SYNTHESIS OF ALENDRONATE SODIUM TRIHYDRATE

This invention describes a process for the synthesis of alendronate sodium trihydrate from the reaction of alendronic acid, either anhydrous or in a hydrated state, in an aqueous slurry with sodium hydroxide in water. The pH is adjusted into the range 4.3 - 4.4, the solution is concentrated and the sodium salt thus formed is isolated by crystallization from water.
TITLE OF THE INVENTION
SYNTHESIS OF ALENDRONATE SODIUM TRIHYDRATE

BACKGROUND OF THE INVENTION

This invention describes a process for the synthesis of alendronate sodium trihydrate from the reaction of alendronic acid, either anhydrous or in a hydrated state, in an aqueous slurry with sodium hydroxide in water. The pH is adjusted into the range 4.3—4.4, the solution is concentrated and the sodium salt thus formed is isolated by crystallization from water.

The current manufacturing process for alendronate sodium trihydrate is a three step manufacturing process that relies on the use of a continuous reactor for the production of sodium Pyrophosphonate from GABA (γ-aminobutyric acid), which is described in U.S. Patent No. 5,510,517. The instant invention provides safety and environmental advantages over the current manufacturing process.

With the current manufacturing process, there is a large decomposition exotherm in Sodium Pyrophosphonate @ ~ 120°C, which results if the reaction mass is allowed to heat adiabatically. Strict controls, such as the emergency quench and the use of a continuous reactor to minimise reaction volumes, contribute to safe running of the reactor. In addition, the crude step involves a pressure hydrolysis. The process of the instant invention eliminates both of these steps, and thus results in a process that is safer to run.

Furthermore, the current process is reliant on the use of hazardous raw material such as Phosphorous Acid, Phosphorous Trichloride (PCl₃) and Methane Sulphonic Acid (MSA). Manipulating these substances on such a large scale represents a significant challenge to manufacturing personnel. Also, the current process produces hazardous waste that must be incinerated. The process of the instant invention eliminates the reliance on hazardous raw materials and limits the production of hazardous wastes.

SUMMARY OF THE INVENTION

This invention provides processes for the preparation of a compound of formula 1:

![Chemical Structure]

comprising reacting alendronic acid with strong base in water; adjusting the pH to 4.3-4.4; concentrating the solution; and crystallizing the salt from water.
A process for preparing a compound of formula I:

comprising the steps:

a) reacting alendronic acid with strong base in water;
b) adjusting the pH to between 4.3 and 4.4;
c) concentrating the solution;
d) crystallizing the salt from water.

A slurry of alendronic acid in water is reacted with a strong base. This step is performed at a temperature of about 40°C to about 60°C. In a subclass of the invention, this step is performed at a temperature of about 58°C to about 60°C. In a class of the invention, the alendronic acid is anhydrous or hydrated. In a subclass of the invention, the alendronic acid is monohydrated. In another class of the invention, the strong base is sodium hydroxide, sodium carbonate or sodium hydrogen carbonate. In a subclass of the invention, the strong base is sodium hydroxide.

After the strong base is reacted with the alendronic acid, the pH is adjusted to between 4.3 and 4.4. The pH can be adjusted with sodium hydroxide or hydrochloric acid, or with other acids and bases as is known in the art.

The solution is then concentrated by methods known in the art, including distillation and reverse osmosis. Optionally, the solution is concentrated by distillation.

Finally, the alendronate sodium trihydrate salt is crystallized from water. This crystallization can also be performed with seeding.

