SOLID AND CRYSTALLINE IBANDRONIC ACID

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Appl. No.: 12/288,025
Filed: Oct. 15, 2008

Related U.S. Application Data
Division of application No. 11/525,804, filed on Sep. 22, 2006, which is a continuation of application No. 11/311,995, filed on Jan. 12, 2006, now abandoned, which is a continuation of application No. 11/165,481, filed on Jun. 22, 2005, now abandoned.

Publication Classification
Int. Cl.
C07F 9/28 (2006.01)

U.S. Cl. .................................................. 564/15

Abstract
Provided are novel crystalline forms of ibandronic acid, physical data, methods for their preparation, and uses therefor. Also provided are methods for purifying and assaying ibandronic acid in any crystalline form.
FIG. 4

X-Ray powder diffraction of form S1 of bandronic acid
FIG. 6

X-Ray powder diffractogram of form S3 ibandronic acid

Deg.

2.0 4.0 6.0 8.0 10.0 12.0 14.0 16.0 18.0 20.0 22.0 24.0 26.0 28.0 30.0 32.0 34.0 36.0 38.0

CPS

4700 4900 5100 5300 5500 5700 5900 6100 6300 6500 6700 6900 7100 7300 7500 7700 7900 8100 8300 8500 8700 8900 9100 9300 9500 9700 9900
FIG. 9

X-Ray powder diffractogram of form S6 ibandronic acid

CPS

2.0 4.0 6.0 8.0 10.0 12.0 14.0 16.0 18.0 20.0 22.0 24.0 26.0 28.0 30.0 32.0 34.0 36.0 38.0

Deg.
FIG. 11

X-Ray powder diffractogram of form S8 ibandronic acid
SOLID AND CRYSTALLINE IBANDRONIC ACID

RELATED APPLICATIONS


BACKGROUND OF THE INVENTION

[0002] Ibandronate Sodium is a third-generation nitrogen-containing bisphosphonate characterized by an aliphatic tertiary amine side chain.

[0003] Ibandronate Sodium is a white crystalline powder. The free acid has MW 319.23 (CAS No.: 114084-78-5). The monosodium salt (anhydrous) of the acid has MW 341.23 (CAS No.: 138844-81-2). The monosodium salt monohydrate has MW 359.23 (CAS No.: 138926-19-9).

[0004] The preparation of ibandronic acid monosodium salt is described in, for example, U.S. Pat. No. 4,927,814. The '814 patent describes the following schemes:

\[
\text{MPA} \quad \xrightarrow{1) \text{H}_3\text{PO}_4 \text{ or } \text{H}_2\text{PO}_4, \text{PCl}_3 \text{ or } \text{POCl}_3, \text{PhCl, 100°C.}} \quad \xrightarrow{2) 6\text{N HCl}} \quad \text{IBD-Ac} \quad \xrightarrow{\text{NaOH}} \quad \text{IBD} \quad \text{IBD-D}
\]

\[
\text{COC} \quad \xrightarrow{\text{Pr(OR)}_3} \quad \text{N} \quad \xrightarrow{\text{OR}} \quad \text{N} \quad \xrightarrow{\text{OR}} \quad \text{OR} \quad \xrightarrow{\text{OR}} \quad \text{OR}
\]

\[
\text{HO} \quad \xrightarrow{\text{POH}} \quad \text{O} \quad \xrightarrow{\text{ONa}^+} \quad \text{OH} \quad \xrightarrow{\text{H}_2\text{O/Acetone}} \quad \text{IBD} \
\]

\[
\text{HO} \quad \xrightarrow{\text{O}} \quad \text{OH} \quad \xrightarrow{\text{H}_2\text{O}} \quad \text{IBD} \
\]

\[
\text{HO} \quad \xrightarrow{\text{OR}} \quad \text{OH} \quad \xrightarrow{\text{OR}} \quad \text{OR} \quad \xrightarrow{\text{OR}} \quad \text{OR}
\]
The preparation of ibandronic acid is taught in U.S. Pat. No. 4,927,814, wherein an ion-exchange chromatography is used in work-up. The present inventors repeated the procedure described in the '814 patent. No solid material was obtained, but an oily precipitate was the crude product. The skilled artisan knows that solids are easier to manipulate than oils. Clearly there is a need for a method of making a solid ibandronic acid.

The monosodium salt of ibandronic acid is marketed under the trade name Boniva®. Boniva® was developed by Hoffmann-La Roche for the treatment of bone disorders such as: hypercalcemia of malignancy, osteolysis, Paget's disease, osteoporosis and metastatic bone disease. Boniva® is also marketed in Europe under the name Bondronat for cancer-related bone complications. Bondronat is available in ampoule with 1 ml concentrate for solution for infusion contains 1.125 mg of Ibandronic acid monosodium salt monohydrate, corresponding to 1 mg of ibandronic acid.

Ibandronic acid can be used as an intermediate in the process for the preparation of Bondronate sodium.

The discovery of new polymorphic forms of a pharmaceutically useful compound provides a new opportunity to improve the performance characteristics of a pharmaceutical product. It enlarges the repertoire of materials that a formulation scientist has available for designing, for example, a pharmaceutical dosage form of a drug with a targeted release profile or other desired characteristic. There is a need in the art for polymorphic forms of ibandronic acid.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides amorphous ibandronic acid.

In another aspect, the present invention provides a method of preparing amorphous ibandronic acid that includes the step of isolating amorphous ibandronic acid from an aqueous solution of ibandronic acid which isolating step is selected from a vacuum evaporation step or a lyophilization step.

In still a further aspect, the present invention relates to a method of making amorphous ibandronic comprising the step of spray drying an aqueous solution of ibandronic acid.

In yet another aspect, the present invention provides solid ibandronic acid.

In one aspect, the present invention provides a process for preparing solid ibandronic acid comprising the steps of:

- combining, at a temperature of about 72°C to about 78°C, a halophosphorous compound and phosphorous acid with N-methyl-N-pentyl propionic acid hydrochloride in a diluent to obtain a reaction mixture;
- maintaining the reaction mixture, while heating to a temperature of about 80°C to about 100°C;
- further combining the reaction mixture with water, whereby two phases, one aqueous and one non-aqueous, are obtained;
- separating the two phases obtained;
- maintaining the aqueous phase at a temperature of about 95°C to about 100°C;
- evaporating the aqueous phase to obtain a residue;
- combining an alcohol with the residue to obtain whereby a suspension is obtained; and
- recovering solid ibandronic acid from the suspension, for example by filtration or centrifugation; and optionally, drying the recovered solid ibandronic acid.

The residue of step f) may be dissolved in water prior to the addition of the alcohol in step g). After the addition of the alcohol, the reaction mixture may be heated in order to facilitate the formation of the precipitate.

In another aspect, the present invention provides crystalline ibandronic acid in several crystalline forms and hydrates and solvates, especially alcoholates, thereof. The present invention also provides ibandronic acid alcoholates.

In yet another aspect, the present invention provides a solid crystalline form of ibandronic acid, denominated form S1, characterized by a powder X-ray diffraction pattern having reflections at about 8.2, 11.5, 11.9, 13.9, 18.6 and 22.2±0.2 deg. 2-theta. The present invention further provides processes for preparing ibandronic acid form S1.

In one aspect, the present invention provides a solid crystalline form of ibandronic acid, denominated form S2, characterized by a powder X-ray diffraction pattern having reflections at about 8.1, 14.2, 16.1, 18.2 and 24.4±0.2 deg. 2-theta. The present invention further provides a process for preparing ibandronic acid form S2.

In another aspect, the present invention provides a solid crystalline form of ibandronic acid, denominated form S3, characterized by a powder X-ray diffraction pattern having reflections at about 4.4, 8.6, 11.2, 17.3, 20.8, 22.5 and 26.0±0.2 deg. 2-theta. The present invention further provides a process for preparing ibandronic acid form S3.

In yet another aspect, the present invention provides a solid crystalline form of ibandronic acid, denominated form S4, characterized by a powder X-ray diffraction pattern having reflections at about 4.4, 8.6, 11.2, 17.3, 20.8, 22.5 and 26.0±0.2 deg. 2-theta. The present invention further provides a process for preparing ibandronic acid form S4.

In one aspect, the present invention provides a solid crystalline form of ibandronic acid, denominated form S5, characterized by a powder X-ray diffraction pattern having reflections at about 4.5, 8.9, 12.0, 16.0, 16.3, 21.4, 22.1 and 26.9±0.2 deg. 2-theta. The present invention further provides processes for preparing ibandronic acid form S5.

In another aspect, the present invention provides a solid crystalline form of ibandronic acid, denominated form S6, characterized by a powder X-ray diffraction pattern hav-
ing reflections at about 5.7, 11.7, 14.3, 18.5, 21.2 and 21.7±0.2 deg. 2-theta. The present invention further provides processes for preparing ibandronic acid form S6.

In yet another aspect, the present invention provides a solid crystalline form of ibandronic acid, denominated form S7, characterized by a powder X-ray diffraction pattern having reflections at about 4.6, 11.5, 16.3, 16.8, 21.0 and 22.8±0.2 deg. 2-theta. The present invention further provides processes for preparing ibandronic acid form S7.

In one aspect, the present invention provides a solid crystalline form of ibandronic acid, denominated form S8, characterized by a powder X-ray diffraction pattern having reflections at about 4.5, 6.0, 11.9, 12.3, 16.2, 17.8 and 21.7±0.2 deg. 2-theta. The present invention further provides processes for preparing ibandronic acid form S8.

In another aspect, the present invention provides a solid crystalline form of ibandronic acid, denominated form S10, characterized by a powder X-ray diffraction pattern having reflections at about 4.8, 6.1, 12.0, 12.3, 16.4, 18.0 and 21.7±0.2 deg. 2-theta. The present invention further provides processes for preparing ibandronic acid form S10.

In yet another aspect, the present invention provides a solid crystalline form of ibandronic acid, denominated form S12, characterized by a powder X-ray diffraction pattern having reflections at about 4.7, 9.0, 11.6, 20.9, 21.1, 21.7, 22.9 and 26.3±0.2 deg. 2-theta. The present invention further provides a process for preparing ibandronic acid form S5.

In one aspect, the present invention provides a solid crystalline form of ibandronic acid, denominated form S13, characterized by a powder X-ray diffraction pattern having reflections at about 4.5, 8.9, 12.0, 16.0, 16.3, 21.3 and 22.1±0.2 deg. 2-theta. The present invention further provides processes for preparing ibandronic acid form S13.

In another aspect, the present invention provides a process for purifying ibandronic acid from inorganic impurities by crystallization from an organic solvent selected from the group consisting of C₂₋₄ alcohols and acetone.

In yet another aspect, the present invention provides a HPLC method of assaying ibandronic acid comprising the steps of: providing a sample solution of a sample of ibandronic acid in a diluent, loading the solution (ca. 50 μL) onto a 250×4.1 mm, Hamilton type PRP-X100 union exchange column, eluting the sample from the column at 2.0 mL/min. with an eluent including nitric acid (HNO₃; 35 vol.%), potassium nitrate (KNO₃; 45 vol.-%) and ethanol (20 vol.-%), and measuring the ibandronic acid content of the eluent at 240 nm wavelength with a UV detector to identify the relevant fractions.

In still a further aspect, the present invention provides a process for purifying ibandronic acid from inorganic impurities comprising the steps of: providing a solution of ibandronic acid containing inorganic impurities in water or methanol; and b) combining the solution with a C₂₋₄ alcohol, especially wherein the C₂₋₄ alcohol is selected from the group consisting of ethanol, 1-propanol, isopropanol (IPA) and tert-butanol whereby ibandronic acid precipitates.

