Abstract:
The invention relates to the process of preparation of Risedronic acid and Risedronate sodium hemipentahydrate in the absence of organic solvents. The process comprises, reacting 3-pyridyl acetic acid with phosphorous acid and phosphorous trichloride to give Risedronic acid which is further reacted with sodium hydroxide in water medium to give Risedronate sodium hemipentahydrate.
IMPROVED PROCESS FOR THE PREPARATION OF RISEDRONATE SODIUM HEMIPENTAHYDRATE

TECHNICAL FIELD OF THE INVENTION

The present invention is directed to an improved, safe and industrially viable process for manufacturing of Risedronic acid (3-pyridyl-1-hydroxyethylidene-l,l-bisphosphonic acid) in the absence of organic solvents.

The further aspect of the invention is to provide a cost-effective process for preparation of substantially pure Risedronate sodium hemipentahydrate (3-pyridyl-1-hydroxyethylidene-l,l-bisphosphonic acid sodium hemipentahydrate) in the absence of organic solvents.

BACKGROUND OF THE INVENTION

Osteoporosis is a disease characterized by a progressive loss of bone mineral. Osteoporosis is also characterized by low bone mass and architectural deterioration of bone tissue leading to enhanced bone fragility and increase in the risk of fracture. The goal of therapy in treatment of osteoporosis is to improve calcium absorption and decrease urinary excretion of calcium thus reversing secondary hyperparathyroidism. The bisphosphonates, for example etidronate, pamidronate, and Risedronate are useful in treating osteoporosis. Risedronate sodium ([l-hydroxy-2(3-pyridinyl)ethylidene]bisphosphonic acid monosodium) salt is marketed under the trade name - Actonel(R) for treatment of osteoporosis.

Different processes were reported for the preparation of Risedronic acid and Risedronate sodium hemipentahydrate by using various solvents. However they have some disadvantages associated with safety, quality and yield.

US6410520 discloses selective crystallization of Risedronate sodium as a monohydrate or hemipentahydrate (pseudopolymorphs). In this patent, it is mentioned that the monohydrate and the hemipentahydrate are hydrated forms and the hemipentahydrate is thermodynamically preferred crystalline form. According to the process disclosed in this patent, 3-pyridyl-1-hydroxyethylidene-l,l-bisphosphonic acid was reacted with sodium
hydroxide in isopropanol and water mixture to give 3-pyridyl-l-hydroxyethylidene-l,l-bisphosphonic acid sodium hemipentahydrate.

WO2007042048 discloses a process for selective crystallisation of monosodium Risedronate monohydrate or monosodium Risedronate hemipentahydrate. And the process comprises as follows: Risedronic acid or Risedronic acid monohydrate is treated with sodium in an alcohol (methanol/ethanol) to give Risedronate sodium hemihydrate, which is further treated with excess water to give Risedronate sodium hemipentahydrate.

WO2007083243 discloses a process of preparation of the Risedronate sodium hemipentahydrate. The process comprises, converting Risedronic acid into an organic amine salt and the resulting salt was reacted with a base (which is capable of giving sodium ion) in a mixture of water and methanol to give Risedronate sodium hemipentahydrate.

WO2005012314 discloses a process for controlling the crystal structure of sodium Risedronate. In this process 3-pyridyl-l-hydroxy-ethylidene-l, 1-bisphosphonic acid was treated with sodium hydroxide in isopropyl alcohol and water medium to provide sodium Risedronate hemipentahydrate.

EPI 86405 (US5583122) describes the preparation of isomer of Risedronic acid by reaction of 2-pyridyl acetic acid with phosphorous acid and phosphorous trichloride in chlorobenzene.

EP1243592 discloses the process of preparation of the Risedronic acid by treating the 3-pyridylacetic acid or its hydrochloride salt with phosphorous acid, phosphorus trichloride in chlorobenzene or fluorobenzene as a solvent.

