-methylpyrrolidone (NMP), dimethylformamide (DMF) and dimethylacetamide (DMA).
- B. Approximately 20-30 mg of ZA:DL-Lysine water complex prepared as in previous applications; Example 12 in PCT US1 123427 and in Example 13 in US 12847568 was dissolved in acetic acid (0.6 mL) at 90 °C in a 7-mL glass vial. The hot solution was polish-filtered through a syringe filter to a clean pre-heated vial. Anti-solvent was added

until the solution turned turbid. The resulting hot solution was stirred with a magnetic stir bar and cooled to room temperature at 20 °C/h. The mixture was stirred at room temperature for approximately 15 hours and solid precipitates were isolated by filtration and were dried at ambient temperature under vacuum (30 in Hg) for 15 hours. The PXRD patterns of the solids were consistent with the patterns obtained from method A. This novel form can be also obtained using dimethylsulfoxide (DMSO), DMF and DMA as anti-solvents.

- C. Approximately 26 mg of ZA:DL Lysine water complex prepared as in previous applications; Example 12 in PCT US1 123427 and in Example 13 in US 12847568 was partially dissolved in acetic acid (10 mL) at 70 °C in a 20-mL glass vial. The hot mixture was polish-filtered through a syringe filter to a clean pre-heated vial. Diethoxymethane (10 mL) was added as an anti-solvent to give a turbid solution. The resulting hot solution was stirred for 15 hours with a magnetic stir bar and cooled to room temperature at 20 °C/h to induce particle formation. The solid precipitates were isolated by filtration and dried at ambient temperature under vacuum (30 in Hg) for 15 hours and its PXRD pattern of the solids was consistent with the patterns obtained from methods A and B.

Example 2: Preparation of zoledronic acid DL-Lysine complex form T methods

- A. Approximately 20-30 mg of ZA:DL-Lysine water complex prepared as in previous applications; Example 12 in PCT US1 123427 and in Example 13 in US 12847568 was dissolved in acetic acid (0.6 mL) at 90 °C in a 7-mL glass vial. The hot solution was polish-filtered through a syringe filter to a clean pre-heated vial. Anti-solvent was added until the solution turned turbid. The resulting hot solution was stored in a refrigerator (4 °C) for to 15 hours to achieve a rapid cooling and induce further particle formation. The solid particulate material were isolated by filtration and dried at ambient temperature under vacuum (30 in Hg) for 15 hours. The PXRD pattern was different from that generated by example 1. This novel form can be obtained using a variety of anti-solvents such as Toluene, butylacetate (BuOAc) and MIBK.
- B. Approximately 20-30 mg of ZA:DL-Lysine water complex prepared as in previous applications; Example 12 in PCT US1 123427 and in Example 13 in US 12847568 was

dissolved in acetic acid (0.6 mL) at 90 °C in a 7-mL glass vial. The hot solution was polish-filtered through a syringe filter to a clean pre-heated vial. Anti-solvent was added until the solution turned turbid. The resulting slurry was stirred with a magnetic stirrer bar for 15 hours and cooled to room temperature at 20 °C/h to affect precipitation. The precipitates were isolated by filtration and dried at ambient temperature under vacuum (30 in Hg) for 15 hours and PXRD patterns of the solids were consistent with that obtained from method A. This novel form can also be obtained using a variety of anti-solvents such as Toluene, BuOAc and NMP.

- C. Approximately 20-30 mg of ZA:DL-Lysine water complex prepared as in previous applications; Example 12 in PCT US1 123427 and in Example 13 in US 12847568 was partially dissolved in acetic acid (10 mL) at 70 °C in a 20-mL glass vial. The hot solution was polish-filtered through a syringe filter to a clean pre-heated vial. Anti-solvent was added until the solution became turbid. The resulting solution was stored in a refrigerator (4 °C) for 15 hours to achieve a rapid cooling and induce particle formation. The solid precipitates were isolated by filtration and were dried at ambient temperature under vacuum (30 in Hg) for 15 hours. The PXRD patterns of the solids were consistent with that obtained from methods A and B. This novel form can also be obtained using a variety of anti-solvents such as ethanol, ethylacetate (EtOAc), isopropanol (IPA), isopropylacetate (IPAc), and diethoxymethane (DEM).
- D. Approximately 20-30 mg of ZA:DL-Lysine water complex prepared as in previous applications; Example 12 in PCT US1 123427 and in Example 13 in US 12847568 was partially dissolved in acetic acid (10 mL) at 70 °C in a 20-mL glass vial. The hot solution was polish-filtered through a syringe filter to a clean pre-heated vial. Anti-solvent heptane was added until the solution turned turbid. The resulting hot slurry was stirred with a magnetic stir bar for 15 hours and cooled to room temperature at 20 °C/h to enhance particle formation. The particulate material was then isolated by filtration and dried at ambient temperature under vacuum (30 in Hg) for 15 hours. The PXRD pattern was consistent with that obtained from methods A, B and C.
- E. 31.7 mg of ZA:DL-Lysine water complex prepared as in previous applications; Example 12 in PCT US1 123427 and in Example 13 in US 12847568 was dissolved in acetic acid (0.6 mL) at 90 °C and stirred with a magnetic stir bar. After 30 minutes of stirring the