**BRIEF DESCRIPTION OF THE FIGURES**

**0038** FIG. 1 illustrates an x-ray diffraction diagram of amorphous ibandronic acid.

**0036** FIG. 2 illustrates a DSC thermogram of amorphous ibandronic acid.

**0039** FIG. 3 illustrates a TGA thermogram of ibandronic acid.

**0040** FIG. 4 illustrates an x-ray diffraction diagram of ibandronic acid form S1.

**0041** FIG. 5 illustrates an x-ray diffraction diagram of ibandronic acid form S2.

**0042** FIG. 6 illustrates an x-ray diffraction diagram of ibandronic acid form S3.

**0043** FIG. 7 illustrates an x-ray diffraction diagram of ibandronic acid form S4.

**0044** FIG. 8 illustrates an x-ray diffraction diagram of ibandronic acid form S5.

**0045** FIG. 9 illustrates an x-ray diffraction diagram of ibandronic acid form S6.

**0046** FIG. 10 illustrates an x-ray diffraction diagram of ibandronic acid form S7.

**0047** FIG. 11 illustrates an x-ray diffraction diagram of ibandronic acid form S8.

**0048** FIG. 12 illustrates an x-ray diffraction diagram of ibandronic acid form S10.

**0049** FIG. 13 illustrates an x-ray diffraction diagram of ibandronic acid form S12.

**0050** FIG. 14 illustrates an x-ray diffraction diagram of ibandronic acid form S13.

**DETAILED DESCRIPTION OF THE INVENTION**

**0052** The present invention provides processes which utilize halo-phosphorous compounds. Such compounds include, but are not limited to, phosphorous trichloride, phosphorous oxychloride, phosphorous pentachloride, phosphorous tribromide, phosphorous oxybromide, phosphorous pentabromide.

**0053** In particular embodiments of the present invention, C₃₋₄ alcohols are used. The C₃₋₄ alcohols have the general structure ROH wherein R is a linear or branched alkyl group having 2 to 4 carbon atoms. Ethanol, 1-propanol (1-propanol), isopropanol (2-propanol, IPA), and tert-butanol (2-methylpropan-2-ol) are preferred C₃₋₄ alcohols.

**0054** The present invention also provides processes that, in particular embodiments, utilize strong acids which do not act as oxidants for amino-phosphonic acids. Such non-oxidizing acids include, but are not limited to, para-toluene sulfonic acid, HCl, HBr, and trichloroacetic acid.

**0055** The present invention provides amorphous ibandronic acid. Amorphous ibandronic acid has an x-ray diffraction diagram not unexpected for an essentially amorphous solid. FIG. 1 shows a representative x-ray diffraction diagram of amorphous ibandronic acid.

**0056** FIG. 2 shows a representative thermogram from differential scanning calorimetry (DSC) for amorphous ibandronic acid. The DSC thermogram does not exhibit any feature that can be clearly associated with a first-order transition like crystal melting.

**0057** FIG. 3 shows a representative thermogram from thermogravimetric analysis (TGA).

**0058** Amorphous ibandronic acid can be prepared by a method that includes an isolation step. An isolation step is a step (procedure) in which a solvent, for example water is removed from a solution of ibandronic acid and can be called a “water-removal” step. This step comprises isolation of amorphous ibandronic acid from a solution of ibandronic acid in a solvent selected from the group consisting of acetonitrile (ACN), dimethylsulfoxide (DMSO), methanol, and water. Preferably, the solvent is water. The isolation step can be a vacuum evaporation (i.e. concentration) step, a lyophilization step, or a spray drying step.
The term “spray drying” broadly refers to processes involving breaking up liquid mixtures into small droplets (atomization) and rapidly removing solvent from the mixture. In a typical spray drying apparatus, there is a strong driving force for evaporation of solvent from the droplets, which may be provided by providing a drying gas. Spray drying processes and equipment are described in Perry’s Chemical Engineer’s Handbook, pgs. 20-54 to 20-57 (Sixth Edition 1984).

By way of non-limiting example only, the typical spray drying apparatus comprises a drying chamber, atomizing means for atomizing a solvent-containing feed into the drying chamber, a source of drying gas that flows into the drying chamber to remove solvent from the atomized-solvent-containing feed, an outlet for the products of drying, and product collection means located downstream of the drying chamber. Examples of such apparatuses include Niro Models PSD-1, PSD-2 and PSD-4 (Niro A/S, Soeborg, Denmark). Typically, the product collection means includes a cyclone connected to the drying apparatus. In the cyclone, the particles produced during spray drying are separated from the drying gas and evaporated solvent, allowing the particles to be collected. A filter may also be used to separate and collect the particles produced by spray drying. The process of the invention is not limited to the use of such drying apparatuses as described above.

Spray drying may be performed in a conventional manner in the processes of the present invention (see, e.g., Remington: The Science and Practice of Pharmacy, 19th Ed., vol. 1, pg. 1627, herein incorporated by reference). The drying gas used in the invention may be any suitable gas, although inert gases such as nitrogen, oxygen-enriched air, and argon are preferred. Nitrogen gas is a particularly preferred drying gas for use in the process of the invention. The amorphous ibandronic acid product produced by spray drying may be recovered by techniques commonly used in the art, such as using a cyclone or a filter. Spray drying of ibandronic acid from a solution of ibandronic acid in water results in amorphous ibandronic acid.

The present invention also provides solid ibandronic acid. When intermediate compounds are Solid substances rather than liquid, it enables the possibility of isolating and purifying the intermediate by crystallization thereby improving the quality of the final product.

The present invention also provides solid ibandronic acid.

Solid ibandronic acid can be prepared by a process that includes the steps of:

1. Combining, at a temperature of about 70°C, to about 78°C, a halo-phosphorous compound and phosphorous acid with N-methyl-N-pentyl propionic acid hydrochloride in a diluent;
2. Maintaining the reaction mixture, while heating to approximately 80°C, to about 100°C;
3. Combining the reaction mixture with water, whereby two phases are obtained;
4. Separating the two phases obtained;
5. Maintaining the aqueous phase at a temperature of about 95°C, to about 110°C;
6. Evaporating the aqueous phase to obtain a residue;
7. Combining a C₈₋₄ alcohol or acetone with the reaction mixture to obtain a precipitate; and
8. Recovering the precipitate of solid ibandronic acid.

Preferably, the halo-phosphorous compound of step a) is added in small aliquots, especially dropwise. Preferably, the diluent in step b) is selected from the group consisting of silicone oil, toluene and a mixture of toluene and phosphoric acid. Preferably, the temperature in step b) is about 75°C.

Preferably, the mixture in step b) is heated to a temperature of about 80°C. Preferably, the C₈₋₄ alcohol in step g) is selected from the group consisting of ethanol, 1-propanol, isopropyl alcohol (IPA) and tert-butanol. Most preferably, the alcohol in step g) is ethanol or IPA. The residue of step f) can be combined with water prior to the addition of the alcohol in step g). After the addition of the C₈₋₄ alcohol, the reaction mixture is optionally heated in order to facilitate the formation of the precipitate.

The present invention further provides crystalline ibandronic acid, hydrates and solvates thereof. The present invention also provides ibandronic acid hydrates. As a general rule, crystalline forms possess the advantage of being readily filterable, easily dried, and stable for extended periods of time without the need for specialized storage conditions.

In another embodiment, the present invention provides a solid crystalline form of ibandronic acid, denominated form S₁, characterized by a powder X-ray diffraction pattern having reflections at about 8.0, 11.3, 13.5, 18.6 and 22.2±0.2 deg. 2-theta. Solid crystalline ibandronic acid form S₁ is further characterized by X-ray powder diffraction pattern having reflections at about 21.6, 23.8, 24.7 and 28.1±0.2 deg. 2-theta. A typical x-ray diffraction diagram for ibandronic acid form S₁ is given in FIG. 4. Form S₁ can be a hemihydrate.

Ibandronic acid form S₁ can be prepared by combining an organic solvent selected from the group consisting of tert-butanol, ethanol, and acetone, with an aqueous solution of ibandronic acid, and maintaining the resulting combination for up to about 24 hours to obtain a precipitate of ibandronic acid form S₁. Preferably, the organic solvent is selected from the group consisting of tert-butanol, ethanol and acetone.

Form S₁ can be also prepared by combining amorphous ibandronic acid and an organic solvent at a temperature that ranges from room temperature to reflux, and maintaining the reaction mixture for a sufficient time to obtain form S₁ in a slurry. Preferably, the organic solvent is selected from the group consisting of tert-butanol, ethanol and acetone.

Ibandronic acid form S₁ can also be prepared in a process that includes the steps of dissolving amorphous ibandronic acid in water, adding acetone to obtain a slurry, and stirring the slurry for a sufficient time to obtain form S₁.

Form S₁ can be also prepared by a process that includes the steps of:

1. Combining, at a temperature of about 70°C, to about 78°C, a halo-phosphorous compound and phosphorous acid with N-methyl-N-pentyl propionic acid hydrochloride in toluene;
2. Maintaining the reaction mixture, while heating to a temperature of about 80°C, to about 100°C;
3. Removing the toluene and adding water to the reaction mixture;
4. Evaporating to obtain a residue;
[0087] f) combining ethanol with the residue to obtain a precipitate; and

[0088] g) recovering crystalline ibandronic acid form S1.

[0089] Preferably, the halo-phosphorous compound of step a) is added in small aliquots, most preferably dropwise. Preferably, the temperature in step a) is about 75°C. Preferably, the reaction mixture in step b) is heated to a temperature of about 80°C.

[0090] In a further embodiment, the present invention further provides a solid crystalline form of ibandronic acid, denominated form S2, characterized by a powder X-ray diffraction pattern having reflections at about 8.1, 14.2, 16.1, 18.2 and 24.4±0.2 deg. 2-theta. Solid crystalline ibandronic acid form S2 can be further characterized by X-ray reflections at about 10.9, 19.2, 22.3, 23.3, and 28.2±0.2 deg. 2-theta. A typical x-ray diffraction diagram for ibandronic acid form S2 is given in FIG. 5.

[0091] Ibandronic acid form S2 can be prepared by providing a solution of amorphous ibandronic acid in methanol; adding acetonitrile solvent to the solution to obtain a slurry and recovering ibandronic acid form S2.

[0092] In a further embodiment, the present invention provides a solid crystalline form of ibandronic acid, denominated form S3, characterized by a powder X-ray diffraction pattern having reflections at about 4.4, 8.8, 11.3, 17.6 and 26.4±0.2 deg. 2-theta. Solid crystalline ibandronic acid form S3 can be further characterized by X-ray reflections at about 21.6, 23.8, 24.7 and 28.1±0.2 deg. 2-theta. A typical x-ray diffraction diagram for ibandronic acid form S3 is given in FIG. 6. Form S3 can exist as a tert-butanolate.

[0093] Ibandronic acid form S3 can be prepared by adding tert-butanol, to an aqueous solution of ibandronic acid, and maintaining the resulting mixture for at least about 24 hours or more to form S3.

[0094] In another embodiment, the present invention provides a solid crystalline form of ibandronic acid, denominated Form S4, characterized by a powder X-ray diffraction pattern having reflections at about 4.4, 8.6, 11.2, 17.3, 20.8, 22.5 and 26.0±0.2 deg. 2-theta. Solid crystalline ibandronic acid Form S4 can be further characterized by X-ray reflections at about 16.2, 20.5 and 21.3±0.2 deg. 2-theta. A typical x-ray diffraction diagram for ibandronic acid Form S4 is given in FIG. 7. Form S4 can be a propanolate.

[0095] Ibandronic acid Form S4 can be prepared by combining at room temperature an aqueous solution of ibandronic acid and 1-propanol until precipitation occurs, and isolating Form S4. Preferably the combination is stirred for at least about 3 hours. Optionally, the combination is heated to a reflux temperature, in order to obtain a stirrable mixture, which is then cooled to room temperature.

[0096] In yet another embodiment, the present invention provides a solid crystalline form of ibandronic acid, denominated Form S5, characterized by a powder X-ray diffraction pattern having reflections at about 4.5, 8.9, 12.0, 16.0, 16.3, 21.4, 22.1 and 26.9±0.2 deg. 2-theta. Solid crystalline ibandronic acid Form S1 can be further characterized by X-ray reflections at about 5.9, 10.5 and 17.8±0.2 deg. 2-theta. A typical x-ray diffraction diagram for ibandronic acid Form S5 is given in FIG. 8. Form S5 exists as a hemihydrate or an iso-propanolate (isopropyl alcohol solvate).