WO2005044831 discloses the process of preparation of bisphosphonic acid [Risedronic acid] by treating with corresponding carboxylic acid or its hydrochloride salt [3-pyridylacetic acid or its hydrochloride] with phosphorous acid, phosphorous trichloride in sulfolane solvent.
Thus the processes disclosed in the prior art for the preparation of the Risedronic acid and Risedronate sodium hemipentahydrate involved the usage of organic solvents. In all the above processes, a problem commonly encountered in the preparation of bisphosphonic acids is cumbersome workup and operations are too complicated to carry out in large scale. Further it was reported in US20070066569 publication that some unknown pyrophoric material is generating during the reaction which leads to fire accidents in the presence of flammable organic solvent in reaction medium. In fact we have experienced fire accidents while carrying the reactions by using chlorobenzene as a solvent. Keeping the above problems in view, a safe and industrially feasible manufacturing process for Risedronic acid and Risedronate sodium hemipentahydrate without using any organic solvent is developed.

**OBJECTIVE OF THE INVENTION**

The main objective of the present invention is to provide a safe and an improved process for the preparation of Risedronic acid in high yield without using any organic solvent, which would be easy to implement on a commercial scale production.

The other objective of the present invention is to provide a process for the preparation of sodium Risedronate hemipentahydrate in high yield and high purity without using any organic solvent.

**SUMMARY OF THE INVENTION**

In accordance with the principle of the present invention, it is provided an improved and safe process for the preparation the Risedronic acid of Formula-II without using any organic solvent. Further the invention also provides the process for preparation of Risedronate sodium hemipentahydrate of Formula-III in high yield and good purity.
This process is illustrated by the following scheme.

Stage I

The method of making Risedronic acid (II) and Risedronate sodium hemipentahydrate (III) comprising the following steps:

A) PREPARATION OF RISEDRONIC ACID (II)

a) addition of 3-pyridyl acetic acid of Formula-I to phosphorous acid in the absence of any organic solvent,

b) addition of phosphorous trichloride to the above reaction mixture at a temperature of about 60°C to about 65°C,

c) heating the reaction mixture at about 70°C to about 75°C for about 7 to 9 hours,

d) cooling the reaction mixture to 50-60°C and removal of unreacted phosphorous trichloride under vacuum,

e) addition of water to the reaction mixture and heating to about 90°C to about 95°C for about 5 to 7 hours,

f) cooling the reaction mixture to about 25°C to about 35°C, whereby Risedronic acid precipitates as a crystalline white powder,

g) isolating the solid material by filtration and dried to give pure crystalline Risedronic acid of Formula-II.
B) PREPARATION OF RISEDRONATE SODIUM HEMIPENTAHYDRATE (III)

a) reacting the Risedronic acid of Formula-II with sodium hydroxide in water medium
   by adjusting the pH 6.5 to 7.0 at about 25°C to about 35°C, where by an
   homogeneous aqueous solution is formed,

b) treating the aqueous solution with an activated carbon and filtered to get clear
   homogenous aqueous solution,

c) adjusting the pH of the aqueous solution to about 4.0 to about 5.0 with acetic acid at
   about 25°C to about 35°C whereby a white crystalline material of Risedronate
   sodium hemipentahydrate of Formula-III separates out,

d) isolation of the white crystalline solid by filtration,

e) drying the material at about 40°C to about 50°C to get pure sodium Risedronate
   hemipentahydrate of Formula-III.

PESCRITPON OF THE FIGURES

Figure 1. X-ray powder diffraction pattern of crystalline Risedronic acid prepared according
   to example-1.

Figure 2. X-ray powder diffraction pattern of crystalline Risedronate sodium hemipentahydrate prepared according to example-2.

DETAILED DESCRIPTION OF THE INVENTION

The process of the present invention is characterized by two stages, first stage
   provides the preparation of Risedronic acid and second stage provides the preparation of
   Risedronate sodium hemipentahydrate.

The present invention provides an improved and cost effective process for the
   preparation of Risedronic acid (3-pyridyl-1-hydroxyethylidene-1,1-bisphosphonic acid) and
   Risedronate sodiumhemipentahydrate (3-pyridyl-1-hydroxyethylidene-1,1-bisphosphonic acid
   sodium hemipentahydrate) in the absence of organic solvents. The first stage of the process
   comprises, reacting 3-pyridylacetic acid with phosphorous acid and phosphorous trichloride
   and followed by hydrolysis in water. Initially the reaction mixture of 3-pyridylacetic acid and
phosphorous acid is heated to about 55°C to about 70°C, more preferably from 60°C to 65°C. Phosphorous trichloride is added to the above mixture slowly at about 60°C to about 65°C. After complete addition of phosphorous trichloride, the reaction mixture is heated to the temperature range from about 70°C to about 75°C and maintained for a period of 7 to 9 hours at the same temperature, more preferably 8 hours to provide a good conversion. Reaction mixture is cooled to the temperature range from about 55°C to about 60°C more preferably to 55°C and vacuum is applied to remove the unreacted phosphorous trichloride. Water is added to the reaction mass and temperature is raised to about 90°C to about 95°C and maintained for 5 to 7 hours more preferably for six hours. Reaction mass cooled to about 25°C to about 35°C and maintained for 2 hours to form the crystals of Risedronic acid (3-pyridyl-l-hydroxyethylidene-l,l-bisphosphonic acid), which is isolated by filtration, washed with water and dried.