solution turned turbid and a precipitate was observed. The solids were isolated by filtration upon cooling to room temperature at 20 °C/h. PXRD pattern of the material was consistent with that obtained from methods A, B, C and D.

- F. Approximately 100 mg of ZA:DL-Lysine water complex prepared as in previous applications; Example 12 in PCT US1 123427 and in Example 13 in US 12847568 was slurried in acetic acid (20 mL) at 70 °C and stirred for 30 minutes. The mixture was cooled to room temperature under ambient conditions and filtered to isolate particulate material. PXRD pattern of the isolated particles was consistent with that obtained from methods A, B, C, D and E.

Example 3. Scale up of zoledronic acid DL-lysine complex form T using method B of Example 2.

Approximately 15 mL of acetic acid was added to 500mg of ZA:DL-Lysine water complex prepared as in previous applications; Example 12 in PCT US1123427 and in Example 13 in US 12847568 to make a slurry. The slurry was heated while stirring until most of the solids were dissolved. The solution was filtered to remove the remaining solids. 2mL of toluene was then added to the filtrate while stirring. The resulting suspension was heated and an additional 8mL of acetic acid was added. After ca. 5 minutes the suspension was removed from heat and left to stir for 18 hours allowing the suspension to cool to room temperature. The particulate material was isolated and left under vacuum (22 in Hg) for 48hrs. T was isolated in ca. 81% yield. The PXRD, of this product, the top profile in Fig.2, shows a similar pattern to that obtained from Example 2 experiments.

This experiment demonstrates the ability to reproduce as well as scale up the process of generating the novel form T 20-fold. The variations on scale or method of preparation would be obvious to the person with ordinary skill in the art.

Example 4. Conversion of Form T to Form S.