Schemes 1 & 2 describe processes for the synthesis of alendronate sodium trihydrate from the reaction of alendronic acid (either anhydrous or hydrated) in an aqueous slurry with sodium hydroxide in water at temperature of 58—60°C. The pH is adjusted into the range 4.3—4.4, the solution is concentrated and the sodium salt thus formed is isolated by crystallization.
SCHEME 1
SYNTHESIS OF ALENDRONATE SODIUM TRIHYDRATE FROM ALENDRONIC ACID MONOHYDRATE

ALENDRONIC ACID MONOHYDRATE

\[ \begin{array}{c}
\text{H}_2\text{N} - \text{C}_2\text{H}_{12}\text{O} - \text{PO} - \text{OH} \\
\text{HO} - \text{PO} - \text{OH} \\
\text{OH}
\end{array} \]

\[ \xrightarrow{\text{Strong base}} \]

\[ \begin{array}{c}
\text{H}_2\text{N} - \text{C}_2\text{H}_{12}\text{O} - \text{PO} - \text{OH} \\
\text{HO} - \text{PO} - \text{O} - \text{Na} \\
\text{OH}
\end{array} \]

\[ \text{H}_2\text{O} \xrightarrow{\text{40 - 60 ℃}} \]

\[ \begin{array}{c}
\text{H}_2\text{N} - \text{C}_2\text{H}_{12}\text{O} - \text{PO} - \text{OH} \\
\text{HO} - \text{PO} - \text{O} - \text{Na} \\
\text{OH}
\end{array} \]

\[ \xrightarrow{\text{pH 4.3 - 4.4}} \]

\[ \begin{array}{c}
\text{H}_2\text{N} - \text{C}_2\text{H}_{12}\text{O} - \text{PO} - \text{OH} \\
\text{HO} - \text{PO} - \text{O} - \text{Na} \\
3\text{H}_2\text{O}
\end{array} \]

ALENDRONATE SODIUM TRIHYDRATE
SCHEME 2
SYNTHESIS OF ALENDRONATE SODIUM TRUHIDRATE FROM ALENDRONIC ACID ANHYDROUS

The following example further illustrates the details for the preparation of the alendronate sodium trihydrate. Those skilled in the art will readily understand that known variations of the conditions and processes of the following preparative procedure can be used to prepare this compound. All temperatures are degrees Celsius unless otherwise noted.

EXAMPLE 1
PREPARATION OF ALENDRONATE SODIUM TRUHIDRATE FROM ALENDRONIC ACID (MONOHYDRATE OR ANHYDROUS)

To a slurry of Alendronate Monohydrate (24.7 g, 92.5 mmol) in water (~ 286 g, 15.88 mol) at 58 - 60°C was added, dropwise a solution of 47% caustic (~ 7.95 g, 3.695 g as NaOH, 92.5 mmol) in water (~ 20 g, 1.11 mol) over ~ 30 minutes. The batch dissolves as the caustic is added. The pH is adjusted into the range 4.3 - 4.4 at 58 - 60°C with sodium hydroxide or hydrochloric acid.

The batch is filtered at 58 - 60°C & concentrated to a final volume of 0.132 lts (228 g/l) where it is cooled to 0 - 5°C (2°C actual) and aged for a minimum of 10 hours. The batch is then isolated and washed with 10 lts of DIW pre-cooled to 1-5°C.

The batch is dried to a LOD specification of 16.1 - 17.1 % w/w.
WHAT IS CLAIMED IS:

1. A process for preparing a compound of formula I:

   (Chemical structure image)

   comprising the steps:

   a) reacting alendronic acid with strong base in water;
   b) adjusting the pH to between 4.3 and 4.4;
   c) concentrating the solution;
   d) crystallizing the salt from water.

2. The process of Claim 1 wherein the alendronic acid is anhydrous or hydrated.

3. The process of Claim 3 wherein the alendronic acid is monohydrated.

4. The process of Claim 1 wherein the strong base is sodium hydroxide, sodium carbonate or sodium hydrogen carbonate.

5. The process of Claim 4 wherein the strong base is sodium hydroxide.

6. The process of Claim 2 wherein step a) is performed at a temperature of about 40°C to about 60°C.

7. The process of Claim 6 wherein step a) is performed at a temperature of about 58°C to about 60°C.

8. The process of Claim 1 wherein the solution is concentrated by distillation.