In second stage, the process comprises conversion of Risedronic acid to Risedronate sodium hemipentahydrate by reaction with sodium hydroxide in aqueous medium followed by adjusting the pH with acetic acid. Risedronic acid prepared in first stage is reacted with a base, which is capable of giving sodium ions more specifically sodium hydroxide (NaOH) to adjust the pH to about 6.5 to about 7.0, more preferably to 6.7 in aqueous medium at about 25°C to about 35°C. Activated carbon is added to the solution and filtered through filter aid bed. To the filtrate, pH is adjusted to about 4.0 to about 5.0, more preferably to 4.6 with an acid more preferably with acetic acid at about 25°C to about 35°C. Crystalline solid of Risedronate sodium hemipentahydrate (3-pyridyl-l-hydroxyethylidene-l,l-bisphosphonic acid sodium hemipentahydrate) is precipitated on stirring for about 3 to about 5 hours more specifically for 4 hours. Isolated the material by known art and dried at about 40°C to about 50°C, more preferably at about 45°C to furnish pure crystalline Risedronate sodium hemipentahydrate.

The following examples to prepare Risedronic acid and Risedronate sodium hemipenta-hydrate will illustrate the nature of the invention in more detail.
Example 1

Preparation of Risedronic acid (3-pyridyl-1-hydroxyethylidene-1,1-bisphosphonic acid)

3-pyridylacetic acid hydrochloride (100 gm, 0.576 moles) and phosphorous acid (103.97 gm, 1.267 moles) were taken in a four necked round bottom flask fitted on a water bath and stirred for ten minutes at ambient temperature (25°C to 30°C). The reaction mixture was heated to 60°C to 65°C and at this temperature phosphorous trichloride (198.12 gm, 1.44 moles) was added slowly in one hour to the reaction mixture. Then the reaction mixture was heated to 70°C to 75°C and maintained for 8 hours at the same temperature. Reaction mixture was cooled to 55°C and the unreacted phosphorous trichloride was distilled at 50°C to 55°C under vacuum. Water (725 ml) was added to the reaction mixture and heated at 90°C to 95°C for six hours. Reaction mass was cooled to ambient temperature (25°C to 30°C) and stirred for 2 hrs. Product is separated as crystalline solid, which was filtered, and dried at 43°C to 45°C under vacuum.

Yield : 130 gms (79.75%)
Purity (HPLC) : 99.83%

Example 2

Preparation of Risedronate sodium hemipentahydrate (3-pyridyl-1-hydroxyethylidene-1,1-bisphosphonic acid sodium hemipentahydrate)

3-pyridyl-1-hydroxyethylidene-1,1-bisphosphonic acid (130 gm) prepared in the example-1 was taken in a four necked round bottom flask and water (520 ml) was added to it. The mixture was stirred for ten minutes at ambient temperature (25°C to 30°C) and pH was adjusted to 6.7 with 40% aqueous sodium hydroxide (NaOH) to get a clear solution. Activated carbon (5 gm) was added to the solution and stirred for fifteen minutes. Filtered the carbon on filter aid bed and washed with water (10 ml). The clear filtrate was taken in a beaker and pH was adjusted to 4.6 with the addition of acetic acid. The product was formed as white crystalline solid on slow stirring for four hours at ambient temperature (25°C to 30°C). The product was filtered, washed with water (10 ml) and dried at 40-45°C to get pure Risedronate sodium hemipentahydrate (3-pyridyl-1-hydroxyethylidene-1,1-bisphosphonic acid sodium hemipentahydrate).

