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(54) **Title:** A NOVEL ONE POT PROCESS FOR PREPARATION OF PANTOPRAZOLE SODIUM SESQUIHYDRATE

(57) **Abstract:** The present invention provides a novel one-pot process for preparation of Pantoprazole sodium sesquihydrate Form-I in the pure form without isolating the pantoprazole base.

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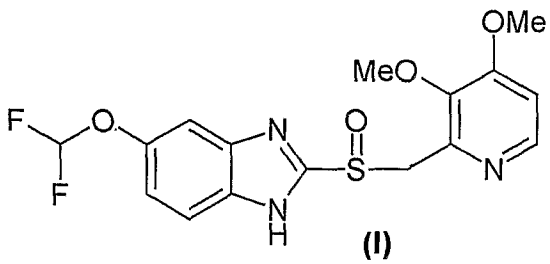
TITLE - A NOVEL ONE POT PROCESS FOR PREPARATION OF PANTOPRAZOLE SODIUM SESQUIHYDRATE

FIELD OF THE INVENTION

The present invention relates to a novel one pot process for the preparation of 5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole sodium salt, commonly known as pantoprazole sodium.

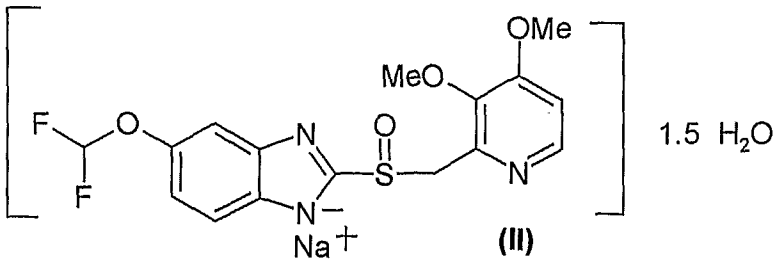
BACKGROUND OF THE INVENTION

5-(Difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole commonly known as pantoprazole having formula (I) is an oral, pharmaceutically active compound having outstanding anti-ulcer activity and belongs to the class of 2-[[(2-pyridinyl) methyl]sulfinyl]-1H-benzimidazoles. It is effectively used in the treatment of gastric ulcers, duodenal ulcers, gastroesophageal reflux disease (GERD), and Zollinger-Ellison Syndrome.



(I)

Pantoprazole is the active ingredient of a pharmaceutical product marketed in the United States by Wyeth-Ayerst Inc. under the brand name Protonix®. It contains a monosodium salt of pantoprazole (hereafter "pantoprazole sodium") in a sesquihydrate state of hydration, which is represented by the formula (II) and named as 5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole sodium salt sesquihydrate.



(II)

PRIOR ART

There are various prior art references, which are disclosing the synthesis of pantoprazole. US Patent No. 4,758,579 claims that pantoprazole and many other fluoroalkoxy substituted benzimidazoles are inhibitors of gastric acid secretion.

The '579 patent describes that the pantoprazole can be prepared by oxidation of 5-(difluoromethoxy)-2-(((3,4-dimethoxypyridine-2-yl)methyl)thio)-1*H*-benzimidazole during reaction with m-chloroperbenzoic acid in methylene chloride, yielding pantoprazole base. Further reaction with aqueous sodium hydroxide solution gives pantoprazole sodium, which is then purified by crystalisation from methanol. The drawback of the reaction is that oxidation is carried out with m-chlorobenzoic acid which is costly as well as forms benzoic acid as a byproduct. The crude pantoprazole is further purified by crystalisation, which adds one additional step as well as hampers the yield of the product. Moreover, the patent is silent about the state of hydration, purity and form of the pantoprazole sodium.

Bernhard Kohl et al. in article J.Med.Chem.1992, 35, 1049-57 describes a process for the preparation of pantoprazole sodium sesquihydrate by adding 6 N sodium hydroxide solution to a solution of pantoprazole in a 6:1 ethanol: methylene dichloride mixture at 20 ° C. After ten minutes, diisopropyl ether was added till the mixture became turbid. After stirring for next two hours, the precipitate is collected by filtration. It is washed with diisopropyl ether, and dried under vacuum at 40 ° C. Thus this process requires a large amount of solvent and anti solvent, which is not environment friendly.