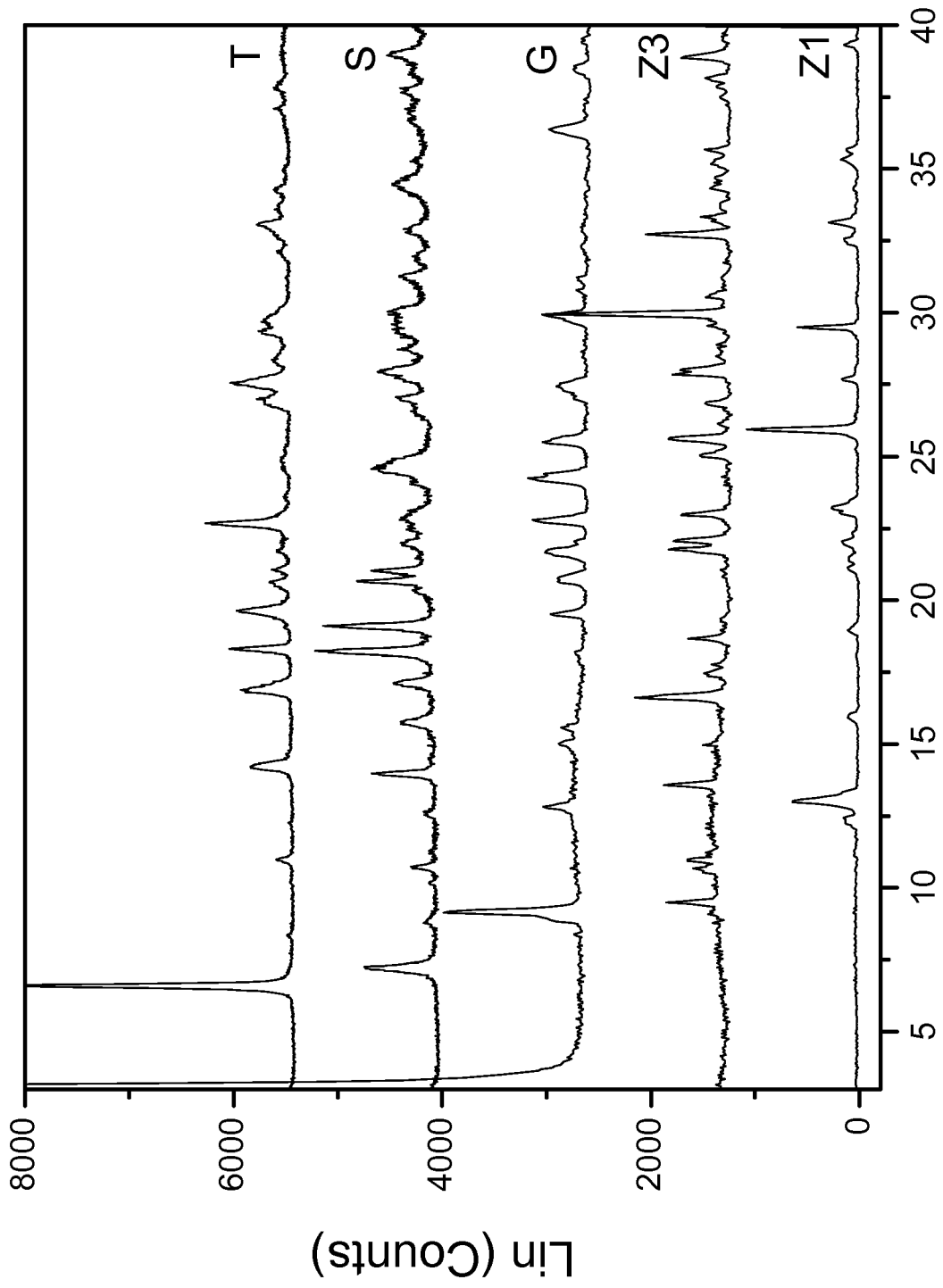
A sample of Form T was stored in closed screw cap vials under ambient conditions in the cupboard for approximately 11 months. The sample was tested after 11 months via powder X-ray diffraction (PXRD) and found to have converted from Form (T) to Form (S).

We Claim:

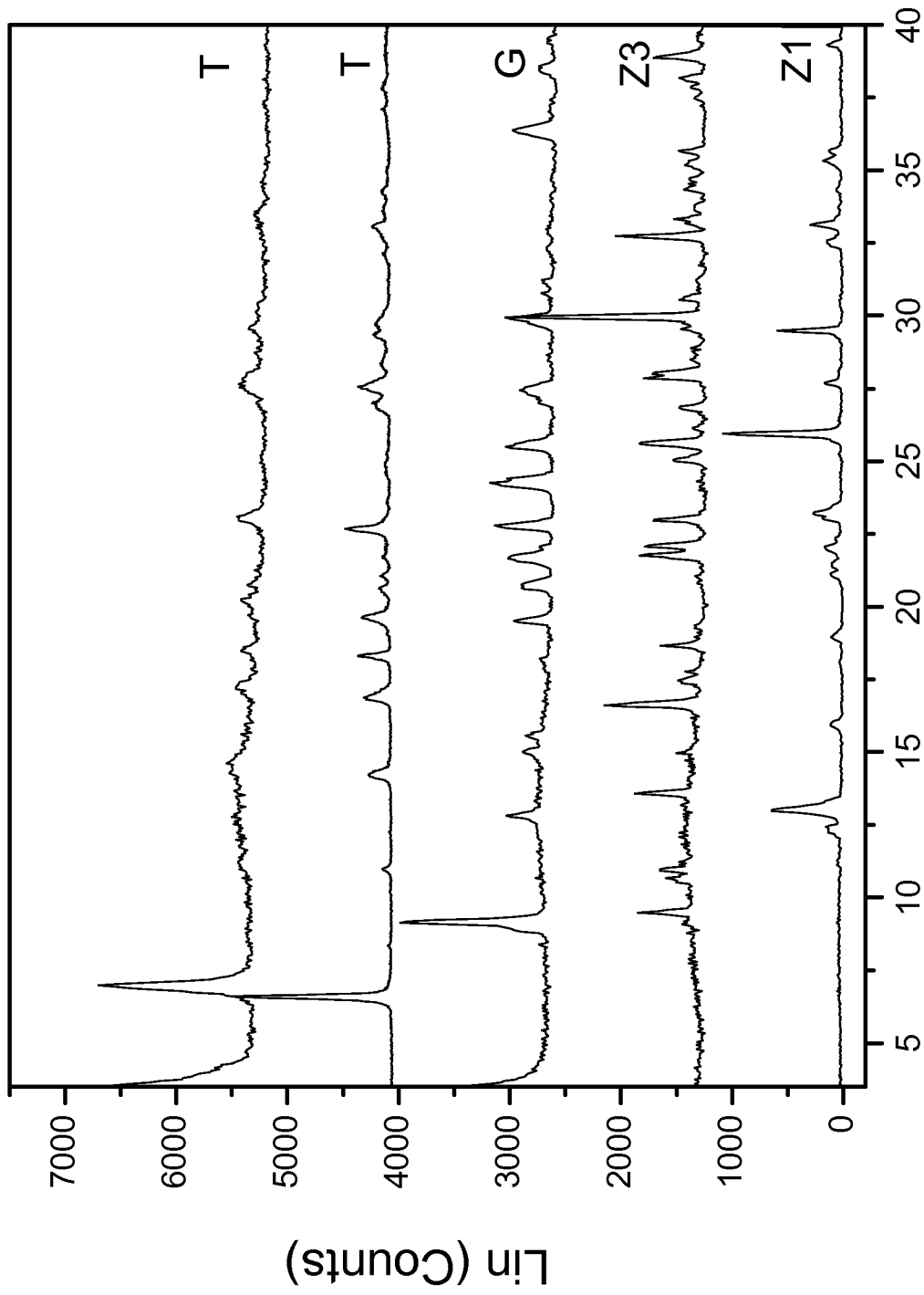
1. A crystalline form of zoledronic acid: DL-lysine.
2. The crystalline form of claim 1, wherein said crystalline form is characterized by a powder X-ray diffraction pattern comprising powder X-ray diffraction peaks at about 6.6, 11.0, 14.2, 18.3, 19.7, 22.7 and 27.6 \pm 0.2 degrees 2-theta.
3. The crystalline form of claim 1, wherein said crystalline form is characterized by a powder X-ray diffraction pattern comprising powder X-ray diffraction peaks at about 7.2, 14.0, 18.3, 19.1, 20.7, 24.6 and 34.4 \pm 0.2 degrees 2-theta.
4. A composition comprising the crystalline form of any one of claims 1-3.
5. A pharmaceutical composition comprising the crystalline form of any one of claims 1-3 and at least one pharmaceutically acceptable carrier.
6. The pharmaceutical composition of claim 5 wherein the pharmaceutical composition is a solid oral composition.
7. The pharmaceutical composition of claim 6, wherein the solid oral composition is a tablet or capsule.
8. The pharmaceutical composition of claim 5, wherein the pharmaceutical composition is a unit dose.
9. A method of treating or preventing a disease for which zoledronic acid is indicated, said method comprising the step of administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition of any one of claims 5-8.
10. The method of claim 10, wherein said disease is selected from the group consisting of osteoporosis, hypercalcemia, cancer induced bone metastasis, Paget' s disease, adjuvant cancer therapy and neoadjuvant cancer therapy.
11. The method of claim 11, wherein said hypercalcemia is tumor induced hypercalcemia (TIH).
12. The method of claim 11, wherein said disease is cancer induced bone metastasis.
13. A method of making the crystalline form of any one of claims 1-3, comprising the steps of: combining zoledronic acid, DL-lysine and acetic acid; forming zoledronic acid:DL-

lysine crystals; and purifying said zoledronic acid:DL-lysine crystals from said acetic acid.

14. The method of claim 15, wherein said method comprises the step of contacting said zoledronic acid, DL-lysine and acetic acid with an antisolvent.
15. The method of claim 16, wherein said antisolvent is selected from the group consisting of ethanol, ethylacetate (EtOAc), isopropanol (IPA), isopropylacetate (IPAc), diethoxymethane (DEM), Toluene, BuOAc, N-methylpyrrolidone (NMP) and a heptane.
16. The method of claim 16, wherein said antisolvent is selected from the group consisting of dimethylsulfoxide (DMSO), dioxane, NMP, dimethylformamide (DMF), dimethylacetamide (DMA), and DEM.



2 - Theta - Scale
FIG. 1



2 - Theta - Scale
FIG. 2