[0097] Ibandronic acid Form S5 can be prepared by a process that includes the steps of:

[0098] a) combining, at a temperature of about 70°C, to about 78°C, a halo-phosphorous compound and phos- phorous acid with N-methyl-N-pentyl propionic acid hydrochloride in a silicone oil to obtain a reaction mixture;

[0099] b) heating the reaction mixture to a temperature of about 80°C to about 100°C, and maintaining while stirring;

[0100] c) combining water with the reaction mixture, whereby two phases, one aqueous, one nonaqueous, are obtained;

[0101] d) separating the two phases obtained;

[0102] e) maintaining the aqueous phase at a reflux temperature;

[0103] f) evaporating the aqueous phase to obtain a residue;

[0104] g) adding IPA to the residue,

[0105] h) maintaining the reaction mixture for 24 hours or more to obtain a precipitate; and

[0106] i) recovering crystalline ibandronic acid Form S5.

[0107] Preferably, the halo-phosphorous compound of step a) is added in small aliquots, most preferably dropwise. Preferably, the temperature in step a) is about 75°C. Preferably, the reaction mixture in step b) is heated to a temperature of about 80°C. The residue of step f) can be dissolved in water prior to the addition of the IPA in step g). Optionally, the mixture of the EPA and the residue is cooled to facilitate precipitation.

[0108] Form S5 can be also prepared by a process including the steps of:

[0109] a) combining, at a temperature of about 70°C to about 78°C, a halo-phosphorous compound and phosphorous acid with N-methyl-N-pentyl propionic acid hydrochloride in toluene to form a multi-phase reaction mixture

[0110] b) maintaining the reaction mixture, while heating to a temperature of about 80°C to about 100°C;

[0111] c) removing the toluene, especially by decanting or any other liquid-liquid separation technique, and combining water with the reaction mixture;

[0112] d) maintaining the reaction mixture at a reflux temperature, and evaporating to obtain a residue;

[0113] e) adding EPA to the residue to obtain a slurry; and

[0114] f) recovering crystalline ibandronic acid Form S5 from the slurry.

[0115] Preferably, the temperature in step a) is about 75°C. Preferably, the reaction mixture in step b) is heated to a temperature of about 80°C. Preferably, the halo-phosphorous compound of step a) is added slowly, in small aliquots, most preferably dropwise. In addition to water, a strong acid which does not act as oxidant for amino-phosphonic acids may be added to the reaction mixture of step c). The acid is thought to hydrolyze the phosphorous intermediates that form during the previous steps. Preferably, the acid is concentrated HCl.

[0116] Ibandronic acid Form S5 can be prepared by stirring a combination of amorphous ibandronic acid with an organic solvent selected from the group consisting of tetrahydrofuran (THF) and ethanol; and recovering Form S5. The combination is optionally heated to reflux temperature.

[0117] In another embodiment, the present invention provides a solid crystalline form of ibandronic acid, denominated Form S6, characterized by a powder X-ray diffraction pattern having reflections at about 5.7, 11.7, 14.3, 18.5, 21.2 and 21.7±0.2 deg. 2-theta. Solid crystalline ibandronic acid Form S6 can be further characterized by X-ray reflections at about
14.8, 22.7, 22.8 and 30.6±0.2 deg. 2-theta. A typical x-ray diffraction diagram for ibandronic acid form S6 is given in FIG. 9. Form S6 can exist as a hemihydrate, tert-butanolate, or a mixture of both.

[0118] Ibandronic acid Form S6 can be prepared by a process including the steps of:

[0119] a) combining, at a temperature of about 70° C. to about 78° C., a halo-phosphorous compound and phosphorous acid with N-methyl-N-pentyl propionic acid hydrochloride in a silicone oil to obtain a reaction mixture;

[0120] b) heating the reaction mixture to a temperature of about 80° C. to about 100° C., and maintaining while stirring;

[0121] c) combining water with the reaction mixture, whereby two phases, one aqueous, one nonaqueous, are obtained;

[0122] d) separating the two phases obtained;

[0123] e) maintaining the aqueous phase at a reflux temperature;

[0124] f) evaporating the aqueous phase to obtain a residue;

[0125] g) dissolving the residue in water, followed by the addition of tert-butanol to obtain a precipitate; and

[0126] h) recovering crystalline ibandronic acid Form S6.

[0127] Preferably, the halo-phosphorous compound of step a) is added slowly, in small aliquots, especially dropwise. Preferably, the temperature in step a) is about 75° C. Preferably, the reaction mixture in step b) is heated to a temperature of about 80° C.

[0128] Form S6 can be also prepared by a process that includes the steps of:

[0129] a) combining, at a temperature of about 70° C. to about 78° C., a halo-phosphorus compound and phosphorous acid with N-methyl-N-pentyl propionic acid hydrochloride in toluene to obtain a multiphase reaction mixture;

[0130] b) maintaining the reaction mixture, while heating to a temperature of at least about 95° C.;

[0131] c) separating the toluene by decantation or any technique for liquid-liquid separation, and adding an acid to the reaction mixture;

[0132] d) maintaining the reaction mixture at a reflux temperature, and evaporating to obtain a residue;

[0133] e) dissolving the residue in water, followed by the addition of tert-butanol to obtain a precipitate;

[0134] f) recovering crystalline ibandronic acid Form S6.

[0135] Preferably, the halo-phosphorous compound of step a) is added dropwise. Preferably, the acid in step c) is a strong acid which does not act as oxidant for amino-phosphonic acids. Most preferably, the acid in step c) is concentrated HCl. Preferably, the temperature in step a) is about 75° C.

[0136] In another embodiment, the present invention provides a solid crystalline form of ibandronic acid, denominated Form S7, characterized by a powder X-ray diffraction pattern having reflections at about 4.6, 11.5, 16.3, 16.8, 21.0 and 22.8±0.2 deg. 2-theta. Solid crystalline ibandronic acid Form S7 can be further characterized by X-ray reflections at about 9.0, 17.7, 19.8 and 21.8±0.2 deg. 2-theta. A typical x-ray diffraction diagram for ibandronic acid Form S7 is given in FIG. 10. Form S7 can exist as a hemihydrate, a 1-propanolate, or an iso-propanolate.

[0137] Ibandronic acid Form S7 can be prepared by a process including the steps of:

[0138] a) combining, at a temperature of about 70° C. to about 78° C., a halo-phosphorous compound and phosphorous acid with N-methyl-N-pentyl propionic acid hydrochloride in a silicone oil to obtain a reaction mixture;

[0139] b) heating the reaction mixture to a temperature of about 80° C. to about 100° C., and maintaining while stirring;

[0140] c) combining the reaction mixture with water, whereby two phases, one aqueous, one nonaqueous, are obtained;

[0141] d) separating the two phases obtained;

[0142] e) maintaining the aqueous phase at a reflux temperature;

[0143] f) concentrating the aqueous phase to obtain a residue;

[0144] g) adding IPA or n-propanol (?) to the residue;

[0145] h) maintaining the reaction mixture for less than 24 hours to obtain a precipitate; and

[0146] i) recovering crystalline ibandronic acid Form S7.

[0147] Preferably, the halo-phosphorous compound of step a) is added slowly, in small aliquots, most preferably dropwise. Preferably, the temperature in step a) is about 70° C. Preferably, the reaction mixture in step b) is heated to a temperature of about 80° C.

[0148] Form S7 can be also prepared by a process including the steps of:

[0149] a) combining, at a temperature of about 70° C. to about 78° C., a halo-phosphorus compound and phosphorous acid with N-methyl-N-pentyl propionic acid hydrochloride in toluene to obtain a multiphase reaction mixture;

[0150] b) maintaining the reaction mixture, while heating to a temperature of about 80° C. to about 100° C.;

[0151] c) separating the toluene, for example by decantation or any technique for liquid-liquid separation, and combining water with the reaction mixture;

[0152] d) maintaining the reaction mixture at a reflux temperature, and concentrating to obtain a residue;

[0153] e) combining 1-propanol with the residue to obtain a precipitate;

[0154] f) recovering crystalline ibandronic acid Form S7.

[0155] Preferably, the halo-phosphorous compound of step a) is added slowly, in small aliquots, most preferably dropwise. Preferably, the temperature in step a) is about 75° C. Preferably, the reaction mixture in step b) is heated to a temperature of about 80° C.

[0156] In yet another embodiment, the present invention provides a solid crystalline form of ibandronic acid, denominated Form S8, characterized by a powder X-ray diffraction pattern having reflections at about 4.5, 6.0, 11.9, 12.3, 16.2, 17.8 and 21.7±0.2 deg. 2-theta. Solid crystalline ibandronic acid Form S8 can be further characterized by X-ray reflections at about 9.0, 16.5 and 18.9, ±0.2 deg. 2-theta. A typical x-ray diffraction diagram for ibandronic acid Form S8 is given in FIG. 11. Form S8 can exist as an ethanolate or an iso-propanolate.

[0157] Ibandronic acid Form S8 can be prepared by a process including the steps of:

[0158] a) combining, at a temperature of about 70° C. to about 78° C., a halo-phosphorous compound and phos-
phorous acid with N-methyl-N-pentyl propionic acid hydrochloride in a silicone oil to obtain a reaction mixture;

[0159] b) heating the reaction mixture to a temperature of about 80°C. to about 100°C., and maintaining while stirring;

[0160] c) combining the reaction mixture with water, whereby two phases, one aqueous, one nonaqueous, are obtained;

[0161] d) separating the two phases obtained;

[0162] e) maintaining the aqueous phase at a reflux temperature;

[0163] f) concentrating the aqueous phase to obtain a residue;

[0164] g) adding a C₂₄₆ alcohol to the residue to obtain a precipitate; and

[0165] h) recovering crystalline ibandronic acid Form S8.

[0166] Preferably, the halo-phosphorous compound of step a) is added slowly, in small aliquots, most preferably dropwise. Preferably, the temperature in step a) is about 75°C. Preferably, the reaction mixture in step b) is heated to a temperature of about 80°C. The residue of step f) may be dissolved in water prior to the addition of the C₂₄₆ alcohol in step g). Preferably, the C₂₄₆ alcohol in step g) is selected from the group consisting of ethanol, 1-propanol and IPA. Most preferably, the C₂₄₆ alcohol in step g) is ethanol.

[0167] In another embodiment, the present invention provides a solid crystalline form of ibandronic acid, denominated Form S10, characterized by a powder X-ray diffraction pattern having reflections at about 4.8, 6.1, 12.0, 12.3, 16.4, 18.0 and 21.7±0.2 deg, 2-theta. Solid crystalline ibandronic acid Form S10 can be further characterized by X-ray reflections at about 18.9, 20.9 and 22.8±0.2 deg, 2-theta. A typical x-ray diffraction diagram for ibandronic acid Form S10 is given in FIG. 12. Form S10 can exist as an ethanolate.

[0168] Ibandronic acid Form S10 can be prepared by a process comprising the steps of:

[0169] a) combining, at a temperature of about 70°C. to about 78°C., a halo-phosphorous compound and phosphorous acid with N-methyl-N-pentyl propionic acid hydrochloride in a silicone oil to obtain a reaction mixture;

[0170] b) heating the reaction mixture to a temperature of about 80°C. to about 100°C., and maintaining while stirring;

[0171] c) combining the reaction mixture with water, whereby two phases, one aqueous, one nonaqueous, are obtained;

[0172] d) separating the two phases obtained;

[0173] e) maintaining the aqueous phase at a reflux temperature;

[0174] f) concentrating the aqueous phase to obtain a residue;

[0175] g) adding ethanol to the residue to obtain a slurry; and

[0176] h) recovering from the slurry crystalline ibandronic acid Form S10.

[0177] Preferably, the halo-phosphorous compound of step a) is added slowly, in small aliquots, most preferably dropwise. Preferably, the reaction mixture in step b) is heated to a temperature of about 80°C. The residue of step f) may be dissolved in water prior to the addition of the ethanol in step g). The reaction mixture in step g) may be seeded with amorphous ibandronic acid following the addition of the ethanol in step g).

[0178] In another embodiment, the present invention provides a solid crystalline form of ibandronic acid, denominated Form S12, characterized by a powder X-ray diffraction pattern having reflections at about 4.7, 9.0, 11.6, 20.9, 21.1, 21.7, 22.9 and 26.3±0.2 deg, 2-theta. Solid crystalline ibandronic acid Form S12 may be further characterized by X-ray reflections at about 13.8, 17.1 and 18.4±0.2 deg, 2-theta. A typical x-ray diffraction diagram for ibandronic acid Form S12 is given in FIG. 13. Form S12 can be a hemihydrate and/or an isopropanolate.