Yield : 130 gms (80.90%)
Purity (HPLC) : 99.93%
CLAIMS

1) A process for preparation of Risedronic acid (3-pyridyl-1-hydroxyethylidene-1,1-bisphosphonic acid) in absence of organic solvents:

a) mixing of 3-pyridylacetic acid and phosphorous acid,
b) heating the above mixture and phosphorous trichloride is added slowly,
c) heating the above mixture and maintained for 7 to 9 hours,
d) distillation of phosphorous trichloride under vacuum and followed by addition of water,
e) heating the reaction mixture,
f) cooling to ambient temperature and maintained for 2 hours to get the crystals of Risedronic acid (3-pyridyl-1-hydroxyethylidene-1,1-bisphosphonic acid) which are filtered and washed with water and dried to give pure crystalline Risedronic acid.

2) The process according to claim 1, the preferred heating temperatures in step (b) ranges from about 60°C to about 65°C and in step (c) ranges from about 70°C to about 75°C.

3) The process according to claim 1 in step (d) the distillation temperature ranges from about 50°C to about 60°C and in step (e) heating temperature ranges from 90°C to about 95°C for about 5 to 7 hours more specifically 6 hours.

4) A selective process for the preparation of Risedronate sodium hemipentahydrate (3-pyridyl-1-hydroxyethylidene-1,1-bisphosphonic acid sodium hemipentahydrate in the absence of organic solvents comprising the following steps:

a) mixing of 3-pyridylacetic acid and phosphorous acid,
b) heating the above mixture and phosphorous trichloride is added slowly,
c) heating the above mixture and maintained for 7 to 9 hours,
d) distillation of phosphorous trichloride under vacuum and followed by addition of water,
e) heating the reaction mixture,
f) cooling to ambient temperature and maintained for 2 hours to get the crystals of Risedronic acid (3-pyridyl-1-hydroxyethylidene-1,1-bisphosphonic acid) which are filtered and washed with water and dried to give pure crystalline Risedronic acid,
g) Risedronic acid formed in step (f) is added in to water followed by adjustment of...
the pH to 6.5 to 7 by addition of base,
h) carbon is added to the above clear solution, stirred and filtered,
i) pH of the filtrate is adjusted to 4.0 to 5.0 by using acid and stirred at ambient
temperature to give crystals of Risedronate sodium hemipentahydrate,
j) filtered the above formed crystals and washed with water and dried to get pure
Risedronate sodium hemipentahydrate (3- pyridyl-l-hydroxyethylidene-1,1-
bisphosphonic acid sodium hemipentahydrate).

5) The process according to claim 4, in step (b) the heating temperature ranges from
about 60°C to about 65°C and in step (c) the heating temperature ranges from about
70°C to about 75°C.

6) The process according to claim 4, in step (d) the distillation temperature ranges from
about 50°C to about 60°C, and in step (e) heating temperature ranges from about 90°C
to about 95°C for about 5 to 7 hours more specifically 6 hours.

7) The process according to claim 4, in step (g) base used is 40% NaOH and in step (i)
acid used is acetic acid.

8) A selective process for the preparation of Risedronate sodium hemipentahydrate
(3-pyridyl-l-hydroxyethylidene-1,1-bisphosphonic acid sodium hemipentahydrate) in
the absence of organic solvents comprising the steps of:

a) Risedronic acid is added to water at ambient temperature followed by adjustment
of the pH to get a clear solution by addition of a base,

b) carbon is added to the above clear solution, stirred and filtered,

c) pH of the filtrate is adjusted to 4.0 to 5.0 by using an acid and stirred for 4 hours at
ambient temperature to give Risedronate sodium hemipentahydrate. (3- pyridyl-l-
hydroxyethylidene-1,1-bisphosphonic acid sodium hemipentahydrate),

d) filter the above solution and washed with water and dried to get pure Risedronate
sodium hemipentahydrate.

9) The process according to claim 8, in step (a) base used is 40% NaOH and in step (c)
acid used is acetic acid.

10) Risedronate sodium hemipentahydrate (3-pyridyl-l-hydroxyethylidene-1,1-
bisphosphonic acid sodium hemipentahydrate) can be prepared by using any of the
processes disclosed in claim 4 and claim 8.
MISSING UPON TIME OF PUBLICATION
A CLASSIFICATION OF SUBJECT MATTER

IPC8: C07F 9/38 (2006.01)
According to International Patent Classification (IPC) or to both national classification and IPC

B FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC8: C07F

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

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