WO 2004/056804 describes the preparation of pantoprazole sodium Sesquihydrate by forming a solution of pantoprazole and sodium hydroxide in a diluents selected from the group consisting of 2-propanol, tetrahydrofuran, acetonitrile, methanol, ethanol, water, mixtures of sec-butanol and methylene dichloride, and ethyl acetate, precipitating crystals of pantoprazole sodium sesquihydrate from the solution, and separating the crystals from the diluents. In this process pantoprazole sodium sesquihydrate is prepared from pantoprazole base, which is prepared separately. It also involves solvents and anti-solvents for the preparation, which increases the manufacturing cost.

US 2004 / 0186139 A1 describes a process for preparing crystalline Form-I of pantoprazole sodium sesquihydrate. Pantoprazole sodium sesquihydrate Form I is synthesized by dissolving pantoprazole free base in a sodium hydroxide solution, filtering the solution and adding an anti-solvent to isolate crystalline Form 1 of pantoprazole sodium sesquihydrate. The drawback of this process is that pantoprazole sodium sesquihydrate Form I is prepared from pantoprazole freebase and NaOH solution. Thus it involves more number of reaction steps as well as it is uneconomical and not environment friendly as it uses solvents and anti-solvents. More over the process does not mention the sulfone impurity.

An article, Organic Process Research & Development 2004, 8, 266-270, describes a single-pot process for the production of Pantoprazole substantially free from sulfone impurity. It involves four to five times separation of organic and aqueous layer and reprecipitation with acetonitrile to obtain the pantoprazole base with sulfone impurity 0.06%. Thus this process is lengthy as well as uneconomical. Moreover, It describes the synthesis of pantoprazole base only, and not of the sodium salt sesquihydrate Form-I.

It is evident that all the prior art process involves preparation, and isolation of pantoprazole base, as a first stage & the second stage is conversion of isolated, dried, pantoprazole base in to pantoprazole sodium salt, which are not economical for industrial scale synthesis due to number of reaction steps and number of reagents used by them. The isolation of pantoprazole sodium sesquihydrate is problematic while using high volume of solvents particularly ethanol. Most of the prior art process uses

crystalisation for purification, which reduces the yield of the pantoprazole sesquihydrate.

Thus there is a need of one pot method for the preparation of pantoprazole sodium sesquihydrate Form-I, of a very high purity, which is obtained without involving any purification step in turn increasing the yield of the product.

SUMMARY OF THE INVENTION

The present invention provides a novel one pot process for the preparation of pantoprazole sodium sesquihydrate Form I in pure form with high yield which involves less number of steps and no purification. Thus the objective is to make the process simple, cost effective and easily scalable.

The other aspect of the invention is to provide a process for the preparation of pantoprazole sodium sesquihydrate, which involves less number as well as less volume of solvents and no use of any anti-solvent. Thus the objective is to make the process environment friendly.

DESCRIPTION OF DRAWING:

FIG. 1 is characteristic X-ray powder diffraction pattern of crystalline Form-I of Pantoprazole sodium sesquihydrate prepared by the inventors. Vertical axis: Intensity (CPS), Horizontal axis; Two Theta (degrees).

The significant two-theta values obtained are 5.348, 7.407, 10.608, 11.522, 12.461, 13.106, and 13.370, 14.552, 15.324, 15.921, 16.184, 16.293, 16.669, 16.877, 17.631, 17.972, 18.478, 18.707, 20.074, 20.583, 21.012, 21.270, 21.602, 21.770, 22.254, 22.880, 23.025, 23.359, 24.105, 24.600, 25.031, 25.387, 25.543, 26.332, 26.749, 27.126, 27.421, 27.866, 28.814, 29.514, 29.729, 30.277, 30.944, 31.758, 32.674, 33.718, 34.235, 34.777, 37.626, 41.363, 43.560, 44.083, 45.502, 46.131

DETAIL DESCRIPTION OF THE INVENTION

The crystalline Form-I of Pantoprazole sodium sesquihydrate of the present invention is characterized by X-ray powder diffractogram, Differential Scanning Colorimetry thermogram and Infrared spectra.

The X-ray powder diffract gram of the crystalline Form-I of pantoprazole sodium sesquihydrate are measured on PANanalytical X'PERT-PRO MPD, with Cu K alpha-1 Radiation source (1.54060 A°),

The X-ray powder diffractogram of the crystalline Form-I of pantoprazole sodium sesquihydrate obtained in the present invention is substantially as depicted in FIG. (1)

The characteristic peaks (in 2-theta values) and their relative intensities (in percentage) of crystalline Form-I of pantoprazole sodium sesquihydrate, obtained in the present process are shown in the following Table (1)