[0179] Ibandronic acid Form S12 can be prepared by a process including the steps of:

[0180] a) combining, at a temperature of about 70°C. to about 78°C., a halo-phosphorous compound and phosphorous acid with N-methyl-N-pentyl propionic acid hydrochloride in a silicone oil to obtain a reaction mixture;

[0181] b) heating the reaction mixture to a temperature of about 80°C. to about 100°C., and maintaining while stirring;

[0182] c) combining water with the reaction mixture, whereby two phases, one aqueous, one nonaqueous, are obtained;

[0183] d) separating the two phases obtained;

[0184] e) maintaining the aqueous phase at a reflux temperature;

[0185] f) concentrating the aqueous phase to obtain a residue;

[0186] g) combining the residue with 1-propanol to obtain a precipitate; and

[0187] h) recovering crystalline ibandronic acid Form S12.

[0188] Preferably, the halo-phosphorous compound of step a) is added slowly, in small aliquots, especially dropwise. Preferably, the temperature in step a) is about 70°C. Preferably, the reaction mixture in step b) is heated to a temperature of about 80°C.

[0189] In yet another embodiment, the present invention provides a solid crystalline form of ibandronic acid, denominated Form S13, characterized by a powder X-ray diffraction pattern having reflections at about 4.5, 8.9, 12.0, 16.0, 16.3, 21.3 and 22.1±0.2 deg, 2-theta. Solid crystalline ibandronic acid Form S13 can be further characterized by X-ray reflections at about 10.5, 17.8 and 26.9±0.2 deg, 2-theta. A typical x-ray diffraction diagram for ibandronic acid Form S13 is given in FIG. 14. Form S13 can exist as an isopropanolate.

[0190] Ibandronic acid Form S13 can be prepared by a process including the steps of:

[0191] a) combining, at a temperature of about 70°C. to about 78°C., a halo-phosphorous compound and phosphorous acid with N-methyl-N-pentyl propionic acid hydrochloride in a silicone oil to obtain a reaction mixture;

[0192] b) heating the reaction mixture to a temperature of about 80°C. to about 100°C., and maintaining while stirring;

[0193] c) combining the reaction mixture with water, whereby two phases, one aqueous, one nonaqueous, are obtained;

[0194] d) maintaining the reaction mixture at a temperature of about 100°C.;
[0195] e) separating the two phases obtained;
[0196] f) maintaining the aqueous phase at a temperature of about 75 °C. to about 100 °C.;
[0197] g) concentrating the aqueous phase to obtain a residue;
[0198] h) adding EPA to the residue to obtain a precipitate; and
[0199] i) recovering crystalline ibandronic acid Form S13.

[0200] Preferably, the halo-phosphorous compound of step a) is added slowly, in small aliquots, especially dropwise. Preferably, the temperature in step a) is about 75 °C. Preferably, the reaction mixture in step b) is heated to a temperature of about 80 °C.

[0201] Ibandronic acid Form S13 can be also prepared by a process including the steps of:

[0202] a) combining, at a temperature of at least about 95 °C., a halo-phosphorous compound and phosphorous acid with N-methyl-N-pentyl propionic acid hydrochloride to obtain a reaction mixture;
[0203] b) maintaining while stirring the reaction mixture at a temperature of about 95 °C. to about 100 °C.;
[0204] c) combining the reaction mixture with water;
[0205] d) cooling the reaction mixture to room temperature and concentrating to obtain a residue;
[0206] e) dissolving the residue in water, followed by the addition of IPA to obtain a precipitate; and
[0207] f) recovering crystalline ibandronic acid Form S13.

Preferably, the halo-phosphorous compound of step a) is added slowly, in small aliquots, especially dropwise.

[0208] Form S13 can be also prepared by providing a solution of ibandronic acid in water at a temperature of about 38° C. to about 50° C., cooling the solution to room temperature, followed by the addition of IPA, and maintaining the mixture at temperature for a sufficient time to obtain Form S13. Preferably, ibandronic acid is dissolved in water at a temperature of about 40° C. to provide the solution.

[0209] The following table summarizes the weight loss by TGA and water content of the novel crystalline forms of ibandronic acid described hereinabove.

<table>
<thead>
<tr>
<th>Form</th>
<th>Weight loss by TGA [%]</th>
<th>Water content by Karl Fisher [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>amorphous</td>
<td>5.1</td>
<td></td>
</tr>
<tr>
<td>S1</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>S2</td>
<td>3.7</td>
<td></td>
</tr>
<tr>
<td>S3</td>
<td>3.0</td>
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<td>S4</td>
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<td>S5</td>
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<td>S6</td>
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<td>S12</td>
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<td></td>
</tr>
<tr>
<td>S13</td>
<td>3.0</td>
<td></td>
</tr>
</tbody>
</table>

[0210] In a further embodiment, the present invention also provides a process for purifying ibandronic acid from inorganic impurities (i.e., reducing the amount of inorganic impurities) that includes the step of dissolving ibandronic acid in water or methanol, and crystallizing by addition of a C24 alcohol. Preferably, the C24 alcohol is selected from the group consisting of ethanol, 1-propanol, IPA and tert-butanol.

[0211] In yet another embodiment, the present invention further provides a HPLC method of assaying ibandronic acid comprising the steps of: dissolving an ibandronic acid sample in a diluent to obtain a sample solution, loading the sample solution (ca. 50 μL) onto a 250x4.1 mm, Hamilton type PRP-X100 anion exchange column, eluting the sample from the column at 2.0 ml/min using a mixture of nitric acid (HNO3: 35 vol-%), potassium nitrate (KNO3: 45 vol-%) and ethanol (20 vol-%) as eluent, and measuring the ibandronic acid content of the relevant sample at 240 nm wavelength with a UV detector. Preferably, the diluent is water.

[0212] Some processes of the present invention involve crystallization out of a particular solvent. One skilled in the art knows that the conditions concerning crystallization can be modified without affecting the form of the polymorph obtained. For example, when mixing ibandronic acid in a solvent to form a solution, warming of the mixture may be necessary to completely dissolve the starting material. If warming does not clarify the mixture, the mixture may be diluted or filtered. To filter, the hot mixture may be passed through paper, glass fiber or other membrane material, or a clarifying agent such as cellulose. Depending upon the equipment used and the concentration and temperature of the solution, the filtration apparatus may need to be preheated to avoid premature crystallization. The conditions may also be changed to induce precipitation. A preferred way of inducing precipitation is to reduce the solubility of the solvent (reduce it “solvulizing power”). The solubility of the solvent—that is its ability to dissolve ibandronic acid—can be reduced, for example, by reducing the temperature of the solvent.

[0213] In yet another embodiment, the present invention provides a process for preparing ibandronate sodium (the sodium salt of ibandronic acid) comprising converting any of the solid or crystalline forms of ibandronic acid hereinabove described to ibandronate sodium by combining the ibandronic acid with an aqueous solution of sodium hydroxide at ambient temperature (about 200 to about 28° C.), concentrating the solution, especially at reduced pressure, to obtain a residue; combining the residue with acetone whereby a precipitate is formed, and recovering ibandronate monosodium.

[0214] In yet another embodiment, the present invention provides ibandronic acid having an assay of ≥99%.

[0215] In a further embodiment, the present invention provides pharmaceutical formulations that include at least on
pharmacologically acceptable excipient and one or more of the novel crystalline forms of the present invention. Pharmaceutical formulations of the present invention contain solid ibandronic acid or crystalline forms thereof, such as one of those disclosed herein, optionally in a mixture with amorphous ibandronic acid. In addition to the active ingredient(s), the pharmaceutical formulations of the present invention can and typically do contain one or more pharmaceutically acceptable excipients. Such excipients are included in the formulations for a variety of purposes.

**[0216]** Diluents increase the bulk of a solid pharmaceutical composition, and may make a pharmaceutical dosage form containing the composition easier for the patient and care giver to handle. Diluents for solid compositions include, for example, microcrystalline cellulose (e.g. Avicel®), microfine cellulose, lactose, starch, pregelatinized starch, calcium carbonate, calcium sulfate, sugar, dextrates, dextrin, dextrose, dibasic calcium phosphate dihydrate, tribasic calcium phosphate, kaolin, magnesium carbonate, magnesium oxide, maltodextrin, mannitol, polyethylene glycolates (e.g. Eudragit®), potassium chloride, powdered cellulose, sodium chloride, sorbitol and tcalc.

**[0217]** Solid pharmaceutical compositions that are compacted into a dosage form, such as a tablet, may include excipients whose functions include helping to bind the active ingredient and other excipients together after compression. Binders for solid pharmaceutical compositions include acacia, alginate acid, carboxymethylcellulose sodium, dextrin, ethyl cellulose, gelatin, guar gum, hydrogenated vegetable oil, hydroxyethyl cellulose, hydroxypropyl cellulose (e.g. Klucel®), hydroxypropyl methylcellulose (e.g. Methocel®), liquid glucose, magnesium aluminim silicate, maltodextrin, methylcellulose, polyethylene glycolates, povidone (e.g. Kollidon®), pregelatinized starch, sodium alginate and starch.

**[0218]** The dissolution rate of a compacted solid pharmaceutical composition in the patient’s stomach may be increased by the addition of a disintegrant to the composition. Disintegrants include alginic acid, carboxyethylcellulose calcium, carboxymethylcellulose sodium (e.g. Ac-Di-Sol®, Primelose®), colloidal silicon dioxide, croscarmellose sodium, crosspovidone (e.g. Kollidon®, Polyplasdone®), guar gum, magnesium aluminim silicate, methyl cellulose, microcrystalline cellulose, polacrilin potassium, powdered cellulose, pregelatinized starch, sodium alginate, sodium starch glycinate (e.g. Explotab®) and starch.

**[0219]** Gliadins can be added to improve the flowability of a non-compact solid composition and to improve the accuracy of dosing. Excipients that may function as gliadins include colloidal silicon dioxide, magnesium trisilicate, powdered cellulose, starch, tcalc and tribasic calcium phosphate.

**[0220]** When a dosage form such as a tablet is made by the compaction of a powdered composition, the composition is subjected to pressure from a punch and dye. Some excipients and active ingredients have a tendency to adhere to the surfaces of the punch and dye, which can cause the product to have pitting and other surface irregularities. A lubricant can be added to the composition to reduce adhesion and ease the release of the product from the dye. Lubricants include magnesium stearate, calcium stearate, glyceryl monostearate, glyceryl palmitostearate, hydrogenated castor oil, hydrogenated vegetable oil, mineral oil, polyethylene glycol, sodium benzoate, sodium lauryl sulfate, sodium stearyl fumarate, stearic acid, talc and zinc stearate.

**[0221]** Flavouring agents and flavor enhancers make the dosage form more palatable to the patient. Common flavoring agents and flavor enhancers for pharmaceutical products that may be included in the composition of the present invention include maltol, vanillin, ethyl vanillin, menthol, citric acid, fumaric acid, ethyl maltol and tartaric acid.

**[0222]** Solid and liquid compositions (suspensions or emulsions) may also be dyed using any pharmaceutically acceptable colorant to improve their appearance and/or facilitate patient identification of the product and unit dosage level.

**[0223]** In liquid pharmaceutical compositions of the present invention, ibandronic acid and any other solid excipients are suspended in a liquid carrier such as water, vegetable oil, alcohol, polyethylene glycol, propylene glycol or glycerin.

**[0224]** Liquid pharmaceutical compositions may contain emulsifying agents to disperse uniformly throughout the composition an active ingredient or other excipient that is not soluble in the liquid carrier. Emulsifying agents that may be useful in liquid compositions of the present invention include, for example, gelatin, egg yolk, casein, cholesterol, acacia, tragacanth, chondrus, pectin, methyl cellulose, carboxomer, cetostearyl alcohol and cetyl alcohol.

**[0225]** Liquid pharmaceutical compositions of the present invention may also contain a viscosity enhancing agent to improve the mouth-feel of the product and/or coat the lining of the gastrointestinal tract. Such agents include acacia, alginate acid bentonite, carborner, carboxymethylcellulose calcium or sodium, cetostearyl alcohol, methyl cellulose, ethylcellulose, gelatin guar gum, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, maltodextrin, polyvinyl alcohol, povidone, propylene carbonate, propylene glycol alginate, sodium alginate, sodium starch glycinate, starch tragacanth and xanthan gum.

