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GREEN APPROACH FOR LARGE SCALE PROCESS OF MESALAMINE: AN ANTI INFLAMMATORY AGENT

Neti Srinivasan and Jaydeepkumar Lilakar*
Dr.Reddys Laboratories Ltd., Integrated Product Development, Innovation Plaza, Bachupalli, Qutubullapur, R R District, 500072, A.P., India
*E-mail: jdlila@yahoo.co.in

ABSTRACT

Mesalamine **1** is as an anti inflammatory agent in treating ulcerative colitis and crohn's disease. Its benefit is believed to be due to a topical effect on the inflamed bowel. Mesalamine is approved for the induction of remission in patients with active, mild to moderate ulcerative colitis. The suppositories are limited to use in proctitis, the enemas to distal colitis (colitis involving only the part of the colon close to the rectum) or proctitis. The mechanism of action of mesalamine in the treatment of gastrointestinal disorders is thought to work as a topical anti-inflammatory agent through the inhibition of cyclooxygenase within the gastrointestinal tract and the subsequent decrease in production of prostaglandins. An ecofriendly, solvent free process for Mesalamine[1] suitable for large scale commercial production is described here.

Key words: Mesalamine and Green chemistry.

INTRODUCTION

Over the past few years, significant research has been directed towards the development of new technologies for environmentally benign (green chemistry)[2], which are both economically and technologically feasible[3]. An important area of green chemistry deals with solvent minimization.

Mesalamine is an amino derivative of salicylic acid and is thought to be the active component of azulfidine, a combination of a sulfa drug. The chemical name of Mesalamine is 5-amino-2-hydroxy benzoic acid. The exact way that Mesalamine works is to reduce the actions of a substance in the body that causes inflammation, tissue damage, and diarrhea. It is used to treat ulcerative colitis, proctitis, and proctosigmoiditis[4].

Several synthetic routes are reported in the literature[5-8] suffers from the draw backs like involves electrolytic reduction of 4-phenyl azo phenol at a current density 2 to 3A/dm^2 , proceeds through diazonium coupling between sulfanilic acid and salicylic acid followed by hydrogenation with hydrogen gas and catalyst end up with low purity. Nitration of salicylic acid resulting 2-hydroxy-5-nitro benzoic acid which associated with impurities, usage of carbon dioxide or containing the heavy metal reagents in the process. The major disadvantage of the reported processes is the poor yield of Active Pharmaceutical Ingredient (API) along with formation of unknown impurities, consists of several steps, electrolytic reductions, which makes the process less viable for commercial production and in producing the regulatory quality product.

5-amino-2-hydroxy benzoic acid is rather a simple compound but is difficult to prepare in high purity and better yields on large scale. To produce high quality final product in an economical manner, we then envisioned the potential route to **1**, which involves smooth operations.

EXPERIMENTAL

Solvents and reagents were purchased from commercial suppliers and were used without further purification. The ^{1}HNMR spectra were obtained in DMSO using a varian Gemini 200 MHz FT NMR spectrometer; the chemical shifts are reported in δ ppm relative to TMS. Mass spectrum (70 eV) were recorded on HP-5989A LCMS spectrometer.

Preparation of 2-Hydroxy-5-nitro benzoic acid 3

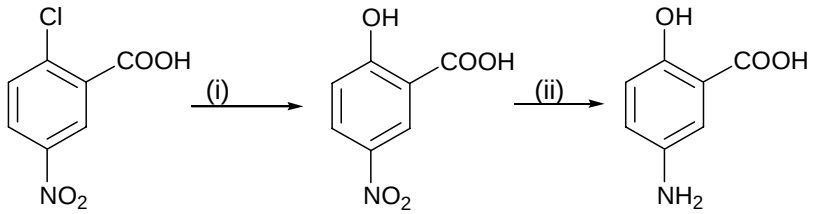
To a stirred solution of potassium hydroxide (70 kg, 1250 mol) and water (250 L) was added **2** (50 kg, 248 mol) over a period of 20 minutes between 25 and 30°C in an autoclave. The reaction mixture was heated to 125-130°C, stirred at the same temperature for 5 hours under 2.5 kg/cm^2 . The reaction mass was cooled to 25°C and acidified to pH 1.0-2.0 using hydrochloric acid (85 L), stirred for 1 hour. The precipitated solid was filtered and washed with water (150 L), and the cake was slurried in water (300 L) at 30°C for 1 hour, filtered, washed with water (150 L) and dried at 65°C for 10 hours to afford **3** 43.5 kg Yield: 43.5 kg (96 %) (Purity: 99.87 %)