TABLE 1

2 θ (°)	Intensity (%)
5.348	100.00
7.407	3.51
10.608	1.30
11.5227	3.18
12.461	1.31
13.106	5.22
13.370	5.39
14.552	6.34
15.324	1.43
15.921	2.61
16.184	4.09
16.293	1.91
16.669	7.69
16.877	7.86
17.631	5.26
17.972	3.07
18.478	1.96
18.707	1.67
20.074	8.82
20.583	18.03
21.012	3.57

21.270	5.00
21.602	4.56
21.77	3.68
22.254	16.47
22.880	7.26
23.025	7.06
23.359	5.42
24.105	6.87
24.600	8.95
25.031	6.12
25.387	6.78
25.543	5.51
26.332	8.61
26.749	6.88
27.126	7.97
27.421	8.32
27.866	9.52
28.814	6.20
29.514	6.51
29.729	5.40
30.277	2.72
30.944	3.02
31.758	50.40
32.674	6.06
33.718	6.27
34.235	3.65
34.777	4.59
37.626	6.21
41.363	2.09
43.560	2.14
44.083	3.04
45.502	22.29

The crystalline Form-I of pantoprazole sodium sesquihydrate of the present invention is also characterized by Differential scanning calorimetry. The Differential scanning calorimetry thermogram exhibits a significant endotherm peak at around 138 ° C.

The crystalline Form-I of pantoprazole sodium sesquihydrate of the present invention is further characterized by Infrared spectrum having significant IR bands around 453, 523.4, 554.9, 583.4, 643.8, 689.18, 710.17, 775.17, 815.3, 837.54, 937.9., 960.1, 985.10, 1041.61, 1072.77, 1089.10, 1119.85, 1170.11, 1276.84, 1305.35, 1362.28, 1376.51, 1427.64, 1465.25, 1491.59, 1589.62, 1653.61, 2072.26, 2602.48, 2846.49, 2997.29, 2942.43, 3186.64., 3364.43, 3487.61, 3552.27

According to this invention, the process for the preparation of pantoprazole sodium sesquihydrate Form I include:

a) condensation of 5-(difluoromethoxy)-2-mercapto-1H-benzimidazole and 2-chloromethyl-3, 4-dimethoxypyridine hydrochloride in a Sodium hydroxide solution and acetone to obtain 5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]thio-1H-benzimidazole;

b) in-situ oxidation of thus obtained 5-(difluoromethoxy)-2-[[(3, 4-dimethoxy-2-pyridinyl) methyl] thio-1H-benzimidazole to a sodium salt of 5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole in presence of sodium hypochlorite

c) the removal of impurities by slurring in dichloromethane, and isolating as a sesquihydrate.

The condensation of 5-(difluoromethoxy)-2-mercapto-1H-benzimidazole and 2-chloromethyl-3, 4-dimethoxypyridine hydrochloride in acetone and water is carried out in presence of sodium hydroxide solution at 20 to 25 °C. The progress of the reaction is monitored by TLC and if the 5-(difluoromethoxy)-2-mercapto-1H-benzimidazole is found unreacted, additional amount of 2-chloromethyl-3, 4-dimethoxypyridine hydrochloride is added again.

The oxidation of formed 5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]thio-1H-benzimidazole is carried out in 5.7% sodium hypochlorite solution diluted with equal volume of water by adding it over a period of three hrs. at 20 to 25 ° C. It is stirred for additional half an hour. The progress of the reaction is checked by TLC and if still incomplete, the required quantity of additional sodium

hypochlorite solution is added. The reaction is quenched with aqueous sodium thiosulphate solution, the solution is treated with activated carbon and filtered. After removal of acetone by distillation under vacuum, the reaction mass was cooled to 20 to 25 ° C.

Dichloromethane was added, and the reaction mass is stirred. Sodium chloride is added over a period of half an hour and the solid is precipitated. The stirring is continued for next half an hour and material is filtered off and dried at 30 ° C under vacuum for overnight. The powdered material slurried with dichloromethane and filtered, dried under vacuum at 40° C to obtain pantoprazole sodium sesquihydrate having HPLC purity 99.90% and sulphone impurity 0.07%.

The pantoprazole sodium sesquihydrate obtained as per the above mentioned process is observed as free flowing, non-solvated crystalline solid, which is well suited for pharmaceutical applications.

The one pot process of the present invention is simple, involves less number of stages, non-hazardous and well suited for commercial production.