**[0226]** Sweetening agents such as sorbitol, saccharin, sodium saccharin, sucrose, aspartame, fructose, mannitol and invert sugar may be added to improve the taste.

**[0227]** Preservatives and chelating agents such as alcohol, sodium benzene, butylated hydroxytoluene, butylated hydroxyanisole and ethylenediamine tetraacetic acid may be added at levels safe for ingestion to improve storage stability.

**[0228]** According to the present invention, a liquid composition may also contain a buffer such as gluconic acid, lactic acid, citric acid or acetic acid, sodium gluconate, sodium lactate, sodium citrate or sodium acetate. Selection of excipients and the amounts used may be readily determined by the formulation scientist based upon experience and consideration of standard procedures and reference works in the field.

**[0229]** The solid compositions of the present invention include powders, granulates, aggregates and compacted compositions. The dosages include dosages suitable for oral, buccal, rectal, parenteral (including subcutaneous, intramuscular and intravenous), inhalant and ophthalmic administration. Although the most suitable administration in any given case will depend on the nature and severity of the condition being treated, the most preferred route of the present invention is oral. The dosages may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the pharmaceutical arts.

**[0230]** Dosage forms include solid dosage forms like tablets, powders, capsules, suppositories, sachets, troches and lozenges, as well as liquid syrups, suspensions and elixirs.

**[0231]** The dosage form of the present invention may be a capsule containing the composition, preferably a powdered or
granulated solid composition of the invention, within either a hard or soft shell. The shell may be made from gelatin and optionally contain a plasticizer such as glycerin and sorbitol, and an opacifying agent or colorant.

The active ingredient and excipients may be formulated into compositions and dosage forms according to methods known in the art.

A composition for tableting or capsule filling may be prepared by wet granulation. In wet granulation, some or all of the active ingredients and excipients in powder form are blended and then further mixed in the presence of a liquid, typically water, that causes the powders to clump into granules. The granule is screened and/or milled, dried and then screened and/or milled to the desired particle size. The granulate may then be tabletted, or other excipients may be added prior to tabletted, such as a glidant and/or a lubricant.

A tableting composition may be prepared conventionally by dry blending. For example, the blended composition of the actives and excipients may be compacted into a slug or a sheet and then compacted into compacted granules. The compacted granules may subsequently be compressed into a tablet.

As an alternative to dry granulation, a blended composition may be compressed directly into a compacted dosage form using direct compression techniques. Direct compression produces a more uniform tablet without granules. Excipients that are particularly well suited for direct compression tabletting include microcrystalline cellulose, spray dried lactose, dicalcium phosphate dihydrate and colloidal silica. The proper use of these and other excipients in direct compression tabletting is known to those in the art with experience and skill in particular formulation challenges of direct compression tabletting.

A capsule filling of the present invention may comprise any of the aforementioned blends and granulates that were described with reference to tableting, however, they are not subjected to a final tableting step.

Having described the invention with reference to certain preferred embodiments, other embodiments will become apparent to one skilled in the art from consideration of the specification. The invention is further defined by reference to the following examples describing in detail the preparation of the composition and methods of use of the invention. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the scope of the invention.

EXAM PLES

Instrumentation

X-ray diffraction data were obtained with a scintag X-Ray powder diffractometer model X'TRA, Cu-tube, solid state detector, a round standard aluminum sample holder with round zero background quartz plate was used. Scanning parameters: Range: 2-40 deg.28: continues scan, Rate: 5 deg./min.

DSC data were obtained with a DSC821e, Mettler Toledo instrument. The sample weight was 3-5 mg. The heating (scan) rate was 10°C/min. Number of holes in the crucible: 3.

TGA data were obtained using a Mettler TG50, sample weight: 7-15 mg, heating 30 rate: 10°C/min.

Karl Fischer data were obtained using a Mettler Toledo DL38, sample weight: 100-200 mg.

Spray drying technique were obtained using "Buchi Mini Spray dryer B-290." The spray parameters are: evaporating capacity-1 lt/hr water (higher for organic solvents); the maximum temperature input-220°C.; Air flow-max of 35 m3/hr; spray gas-compressed air or nitrogen 200-800 lit/hr, 5-8 bar; Nozzel diameter-0.7 mm (standard); Nozzel cap-1.4 mm and 1.5 mm.

Example 1
Amorphous Ibandronic Acid

An aqueous solution (40% w/w) of Ibandronic acid (150 ml) was evaporated under vacuum (20-30 mmHg) until dryness while heating the flask in a water bath (up to 70°C.) to obtain Amorphous Ibandronic acid (67 gr).

Example 2
Amorphous Ibandronic Acid

An aqueous solution (40% w/w) of Ibandronic acid (303 gr) was freeze-dried (~50°C, 0.5 mmHg) for 3 days to obtain Amorphous Ibandronic acid (120 gr).

Example 3
Amorphous Ibandronic Acid

Phosphorous trichloride (3.3 ml) was added to a stirred suspension of MPPA.HCl (8 g) in silicon oil (40 ml) at 75°C. Two additional portions of phosphorous trichloride (2x3.3 ml) were added during 2 hours after heating the reaction mixture to 81°C. Two portions of phosphous acid (2x3.1 g) were thereafter added during 2 hours. The reaction mixture was stirred at 81°C. for 22 hours. Water (40 ml) was added drop-wise at 81°C. The resulting phases were separated and the aqueous phase was heated to 90°C. for 16 hours. The obtained solution was cooled to room temperature and then was evaporated to obtain an oily residue. The oily residue was dissolved in water (7 ml) at room temperature. To the obtained solution, IPA (280 ml) was added. The obtained sticky precipitate was heated to reflux and then was cooled to room temperature, after complete dissolution. Then the IPA was decanted-off and the residue was dried in vacuum oven at 50°C. for 20 hours to obtain 4.4 g of amorphous ibandronic acid.

Example 4
Amorphous Ibandronic Acid

Phosphorous trichloride (3.3 ml) was added to a stirred suspension of MPPA.HCl (8 g) in silicon oil (40 ml) at 75°C. Two additional portions of phosphorous trichloride (2x3.3 ml) were added during 2 hours after heating the reaction mixture to 81°C. Then two portions of phosphous acid (2x3.1 g) were added during 2 hours. The reaction mixture was stirred at 81°C. for 22 hours. Water (40 ml) was added drop-wise at 81°C. Then the phases were separated and the aqueous phase was heated to 90°C. for 16 hours. The obtained solution was cooled to room temperature and then was evaporated to obtain an oily residue. The oily residue was dissolved in water (7 ml) at room temperature. The obtained solution was heated to 70°C. Then hot IPA (280 ml) (73°C.) was added drop-wise. The solution was cooled to room temperature. The solution was stirred at room temperature for 21
hours. Then the IPA was decanted-off and the residue was dried in vacuum oven at 50°C for 21 hours to obtain 4.6 g of amorphous ibandronic acid.

Example 5
Ibandronic Acid Crystal Form S1

[0247] Amorphous ibandronic acid (3.0 g) was dissolved in water (4 mL) at room temperature. Acetone (70 mL) was added to the stirred solution. White slurry was obtained while stirring at room temperature for 68 hours. The precipitate was isolated by vacuum filtration, washed with acetone (2×25 mL) and dried in a vacuum oven at 50°C for 24 hours to obtain 2.5 g of ibandronic acid crystal form S1.

Example 6
Ibandronic Acid Crystal Form S1

[0248] 40% w/w aqueous solution of ibandronic acid (22.2 g) was concentrated under vacuum. To the concentrated solution (15.71 g), tert-butanol was added drop-wise at room temperature in two portions (2×50 mL) and the mixture was stirred at this temperature for 4 hours. The obtained precipitate was isolated by vacuum filtration, washed with tert-butanol (1×15 mL) and dried in a vacuum oven at 50°C for 24 hours to obtain 5.5 g of ibandronic acid crystal form S1.

Example 7
Ibandronic Acid Crystal Form S1

[0249] 40% w/w aqueous solution of ibandronic acid (16.8 g) was concentrated under vacuum. To the concentrated solution (12.1 g), absolute ethanol (100 mL) was added drop-wise at room temperature and the mixture was stirred at this temperature for 4.5 hours. The obtained precipitate was isolated by vacuum filtration, washed with absolute ethanol (2×25 mL) and dried in a vacuum oven at 50°C for 23 hours to obtain 5.2 g of ibandronic acid crystal form S1.

Example 8
Ibandronic acid crystal Form S1

[0250] Amorphous ibandronic acid (3.0 g) was dissolved in methanol (12 mL) at room temperature. Acetone (40 mL) was added in one portion to the stirred solution. The obtained slurry was stirred at room temperature for 72 hours. The resulting precipitate was isolated by vacuum filtration, washed with acetone (2×12.5 mL) and dried in a vacuum oven at 50°C for 22 hours to obtain 2.5 g of ibandronic acid crystal form S1.

Example 9
Ibandronic Acid Crystal Form S1

[0251] Amorphous ibandronic acid (3.0 g) was stirred in acetone (15 mL) at reflux temperature for 5 hours. The slurry was cooled to room temperature and then it was stirred at this temperature for 16 hours. The product was dried in a vacuum oven at 50°C for 24 hours to obtain 2.8 g of ibandronic acid crystal form S1.

Example 10
Ibandronic Acid Crystal Form S1

[0252] Amorphous ibandronic acid (3.0 g) was stirred in absolute ethanol (20 mL) at reflux temperature for 2.5 hours. The slurry was cooled to room temperature and then it was stirred at this temperature for 40.5 hours. The product was isolated by vacuum filtration, washed with absolute ethanol (2×20 mL) and dried in a vacuum oven at 40°C for 25 hours to obtain 2.8 g of ibandronic acid crystal form S1.

Example 11
Ibandronic Acid Crystal Form S1

[0253] 40% w/w aqueous solution of ibandronic acid (10.95 g) was concentrated under vacuum. To the concentrated solution (7.5 g), acetone was added at room temperature in two portions (2×45 mL) and the mixture was stirred at this temperature for 22 hours. The obtained precipitate was isolated by vacuum filtration, washed with acetone (2×20 mL) and dried in a vacuum oven at 50°C for 70 hours to obtain 2.9 g of ibandronic acid crystal form S1.

Example 12
Ibandronic Acid Crystal Form S1

[0254] Phosphorous oxychloride (17 mL) was added drop-wise to a stirred suspension of MPA.HCl (10 g) and phosphorous acid (14.8 g) in toluene (70 mL) at 75°C. The reaction mixture was heated to 80°C and was stirred at this temperature for 26 hours. The reaction mixture was cooled to room temperature. The toluene was decanted-off and the residue was stirred under reflux with water (70 mL) for 15.5 hours. The obtained solution was cooled to room temperature and then it was evaporated to obtain an oily residue (34.3 g). Absolute ethanol (853 mL) was added gradually to the oily residue while stirring at room temperature for 45 hours. The obtained precipitate was isolated by vacuum filtration, washed with absolute ethanol (2×97 mL) and dried in a vacuum oven at 50°C for 24 hours to obtain 6.7 g of ibandronic acid crystal form S1.

Example 13
Ibandronic Acid Crystal Form S2

[0255] Amorphous ibandronic acid (3.0 g) was dissolved in methanol (12 mL) at room temperature. Acetonitrile (ACN) (40 mL) was added in one portion to the stirred solution. The obtained slurry was stirred at room temperature for 72 hours. The precipitate was isolated by vacuum filtration, washed with ACN (2×30 mL) and dried in a vacuum oven at 50°C for 21.5 hours to obtain 2.4 g of ibandronic acid crystal form S2.

Example 14
Ibandronic Acid Crystal Form S3

[0256] 40% w/w aqueous solution of ibandronic acid (11 g) was concentrated under vacuum. To the concentrated solution (7.6 g), tert-butanol (50 mL) was added at room temperature. The obtained slurry was stirred at this temperature for 72 hours. Then the precipitate was isolated by vacuum filtration,
washed with tert-butanol (2×40 mL) and dried in a vacuum oven at 50°C for 22.5 hours to obtain 4.2 g of ibandronic acid crystal form S3.