^{1}H NMR (400 MHz, DMSO): δ 11.2 (s, 1H), 8.5 (m, 2H), 7.3 (s, 1H), 5.2 (s, 1H). MS *m/z* 183; Anal. Calcd. for $C_7H_5NO_5$

Preparation of 5-amino-2-hydroxy benzoic acid 1

Compound **3** (40 kg, 218 mol) was added slowly to a stirred mixture of water (320 L) and sodium carbonate (16.3 kg, 153 mol), stirred for 30 minutes and the mass pH maintained between 8.0 and 9.5. 10% Raney Nickel (8 L) along with water (80 L) was added to the above solution. The resultant mixture was hydrogenated at atmospheric pressure at 60°C for 6 hours. 5% sodium hydroxide (130 L) was added to the mass at 25°C, stirred for 30 minutes. The catalyst was filtered through celite, and washed with water (80 L). The solution was acidified to pH 2.5-3.0 with hydrochloric acid (33 L) and stirred for 1 hour. The obtained compound was filtered, washed with water (40L). To the solution of wet cake and water (560 L) and hydrochloric acid (41 L), active charcoal (2.8 kg) was added, and the contents were heated to 70°C, maintained at the same temperature for 2 hours. Filtered the total solution through celite, washed with water (28 L). Active charcoal (2.8 kg) was added to the filtrate, stirred at a temperature of 70°C for 2 hours, filtered through celite and washed with water (28 L). To the obtained filtrate, pH was adjusted to 3.0-3.5 with aq. sodium bicarbonate solution (15 L), stirred for 1 hour, filtered the solid and washed with water (42 L), dried the solid at 80°C for 9 hours to give the title compound **1** as a off white colored powder. Yield: 27.5 kg (82 %) (Purity: 99.9 %)

^{1}H NMR (400 MHz, DMSO): δ 11.0 (s, 1H), 7.2 (s, 2H), 6.4 (m, 2H), 5.0 (s, 1H), 3.8 (s, 1H), MS *m/z* 183; Anal. Calcd. for $C_7H_7NO_3$



2 **3** **1**

Reagents and conditions: (i) Aq. KOH, 125-130°C, 5 hrs (ii) 10 % Raney Ni, Na_2CO_3, H_2, 3.0-3.5 kg/cm2 , 60°C, 6 hrs

Scheme-1 : Proposed Synthetic scheme of Mesalamine

RESULTS AND DISCUSSION

Our approach (Scheme-6) started with 2-chloro-5-nitro benzoic acid, treated with aqueous potassium hydroxide to obtain the intermediate **3** in quantitative yield 96 %, followed by the reduction of nitro group with raney nickel in presence of aqueous sodium carbonate yielded **1** with 82 % yield and 99.9 % purity by HPLC.

In the preparation of **3** by increasing the temperature to 130°C in a closed system (autoclave), inbuilt pressure around 2.5 kg/cm^2 has been developed; which favored the reaction smoothly in 5 hours and shortened the reaction time cycle. Reduction also carried out in water medium at basic condition under 2.5 kg/cm^2 pressure. pH played a vital role during the reaction and identified that 8.0-9.5 range is more

suitable for the reduction. Further product was isolated at the optimum pH followed by water slurry makes the process is more economical, solvent free, quantitative yields, large scale process and more suitable for the regulatory quality process.

CONCLUSION

We have provided an industrially viable and scalable manufacturing process for Mesalamine meeting the regulatory norms in terms of quality.

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