Thus in brief, all the prior art processes describes the preparation of pantoprazole sodium sesquihydrate Form I by condensing the 5-(difluoromethoxy)-2-mercapto-1H-benzimidazole and 2-chloromethyl-3, 4-dimethoxypyridine hydrochloride to obtain 5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]thio-1H-benzimidazole which is oxidized and thus obtained pantoprazole sodium was converted to pantoprazole free base. The free base is converted to sodium salt. If required the sodium salt is purified and sesquihydrate is isolated. Although the sodium salt is formed after oxidation but nobody could isolate it rather they neutralize it to isolate freebase and again convert it to sodium salt. Thus increasing the process by one more additional step. But in our inventive process, we isolate the pure pantoprazole sodium sesquihydrate directly after in-situ oxidation without involving any purification.

The invention can be illustrated by the following example, which is for illustration purpose only and is not intended to limit the scope of the invention in any way.

EXAMPLE

In a two-litre flask, a solution of 24 g of sodium hydroxide in 150 ml of distilled water was charged and cooled to 20 to 25 °C. A solution of 5-(difluoromethoxy) -2-mercapto-1H-benzimidazole (50 g) in acetone (250 ml) was added to it and stirred for

half an hour. A solution of 2-chloromethyl-3, 4-dimethoxypyridine hydrochloride (56 g) in distilled water (150 ml) was added over a period of one hr while maintaining the temperature in the range of 23 to 25^0 C. It was stirred for next half an hour and progress of the reaction was monitored by TLC. If unreacted 5-(difluoromethoxy) -2-mercapto-1H-benzimidazole is still present, 0.50 g of 2-chloromethyl-3, 4-dimethoxypyridine hydrochloride was added, and stirring was continued for next half an hour. Aqueous Sodium hypochlorite solution (5.7%, 300 ml) diluted with equal volume of water was added to it over a period of three hrs. at 20 to 25 ° C and stirred for additional half an hour. The progress of the reaction was checked by TLC and if still incomplete, the required quantity of additional sodium hypochlorite solution was added. The reaction was quenched with aqueous solution of sodium thiosulphate (8 g of sodium thiosulphate dissolved in 25 ml of distilled water). It was stirred at RT for next half an hr. Reaction mass was filtered off on the Celite bed, the insoluble material were dissolved in 200 ml of acetone and filtered. The solution was treated with activated carbon, and filtered. Acetone was distilled off under vacuum and cooled to 25 ° C.

The reaction mass was stirred with 500 ml of dichloromethane. Sodium chloride (17 to 20 % of the volume of aqueous layer) was added over a period of half an hour and the solid was precipitated. The stirring was continued for next half an hour and material was filtered off and dried at 30 ° C for overnight. It was powdered and slurried with 400 ml of dichloromethane, followed by washing with 2X100 ml of dichloromethane and dried under vacuum at 40° C to obtain pantoprazole sodium sesquihydrate (65 g) having HPLC purity 99.90% and sulphone impurity 0.07%. The water content was 5.90% (measured by TGA). The characteristic X-ray powder diffraction pattern, and the significant two-theta values confirm that the obtained product is pantoprazole sodium sesquihydrate.

We claim:

1. A process for preparation of highly pure pantoprazole sodium sesquihydrate comprising:
   a) condensation of 5-(difluoromethoxy)-2-mercapto-1H-benzimidazole and 2-chloromethyl-3, 4-dimethoxypyridine hydrochloride in aqueous sodium hydroxide solution and acetone to obtain 5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]thio-1H-benzimidazole;
   b) the in-situ oxidation of obtained 5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]thio-1H-benzimidazole in presence of sodium hypochlorite to obtain a reaction mass
   c) terminating the oxidation, by adding aqueous solution of sodium thiosulphate
   d) removal of all the water miscible solvent under vacuum
   e) addition of chlorinated hydrocarbon solvent or ester solvent
   f) precipitation of sodium salt of 5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole by addition of sodium chloride
   g) filtration of the precipitated sodium salt
   h) further slurring of the precipitated sodium salt in chlorinated hydrocarbon solvent or ester solvent
   i) filtration of the slurry, followed by drying under vacuum at 25 to 30 ° C, to get pantoprazole sodium sesquihydrate.
2. A process as claimed in claim 1, wherein the condensation in (a) is carried out at a temperature between 0 to 35 ° C, preferably 25 to 30° C
3. A process as claimed in claim 1, wherein the water miscible solvent in (d) is selected from the group comprising of acetone, acetonitrile, dioxane, tetrahydrofuran, preferably acetone.
4. A process as claimed in claim 1, wherein the inert chlorinated hydrocarbon solvent in (e) and (h) is selected from the group consisting of dichloromethane, dichloroethane, chloroform, preferably dichloromethane &

the ester solvent is selected from the group consisting of ethyl acetate, methyl acetate, n-butyl acetate, tert. Butyl acetate etc., preferably ethyl acetate.