Example 15
Ibandronic Acid Crystal Form S4

[0257] 40% w/w aqueous solution of ibandronic acid (19.7 g) was concentrated under vacuum. To the concentrated solution (12.5 g), 1-propanol (150 mL) was added gradually at room temperature. The un-stirrable product was heated to reflux to obtain viscous stirrable mixture. The mixture was cooled to room temperature and stirred at this temperature for 16 hours. The obtained precipitate was isolated by vacuum filtration, washed with 1-propanol (2×17 mL) and dried in a vacuum oven at 50°C for 24 hours to obtain 6.6 g of ibandronic acid crystal form S4.

Example 16
Ibandronic Acid Crystal Form S5

[0258] 40% w/w aqueous solution of ibandronic acid (23.7 g) was concentrated under vacuum. To the concentrated solution (14 g), 1-propanol (100 mL) was added drop-wise at room temperature and the mixture was stirred at this temperature for 3 hours. The obtained precipitate was isolated by vacuum filtration, washed with 1-propanol (2×35 mL) and dried in a vacuum oven at 50°C for 24 hours to obtain 10.2 g of ibandronic acid crystal form S4.

Example 17
Ibandronic Acid Crystal Form S5

[0259] Phosphorous trichloride (10.9 mL) was added dropwise to a stirred suspension of MPA.HCl (7 g) and phosphoric acid (10.3 g) in silicon oil (49 mL) at 75°C. The reaction mixture was heated to 80°C. Two additional portions of phosphorous trichloride (1×1.5 mL and 1×1 mL) were added gradually to the stirred reaction mixture at ~80°C. The reaction mixture was stirred at this temperature for 50 hours. Water (49 mL) was added drop-wise at 70°C. The phases were separated and the aqueous phase was heated to reflux for 15.5 hours. The obtained solution was cooled to room temperature and then was evaporated until dryness to obtain an oily residue (27.2 g). The oily residue was dissolved in water (4 mL). To the obtained solution, IPA (209 mL) was added drop-wise at room temperature and the mixture was stirred at this temperature for 24 hours. The obtained precipitate was isolated by vacuum filtration, washed with IPA (2×52 mL) and dried in a vacuum oven at 50°C for 24 hours to obtain 9.9 g of ibandronic acid crystal form S5.

Example 18
Ibandronic Acid Crystal Form S5

[0260] Phosphorous trichloride (8.2 mL) was added dropwise to a stirred suspension of MPA.HCl (7 g) and phosphoric acid (3.9 g) in toluene (35 mL) at 75°C. The reaction mixture was heated to 95°C and was stirred at this temperature for 23 hours. The toluene was decanted-off and the residue was stirred under reflux (96°C) with 6N HCl (104 mL) for 43 hours. The obtained solution was cooled to room temperature and was then concentrated to obtain an oily residue (8.1 g). The oily residue was dissolved in water (4 mL). To the obtained solution, IPA (196 mL) was added drop-wise at room temperature and the mixture was stirred at this temperature for 72 hours. The obtained precipitate was isolated by vacuum filtration, washed with IPA (2×40 mL) and dried in a vacuum oven at 50°C for 24 hours to obtain 4.5 g of ibandronic acid crystal form S5.

Example 19
Ibandronic Acid Crystal Form S5

[0261] Phosphorous oxychloride (50 mL) was added dropwise to a stirred suspension of MPA.HCl (30 g) and phosphoric acid (44 g) in silicone oil (210 mL) at 75°C. The reaction mixture was heated to 81°C. Two additional portions of phosphorous oxychloride (1×6.7 mL and 1×4 mL) were added gradually to the stirred reaction mixture at 81°C. The reaction mixture was stirred at this temperature for 50 hours. Water (210 mL) was added drop-wise to the solution and the mixture was stirred for 1 hr. Then the phases were separated and the aqueous phase was heated to reflux for 16.5 hours. The obtained solution was cooled to room temperature and then was evaporated until dryness to obtain an oily residue (125.6 g). The oily residue was dissolved in water (19 mL). To the obtained solution, IPA (1760 mL) was added at room temperature and the mixture was stirred at this temperature for 24 hours and then was cooled to 7°C and stirred this temperature for 72 hrs. The obtained precipitate was isolated by vacuum filtration, washed with IPA (2×100 mL) and dried in a vacuum oven at 50°C for 25 hours to obtain 22 g of ibandronic acid crystal form S5.

Example 20
Ibandronic Acid Crystal Form S5

[0262] Amorphous ibandronic acid (3.0 g) was stirred in THF (20 mL) at reflux temperature for 2.5 hours to obtain almost complete dissolution. The mixture was cooled to room temperature and then it was stirred at this temperature for 21 hours. The obtained precipitate was isolated by vacuum filtration under nitrogen flow, washed with THF (2×15 mL) and dried in a vacuum oven at 40°C for 23.5 hours to obtain 2.7 g of ibandronic acid crystal form S5.

Example 21
Ibandronic Acid Crystal Form S5

[0263] Amorphous ibandronic acid (3.0 g) was stirred in Absolute Ethanol (30 mL) at room temperature. The slurry was stirred at room temperature for 72 hours. The product was isolated by vacuum filtration, washed with Absolute Ethanol (2×20 mL) and dried in a vacuum oven at 50°C for 22 hours to obtain 2.9 g of ibandronic acid crystal form S5.

Example 22
Ibandronic Acid Crystal Form S5

[0264] Phosphorous oxychloride (17 mL) was added dropwise to a stirred suspension of MPA.HCl (10 g) and phosphoric acid (14.8 g) in toluene (70 mL) at 75°C. The reaction mixture was heated to 80°C and was stirred at this temperature for 26 hours. The reaction mixture was cooled to room temperature. The toluene was decanted-off and the residue was stirred under reflux with water (70 mL) for 15.5 hours. The obtained solution was cooled to room temperature and then was evaporated until dryness to obtain an oily residue (34.3 g). IPA (834 mL) was added gradually to the oily residue while stirring at room temperature during 72 hours. The
obtained precipitate was isolated by vacuum filtration, washed with IPA (2×84 mL) and dried in a vacuum oven at 50°C for 23 hours to obtain 12.8 g of ibandronic acid crystal form S5.

Example 23

Ibandronic Acid Crystal Form S5

[0265] Phosphorous trichloride (15.6 mL) was added drop-wise to a stirred suspension of MPA.HCl (10 g) and phosphorous acid (14.7 g) in silicon oil (70 mL) at 75°C. The reaction mixture was heated to 80°C. Two additional portions of phosphorous trichloride (1×2 mL and 1×1.3 mL) were added gradually to the stirred reaction mixture at 80°C. The reaction mixture was stirred at this temperature for 48 hours. Water (70 mL) was added drop-wise at 80°C. The phases were separated and the aqueous phase was heated to reflux for 16 hours. The obtained solution was cooled to room temperature and then was evaporated until dryness to obtain an oily residue (38.2 g). IPA (746 mL) was added to the oily residue at room temperature and the mixture was stirred at this temperature for 53.5 hours. The obtained precipitate was isolated by vacuum filtration, washed with IPA (2×83 mL) and dried in a vacuum oven at 50°C for 24.5 hours to obtain 11.1 g of ibandronic acid crystal form S5.

Example 24

Ibandronic Acid Crystal Form S6

[0266] Phosphorous trichloride (10.9 mL) was added drop-wise to a stirred suspension of MPA.HCl (7 g) and phosphorous acid (10.3 g) in silicon oil (49 mL) at 75°C. The reaction mixture was heated to 80°C. Two additional portions of phosphorous trichloride (1×1.5 mL and 1×1 mL) were added gradually to the stirred reaction mixture at ~80°C. The reaction mixture was stirred at this temperature for 50 hours. Water (49 mL) was added drop-wise at 79°C. The phases were separated and the aqueous phase was heated to reflux for 15.5 hours. The obtained solution was cooled to room temperature and then was evaporated until dryness to obtain an oily residue (27.2 g). The oily residue was dissolved in water (3.8 mL). To the obtained solution, tert-butanol (191 mL) was added at room temperature and the mixture was stirred at this temperature for 42 hours. The obtained precipitate was isolated by vacuum filtration, washed with tert-butanol (2×38 mL) and dried in a vacuum oven at 50°C for 25.5 hours to obtain 6.2 g of ibandronic acid crystal form S6.

Example 25

Ibandronic Acid Crystal Form S7

[0268] Phosphorous trichloride (15.6 mL) was added drop-wise to a stirred suspension of MPA.HCl (10 g) and phosphorous acid (14.7 g) in silicon oil (70 mL) at 75°C. The reaction mixture was heated to 80°C. Water (70 mL) was added drop-wise at 80°C. Then the phases were separated and the aqueous phase was heated to reflux for 18 hours. The obtained solution was cooled to room temperature and then was evaporated until dryness to obtain an oily residue (24.5 g). IPA (443 mL) was added gradually to the oily residue and the mixture was stirred at room temperature for 18 hours. The obtained precipitate was isolated by vacuum filtration, washed with IPA (1×80 mL) and dried in a vacuum oven at 50°C for 24 hours to obtain 9.8 g of ibandronic acid crystal form S7.

Example 26

Ibandronic Acid Crystal Form S8

[0269] Phosphorous oxychloride (17 mL) was added drop-wise to a stirred suspension of MPA.HCl (10 g) and phosphorous acid (14.8 g) in toluene (70 mL) at 75°C. The reaction mixture was heated to 80°C, and was stirred at this temperature for 26 hours. The reaction mixture was cooled to room temperature. The toluene was decanted-off and the residue was stirred under reflux with water (70 mL) for 15.5 hours. The obtained solution was cooled to room temperature and then was evaporated until dryness to obtain an oily residue (34.3 g). 1-Propanol (695 mL) was added gradually to the oily residue while stirring at room temperature during 18 hours. The obtained precipitate was isolated by vacuum filtration, washed with 1-propanol (2×39 mL) and dried in a vacuum oven at 50°C for 24 hours to obtain 10.8 g of ibandronic acid crystal form S8.

Example 27

Ibandronic Acid Crystal Form S9

[0270] Phosphorous trichloride (18.7 mL) was added drop-wise to a stirred suspension of MPA.HCl (12 g) and phosphorous acid (17.6 g) in silicone oil (84 mL) at 75°C. The reaction mixture was heated to 80°C. Two additional portions of phosphorous trichloride (1×2.5 mL and 1×1.5 mL) were added gradually to the stirred reaction mixture at 80°C. The reaction mixture was stirred at this temperature for 51.5 hours. Water (84 mL) was added drop-wise to the solution, stirred for 15 minutes. The phases were separated and the aqueous phase was heated to reflux for 16 hours. The obtained solution was cooled to room temperature and stirred at this temperature for 12 hours. A portion (23 mL) of this solution (24.8 g) was concentrated to obtain an oily residue (11.26 g). The oily residue was dissolved in water (1.7 mL). To the obtained solution, IPA (87 mL) was added drop-wise at room temperature and the mixture was stirred at this temperature for 70 hours. The obtained precipitate was isolated by vacuum
filtration, washed with IPA (2x25 mL) and dried in a vacuum oven at 50° C. for 25 hours to obtain 3.27 g of ibandronic acid crystal form S8.

Example 29
Ibandronic Acid Crystal Form S8

Phosphorous trichloride (18.7 mL) was added dropwise to a stirred suspension of MPA.HCl (12 g) and phosphorous acid (17.6 g) in silicone oil (84 mL) at 75° C. The reaction mixture was heated to 80° C. Two additional portions of phosphorous trichloride (1x2.5 ml and 1x1.5 mL) were added gradually to the stirred reaction mixture at 80° C. The reaction mixture was stirred at this temperature for 51.5 hours. Water (84 mL) was added drop-wise to the solution and the mixture stirred for 15 minutes. The phases were separated and the aqueous phase was heated to reflux for 16 hours. The obtained solution was cooled to room temperature and stirred at this temperature for 12 hours. A portion (23 mL) from this solution (27 g) was evaporated until dryness to obtain an oily residue (11 g). The oily residue was dissolved in water (1.6 mL). To the obtained solution, 1-propanol (160 mL) was added drop-wise at room temperature and the mixture was stirred at this temperature for 20 hours. The obtained precipitate was isolated by vacuum filtration, washed with IPA (2x10 mL) and dried in a vacuum oven at 50° C. for 25 hours to obtain 3.16 g of ibandronic acid crystal form S8.

Example 30
Ibandronic Acid Crystal Form S8

Phosphorous oxychloride (20 mL) was added drop-wise to a stirred suspension of MPA.HCl (12 g) and phosphorous acid (17.6 g) in silicone oil (84 mL) at 75° C. The reaction mixture was heated to 80° C. Two additional portions of phosphorous oxychloride (1x2.7 ml and 1x1.6 mL) were added gradually to the stirred reaction mixture at 80° C. The reaction mixture was stirred at this temperature for 50 hours. Water (84 mL) was added drop-wise to the solution, stirred for 20 minutes. The phases were separated and the aqueous phase was heated to reflux for 17 hours. The obtained solution was cooled to room temperature and stirred at this temperature for 12 hours. A portion (24 mL) from this solution (24 g) was concentrated to obtain an oily residue (21.65 g). The oily residue was dissolved in water (1.9 mL). To the obtained solution, IPA (177 mL) was added drop-wise at room temperature and the mixture was stirred at this temperature for 23 hours. The obtained precipitate was isolated by vacuum filtration, washed with IPA (2x20 mL) and dried in a vacuum oven at 50° C. for 26.5 hours to obtain 2.37 g of ibandronic acid crystal form S8.

Example 31
Ibandronic Acid Crystal Form S8

Phosphorous trichloride (15.6 mL) was added dropwise to a stirred suspension of MPA.HCl (10 g) and phosphorous acid (14.7 g) in silicone oil (70 mL) at 75° C. The reaction mixture was heated to 80° C. Two additional portions of phosphorous trichloride (1x2 mL and 1x1.3 mL) were added gradually to the stirred reaction mixture at 80° C. The reaction mixture was stirred at this temperature for 48 hours. Water (70 mL) was added drop-wise at 80° C. Then the phases were separated and the aqueous phase was heated to reflux for 16 hours. The obtained solution was cooled to room temperature and then was evaporated until dryness to obtain an oily residue (38.2 g). Absolute ethanol (766 mL) was added to the oily residue at room temperature and the mixture was stirred at this temperature for 53 hours. The obtained precipitate was isolated by vacuum filtration, washed with absolute ethanol (2x61 mL) and dried in a vacuum oven at 50° C. for 25.5 hours to obtain 7.7 g of ibandronic acid crystal form S8.

Example 32
Ibandronic Acid Crystal Form S8

Phosphorous trichloride (57 mL) was added dropwise to a stirred suspension of MPA.HCl (30 g) and phosphorous acid (44 g) in silicone oil (210 mL) at 75° C. The reaction mixture was heated to 80° C. Two additional portions of phosphorous trichloride (1x6.25 mL and 1x3.75 mL) were added gradually to the stirred reaction mixture at 80° C. The reaction mixture was stirred at this temperature for 48 hours. Water (210 mL) was added drop-wise at 80° C. and stirred at this temperature for 30 minutes. The phases were separated and the aqueous phase was heated to reflux for 17 hours. The solution was cooled to room temperature and then concentrated to obtain an oily residue (121.1 g). The oily residue was dissolved in water (18 mL). Absolute ethanol (3027 mL) was added to the solution at room temperature and the mixture was stirred at this temperature for 72 hours. Cooling to 5° C. and stirring at this temperature for 7 hours. The obtained precipitate was isolated by vacuum filtration, washed with absolute ethanol (2x48 mL) and dried in a vacuum oven at 50° C. for 23.5 hours to obtain 35.64 g of ibandronic acid crystal form S8.

Example 33
Ibandronic Acid Crystal Form S10

Phosphorous oxychloride (50 mL) was added drop-wise to a stirred suspension of MPA.HCl (30 g) and phosphorous acid (44 g) in silicone oil (210 mL) at 75° C. The reaction mixture was heated to 80° C. Two additional portions of phosphorous oxychloride (1x6.7 mL and 1x4 mL) were added gradually to the stirred reaction mixture at 80° C. The reaction mixture was stirred at this temperature for 51 hours. Water (210 mL) was added drop-wise at 80° C. and stirred at this temperature for 30 minutes. The phases were separated and the aqueous phase was heated to reflux for 16.5 hours. The solution was cooled to room temperature and then was evaporated until dryness to obtain an oily residue (128.5 g). The oily residue was dissolved in water (19 mL). Absolute ethanol (3210 mL) was added to the solution at room temperature and the mixture was stirred at this temperature for 39 hours. The mixture was seeded with ibandronic acid and stirred for 4.5 hours. The mixture was cooled to 0° C. and stirred at this temperature for 72 hours. The obtained precipitate was isolated by vacuum filtration, washed with absolute ethanol and dried in a vacuum oven at 50° C. for 23 hours to obtain 13.82 g of ibandronic acid crystal form S10.

Example 34
Ibandronic Acid Crystal Form S10

Phosphorous trichloride (15.6 mL) was added dropwise to a stirred suspension of MPA.HCl (10 g) and phosphorous acid (14.7 g) in silicone oil (70 mL) at 70° C. The reaction
mixture was heated to 80° C. and was stirred at this temperature for 23.5 hours. Water (70 mL) was added drop-wise at 80° C. The phases were separated and the aqueous phase was heated to reflux for 18 hours. The obtained solution was cooled to room temperature and then concentrated to obtain an oily residue (24.5 g). Absolute ethanol (597 mL) was added to the oily residue and the mixture was stirred at room temperature for 20.5 hours. The obtained precipitate was isolated by vacuum filtration, washed with absolute ethanol (2×20 mL) and dried in a vacuum oven at 50° C. for 31 hours to obtain 7.3 g of ibandronic acid crystal form S10.

Example 35
Ibandronic Acid Crystal Form S10

[0277] Phosphorous trichloride (18.7 mL) was added drop-wise to a stirred suspension of MPA.HCl (12 g) and phosphoric acid (17.6 g) in silicone oil (84 mL) at 75° C. The reaction mixture was heated to 80° C. Two additional portions of phosphorous trichloride (1×2.5 mL and 1×1.5 mL) were added gradually to the stirred reaction mixture at 80° C. The reaction mixture was stirred at this temperature for 52 hours. Water (84 mL) was added drop-wise to the solution, stirred for 15 minutes. Then the phases were separated and the aqueous phase was heated to reflux for 16 hours. The obtained solution was cooled to room temperature and stirred at this temperature for 13 hours. A portion (25 mL) from this solution (27.31 g) was evaporated until dryness to obtain an oily residue (11.25 g). The oily residue was dissolved in water (1.7 mL). To the obtained solution, abs. ethanol (270 mL) was added drop-wise at room temperature and the mixture was stirred at this temperature for 20 hours. The obtained precipitate was isolated by vacuum filtration, washed with abs. ethanol (2×12.5 mL) and dried in a vacuum oven at 50° C. for 24 hours to obtain 8.56 g of ibandronic acid crystal form S10.

Example 36
Ibandronic Acid Crystal Form S10

[0278] Phosphorous oxychloride (20 mL) was added drop-wise to a stirred suspension of MPA.HCl (12 g) and phosphoric acid (17.6 g) in silicone oil (84 mL) at 75° C. The reaction mixture was heated to 80° C. Two additional portions of phosphorous oxychloride (1×2.7 mL and 1×1.6 mL) were added gradually to the stirred reaction mixture at 80° C. The reaction mixture was stirred at this temperature for 50 hours. Water (84 mL) was added drop-wise to the solution, stirred for 20 minutes. The phases were separated and the aqueous phase was heated to reflux for 13 hours. The obtained solution was cooled to room temperature and stirred at this temperature for 12 hours. A portion (24 mL) from this solution (29 g) was concentrated to obtain an oily residue (12.8 g). The oily residue was dissolved in water (1.9 mL). To the obtained solution, abs. ethanol (300 mL) was added drop-wise at room temperature and the mixture was stirred at this temperature for 25 hours. The obtained precipitate was isolated by vacuum filtration, washed with abs. ethanol (2×20 mL) and dried in a vacuum oven at 50° C. for 24 hours to obtain 1.81 g of ibandronic acid crystal form S10.

Example 37
Ibandronic Acid Crystal Form S12

[0279] Phosphorous trichloride (15.6 mL) was added drop-wise to a stirred suspension of MPA.HCl (10 g) and phosphoric acid (14.7 g) in silicone oil (70 mL) at 70° C. The reaction mixture was heated to 80° C. and was stirred at this temperature for 23.5 hours. Water (70 mL) was added drop-wise at 80° C. The phases were separated and the aqueous phase was heated to reflux for 18 hours. The obtained solution was cooled to room temperature and then was evaporated until dryness to obtain an oily residue (24.5 g). 1-Propanol was added to the oily residue at room temperature in two portions (2×25 mL) and the mixture was stirred at this temperature for 17.5 hours. The obtained precipitate was isolated by vacuum filtration, washed with 1-propanol (2×20 mL) and dried in a vacuum oven at 50° C. for 22.5 hours to obtain 10.1 g of ibandronic acid crystal form S12.

Example 38
Ibandronic Acid Crystal Form S13

[0280] Phosphorous oxychloride (11.7 mL) was added drop-wise to a stirred suspension of MPA.HCl (7 g) and phosphoric acid (10.3 g) in silicone oil (49 mL) at 75° C. The reaction mixture was heated to 80° C. An additional portion of phosphorous oxychloride (1×1.6 mL) was added to the reaction mixture at 80° C. after 45.5 hours. The reaction mixture was stirred at 80° C. for additional 2.5 hours. Water (49 mL) was added drop-wise at 80° C. The phases were separated and the aqueous phase was heattied to 100° C. for 18 hours. The obtained solution was cooled to room temperature and then was concentrated to obtain an oily residue (26.7 g). The oily residue was dissolved in water (4 mL). To the obtained solution, IPA (360 mL) was added drop-wise while stirring at room temperature during 48 hours. The obtained precipitate was isolated by vacuum filtration, washed with IPA (1×20 mL) and dried in a vacuum oven at 50° C. for 24.5 hours to obtain 1.84 g of ibandronic acid crystal form S13.

Example 39
Ibandronic Acid Crystal Form S13

[0281] MPA.HCl (7 g) was added to melted phosphorous acid (3.4 g) while stirring in an oil-bath at 95° C. Phosphorous trichloride (5.8 mL) was added drop-wise. The mixture was stirred at 95-100° C. (in an oil-bath) for 25.5 hours. Without cooling, but removing the oil-bath, water (21 mL) was added drop-wise. The reaction mixture was stirred at 97° C. for 16 hours. The obtained solution was cooled to room temperature. Insoluble particles were filtered off and the filtrate was concentrated to obtain an oily residue (12.9 g). The oily residue was dissolved in water (1.9 mL). To the obtained solution, IPA (290 mL) was added gradually while stirring at room temperature during 100 hours. The obtained precipitate was isolated by vacuum filtration, washed with IPA (2×30 mL) and dried in a vacuum oven at 50° C. for 24 hours to obtain 8.11 g of ibandronic acid crystal form S13.

Example 40
Ibandronic Acid Crystal Form S13

[0282] Phosphorous trichloride (50 mL) was added drop-wise to a stirred suspension of MPA.HCl (30 g) and phosphoric acid (44 g) in silicone oil (210 mL) at 75° C. The reaction mixture was heated to 80° C. Two additional portions of phosphorous trichloride (1×6.25 mL and 1×3.75 mL) were added gradually to the stirred reaction mixture at 80° C. The reaction mixture was stirred at this temperature for 48.5
hours. Water (210 mL) was added drop-wise to the solution and the mixture stirred for 15 minutes. The phases were separated and the aqueous phase was heated to reflux for 16.5 hours. The obtained solution was cooled to room temperature and then was concentrated to obtain an oily residue (121.3 g). The oily residue was dissolved in water (18 mL). To the obtained solution, IPA (1698 mL) was added at room temperature and the mixture was stirred at this temperature for 22 hours and then was cooled to 4°C and stirred this temperature for 4 hrs. The obtained precipitate was isolated by vacuum filtration, washed with IPA (2×43 mL) and dried in a vacuum oven at 50°C for 47 hours to obtain 39 g of ibandronic acid crystal form S13.

Example 41

Ibandronic Acid Crystal Form S13

[0283] Ibandronic acid (97 g) was dissolved in water (90 mL) at 40°C. The solution was cooled to room temperature and IPA (1100 mL) was added, stirred at this temperature for 22 hrs. The obtained precipitate was isolated by vacuum filtration, washed with IPA (2×50 mL) and dried in a vacuum oven at 50°C for 25 hours to obtain 97.6 g of ibandronic acid crystal form S13.

Example 42

Comparative Example

Repetition of Example 9 of U.S. Pat. No. 4,927,814

[0284] 15 g N-Methyl-N-pentylaminopropionic acid (MPA.HCl) were kept for 23 hours at 100°C with 8.8 g phosphorous acid and 18.7 ml phosphorous trichloride in 75 ml chlorobenzene. The solvent was then decanted off and the residue was stirred under reflux with 222 ml 6N HCl for 12.5 hours. Insoluble material was filtered off and the filtrate was concentrated and applied to column of Amberlite IR 120 (H+). The elution with water was monitored by HPLC. The desired fractions were combined, evaporated and stirred up with acetone to obtain a sticky oily precipitate as a crude product. (The HPLC method for monitoring the ion-exchange chromatography is the one described in this application).

Example 44

Comparative Example

Repetition of Example 9 of U.S. Pat. No. 4,927,814—with Acetonitrile Used Instead of Acetone

[0286] 15 g N-Methyl-N-pentylaminopropionic acid (MPA.HCl) were kept for 23 hours at 100°C with 8.8 g phosphorous acid and 18.7 ml phosphorous trichloride in 75 ml chlorobenzene. The solvent was then decanted off and the residue was stirred under reflux with 222 ml 6N HCl for 12.5 hours. Insoluble material was filtered off and the filtrate was concentrated and applied to column of Amberlite IR 120 (H+). The elution with water was monitored by HPLC. The desired fractions were combined, evaporated and stirred up with acetone to obtain a sticky oily precipitate as a crude product. (The HPLC method for monitoring the ion-exchange chromatography is the one described in this application).

HPLC Assay

[0287] Column: Hamilton type PRP-X100, Anion exchange, 250×4.1 mm
Temp.: 35°C.
Eluent: 35% HNO₃, 45% KNO₃, 20% EtOH
Flow: 2.0 mL/min
Injection volume: 50 μL
Detector: 240 nm

[0289] The following samples were analyzed according to the above method:

<table>
<thead>
<tr>
<th>Example No.</th>
<th>Crystallization medium</th>
<th>Polymorph</th>
<th>% area of PO₄⁺</th>
<th>% area of PO₄⁻</th>
<th>% area of Cl⁻</th>
</tr>
</thead>
<tbody>
<tr>
<td>32</td>
<td>EtOH</td>
<td>S8</td>
<td>0.4</td>
<td>ND*</td>
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<td>33</td>
<td>EtOH</td>
<td>S10</td>
<td>0.2</td>
<td>0.2</td>
<td>ND*</td>
</tr>
</tbody>
</table>

*ND* = not detected

Example 45

Amorphous Ibandronic Acid

[0291] Ibandronic acid (9 g) was dissolved in water (18 ml) at room temperature. The solution was divided into three portions, and each portion was spray dried using a Buchi mini spray dryer B-290 using a standard nozzle 0.7 mm in diameter with a nozzle cap of 1.4 or 1.5 mm. The solution feed rate was about 1 L/h. The spray gas was set at 200–800 L/h at a pressure of 5–8 bar. In each instance, amorphous ibandronic acid was obtained.

[0292] For portion 1, nitrogen gas was at an inlet temperature of 50°C. The evaporated solvent and nitrogen left the spray dryer at a temperature of 41–36°C.
For portion 2, nitrogen gas was at an inlet temperature of 100°C. The evaporated solvent and nitrogen left the spray dryer at a temperature of 71-72°C.

For portion 3, nitrogen gas was at an inlet temperature of 150°C. The evaporated solvent and nitrogen left the spray dryer at a temperature of 100°C.

Each of the three products was analyzed by powder x-ray diffraction and found to be amorphous.

Example 46

Conversion of Ibandronic Acid to Monosodium Ibandronate

Ibandronic acid (4.5 g) was dissolved in water (45 ml) at room temperature. A solution of 1N aq. NaOH (14 ml) was added in one portion. The reaction mixture was stirred at room temperature for 2.5 hours. Then the solution was concentrated under reduced pressure and was poured into Acetone (45 ml) at room temperature. A white precipitate was obtained immediately. The obtained slurry was stirred at room temperature for 72 hours. The product was isolated by vacuum filtration, washed with Acetone (2x20 ml) and dried in a vacuum oven at 50°C for 22 hours to obtain 4.45 g of ibandronate monosodium salt (pH=4.26).

What is claimed is:

1. A crystalline form of ibandronic acid selected from the group consisting of:
   a) the crystalline form of ibandronic acid characterized by x-ray reflections at about 8.2, 11.5, 11.9, 13.9, 18.6, and 22.2±0.2° 20;
   b) the crystalline form of ibandronic acid characterized by x-ray reflections at about 8.1, 14.2, 16.1, 18.2, and 24.4±0.2° 20;
   c) the crystalline form of ibandronic acid characterized by x-ray reflections at about 4.4, 8.8, 11.3, 17.6, and 26.4±0.2° 20;
   d) the crystalline form of ibandronic acid characterized by x-ray reflections at about 8.6, 11.2, 17.3, 20.8, 22.5 and 26.0±0.2° 20;
   e) the crystalline form of ibandronic acid characterized by x-ray reflections at about 4.5, 8.9, 12.0, 16.0, 16.3, 21.4, 22.1 and 26.9±0.2° 20;
   f) the crystalline form of ibandronic acid characterized by x-ray reflections at about 5.7, 11.7, 14.3, 18.5, 21.2 and 21.7±2° 20;
   g) the crystalline form of ibandronic acid characterized by x-ray reflections at about 4.6, 11.5, 16.3, 16.8, 21.0 and 22.8±0.2° 20;
   h) the crystalline form of ibandronic acid characterized by x-ray reflections at about 4.5, 6.0, 11.9, 12.3, 16.2, 17.8 and 21.7±0.2° 20;
   i) the crystalline form of ibandronic acid characterized by x-ray reflections at about 4.5, 6.1, 12.0, 12.3, 16.4, 18.0 and 21.7±0.2° 20;
   j) the crystalline form of ibandronic acid characterized by x-ray reflections at about 4.7, 9.0, 11.6, 20.9, 21.1, 21.7, 22.9 and 26.3±0.2° 20; and
   k) the crystalline form of ibandronic acid characterized by x-ray reflections at about 4.5, 8.9, 12.0, 16.0, 16.3, 21.3±0.2° 20.

2. The crystalline form of ibandronic acid of claim 15 characterized by x-ray reflections at about 8.2, 11.5, 11.9, 13.9, 18.6, and 22.2±0.2° 20, denominated form S1, and further characterized by x-ray reflections at about 21.6, 23.8, 24.7 and 28.1±0.2° 20.

3. The crystalline form of ibandronic acid of claim 16 having a powder x-ray diffraction diagram substantially as shown in FIG. 4.

4. The crystalline form of ibandronic acid of claim 17, wherein the crystalline form is hemihydrate.

5. The crystalline form of ibandronic acid of claim 15 characterized by x-ray reflections at about 8.1, 14.2, 16.1, 18.2, and 24.4±0.2° 20, denominated form S2, and further characterized by x-ray reflections at about 10.9, 19.2, 22.3, 23.3, and 28.2±0.2° 20.

6. The crystalline form of ibandronic acid of claim 18 having a powder x-ray diffraction diagram substantially as shown in FIG. 5.

7. The crystalline form of ibandronic acid of claim 19 characterized by x-ray reflections at about 4.4, 8.8, 11.3, 17.6, and 26.4±0.2° 20, denominated form S3, and further characterized by x-ray reflections at about 21.6, 23.8, 24.7 and 28.1±0.2° 20.

8. The crystalline form of ibandronic acid of claim 20 having a powder x-ray diffraction diagram substantially as shown in FIG. 6.

9. The crystalline form of ibandronic acid of claim 21, wherein the crystalline form is a tert-butanolate.

10. The crystalline form of ibandronic acid of claim 22 characterized by x-ray reflections at about 4.4, 8.6, 11.2, 17.3, 20.8, 22.5 and 26.0±0.2° 20, denominated form S4, and further characterized by x-ray reflections at about 16.2, 20.5 and 21.3±0.2° 20.

11. The crystalline form of ibandronic acid of claim 23 having a powder x-ray diffraction diagram substantially as shown in FIG. 7.

12. The crystalline form of ibandronic acid of claim 24, wherein the crystalline form is a propanolate.

13. The crystalline form of ibandronic acid of claim 25 characterized by x-ray reflections at about 4.5, 8.9, 12.0, 16.0, 16.3, 21.4, 22.1 and 26.9±0.2° 20, denominated form S5, and further characterized by x-ray reflections at about 5.9, 10.5 and 17.8±0.2° 20.

14. The crystalline form of ibandronic acid of claim 26 having an x-ray diffraction diagram substantially as shown in FIG. 8.

15. The crystalline form of ibandronic acid of claim 27, wherein the crystalline form is a hemihydrate or an iso-propanolate.

16. The crystalline form of ibandronic acid of claim 28 characterized by x-ray reflections at about 4.7, 11.7, 14.3, 18.5, 21.2 and 22.8±0.2° 20.

17. The crystalline form of ibandronic acid of claim 30 having a powder x-ray diffraction diagram substantially as shown in FIG. 9.

18. The crystalline form of ibandronic acid of claim 31, wherein the crystalline form is a hemihydrate or a tert-butanolate.

19. The crystalline form of ibandronic acid of claim 32 characterized by x-ray reflections at about 4.6, 11.5, 16.3, 16.8, 21.0 and 22.8±0.2° 20, denominated form S7, and further characterized by x-ray reflections at about 9.0, 17.7, 19.8 and 21.8±0.2° 20.
20. The crystalline form of ibandronic acid of claim 33 having a powder x-ray diffraction diagram substantially as shown in FIG. 10.

21. The crystalline form of ibandronic acid of claim 34, wherein the crystalline form is a hemihydrate, a 1-propanolate, or an iso-propanolate.

22. The crystalline form of ibandronic acid of claim 15 characterized by x-ray reflections at about 4.5, 6.0, 11.9, 12.3, 16.2, 17.8 and 21.7°±0.2°2θ, denominated form S8, and further characterized by x-ray reflections at about 9.0, 16.5 and 18.9°±0.2°2θ.

23. The crystalline form of ibandronic acid of claim 36 having a powder x-ray diffraction diagram substantially as shown in FIG. 11.

24. The crystalline form of ibandronic acid of claim 37, wherein the crystalline form is an ethanolate or an iso-propanolate.

25. The crystalline form of ibandronic acid of claim 15 characterized by x-ray reflections at about 4.8, 6.1, 12.0, 12.3, 16.4, 18.0 and 21.7°±0.2°2θ, denominated form S10, and further characterized by x-ray reflections at 18.9, 20.9 and 22.8°±0.2°2θ.

26. The crystalline form of ibandronic acid of claim 39 having a powder x-ray diffraction diagram substantially as shown in FIG. 12.

27. The crystalline form of ibandronic acid of claim 41, wherein the crystalline form is an ethanolate.

28. The crystalline form of ibandronic acid of claim 15 characterized by x-ray reflections at about 4.7, 9.0, 11.6, 20.9, 21.1, 21.7, 22.9 and 26.3°±0.2°2θ, denominated form S12, and further characterized by x-ray reflections at about 13.8, 17.1 and 18.4°±0.2°2θ.

29. The crystalline form of ibandronic acid of claim 42 having a powder x-ray diffraction diagram substantially as shown in FIG. 13.

30. The crystalline form of ibandronic acid of claim 43, wherein the crystalline form is a hemihydrate or an iso-propanolate.

31. The crystalline form of ibandronic acid of claim 15 characterized by x-ray reflections at about 4.5, 8.9, 12.0, 16.0, 16.3, 21.3°±0.2°2θ, denominated from S13, and further characterized by x-ray reflections at about 10.5, 17.8 and 26.9°±0.2°2θ.

32. The crystalline form of ibandronic acid of claim 45 having a powder x-ray diffraction diagram substantially as shown in FIG. 14.

33. The crystalline form of ibandronic acid of claim 46, wherein the crystalline form is an iso-propanolate.

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