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An Improved Process for the Production of Rabeprazole Sodium Substantially Free from the Impurities§

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Abstract:

The present work details the journey towards development of a simple and cost-viable process for large-scale synthesis of rabeprazole sodium substantially free from the impurities. The detailed study of different parameters affecting the quality and yield percentage of the compound has been presented. Yield is increased from 40% (reported process) to 75% with the improved process at sulfoxidation stage.

Introduction

Rabeprazole sodium, 2-{[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]methyl]sulfinyl}-1*H*-benzimidazole sodium (**1**) is a proton pump inhibitor, inhibits the action of H^+-K^+ ATPase in parietal cells,[1−5] and is used for the prevention and treatment of gastric acid related diseases. It has also demonstrated efficacy in healing and symptom relief of gastric and duodenal ulcers and has shown a high eradication rate of the microorganism, *Helicobacter pylori* when associated with antimicrobial therapy.[6,7]

Literature studies reveal different methods[8−11] for the preparation of rabeprazole sodium (**1**). The general method for the preparation of **1** involved condensation[8] of thiol derivative **2** with chloromethyl pyridine derivative **3** in the presence of an inorganic base. Oxidation of the resulting sulfide derivative **4**, with a suitable oxidizing agent to furnish rabeprazole **1a**, is followed by the preparation of rabeprazole sodium **1** as shown in the Scheme 1.

Results and Discussion

The most important and critical step in this process is the oxidation, which suffers from certain disadvantages such as use of a high volume of chloroform, low yield, and number of purifications involved. Further, there is a possibility of forming two major impurities,[12,13] namely, rabeprazole sulfone **5** and rabeprazole *N*-oxide **6** due to the over-oxidation of rabeprazole **1a**. The *N*-oxide impurity **6** was observed in the range of 0.02−0.05% in the lab experimental studies, while sulfone impurity **5** was seen as major impurity. Due to structural similarity of sulfone **5** with the parent compound, its complete removal proved to be problematic.

Reported procedures did not give any better results when experiments were conducted with various oxidizing agents[9] such as peracids, peresters, peroxides, and tertiary butylhydroperoxide[10] with $VO(acac)_4$.

The traditional approach[11] involved oxidation of the sulfide derivative **4** with *m*-chloroperoxybenzoic acid (*m*-CPBA) in chloroform. Adjustment of pH and extraction of the product **1a** into chloroform and dilution with methyl *tertiary* butyl ether (MTBE) at low temperature gave fine crystals of **1a**. Crude **1a** was purified in aqueous basic methanol at pH 8.5−9.0. The drawback of this process is that the reaction has to be conducted using 0.8 equiv of *m*-CPBA, which led to only 60% reaction completion and consequently poor yield (40%). When the reaction was conducted with 1.0 equiv of *m*-CPBA, sulfone **5** was formed at levels of up to 2%. All these reported processes produced sulfone **5** more, and another major drawback in many of the previous processes is the usage of heavy metal reagents such as vanadium, which were proved to be difficult to remove.

Sodium hypochlorite was found to be a better reagent[8,14] for oxidation of **1a** in the presence of alkaline basic medium where the sulfone impurity **5** was present at less than 0.20% and two unknown impurities were observed in the range of

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(1) Morri, M.; Takeguchi, N. *J. Biol. Chem.* **1993**, *268*, 21553–21559.
(2) Nakai, H.; Shimamura, Y.; Kanazawa, T.; Yasuda, S.; Kayano, M. *J. Chromatogr., Sect. B* **1994**, *660*, 211–220.
(3) Fujisaki, H.; Shibata, H.; Oketani, K.; Murakami, M.; Fujimoto, M.; Wakabayashi, T.; Yamatsu, I.; Yamaguchi, M.; Sakai, H.; Takeguchi, N. *Biochem. Pharmacol.* **1991**, *42*, 321–328.
(4) Takeguchi, N.; Yamanouchi, T.; Sakai, H.; Mora, M. *Jpn. J. Physiol.* **1992**, *42*, 75–88.
(5) Carswel, C. I.; Goa, K. L. *Drugs* **2001**, *61*, 2327–2356.
(6) Barth, J.; Hahne, W. *Aliment. Pharmacol. Ther.* **2002**, *16*, 31–33.
(7) Garcia, C. V.; Nudelman, N. S.; Steppe, M.; Schapoval, E. E. S. *J. Pharm. Biomed. Anal.* **2008**, *46*, 88–93.
(8) Souda, S.; Ueda, N.; Miyazawa, S.; Tagami, K.; Nomoto, S.; Okita, M.; Shimomura, N.; Kaneko, T.; Fujimoto, M.; Murakami, M.; Oketani, K.; Fujisaki, H.; Shibata, H.; Wakabayashi, T. U.S. Patent 5,045,552, 1991.
(9) Moormann, A. E.; Becker, D. P.; Flynn, D. L.; Li, H.; Villamil, C. I. Method of Using (H^+/K^+)ATPase Inhibitors as Antiviral Agents. U.S. Patent 5,945,425, 1999.
(10) Ilya, A.; Marioara, M. Process for the Production of Substituted 2-(2-Pyridylmethyl)sulfinyl-1*H*-benzimidazoles. U.S. Patent 2003/0036554A1, 2003.
(11) Broeckx, R.; Laurent, M.; De Smaele, D.; Leurs, S.; Marcel, H. Improved Process for Preparing Benzimidazole Type Compounds. WO Patent 03/008406A1, 2002.
(12) Pingili, R. R.; Jambula, M. R.; Ganta, M. R.; Ghanta, M. R.; Sajja, E.; Sundaram, V.; Boluggdu, V. B. *Pharmazie* **2005**, *60*, 814–818.
(13) (a) Ganta, M. R.; Boluggodu, V. B.; Padi, P. R.; Sudhakar, P.; Moses Babu, J.; Vyas, K.; Pingili, R. R.; Mukkanti, K. *J. Pharm. Biomed. Anal.* **2007**, *43*, 1262–1269. (b) Ganta, M. R.; Mukkanti, K.; Boluggodu, V. B.; Padi, P. R. *Synth. Commun.* **2009**, *39*, 278–290.
(14) Pathi, S. L.; Kankan, R. N.; Rao, D. R. New Process for the Synthesis of Proton Pump Inhibitors. WO Patent WO 2006/117802 A2, 2006.

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Scheme 1. **Scheme for the preparation of 1**

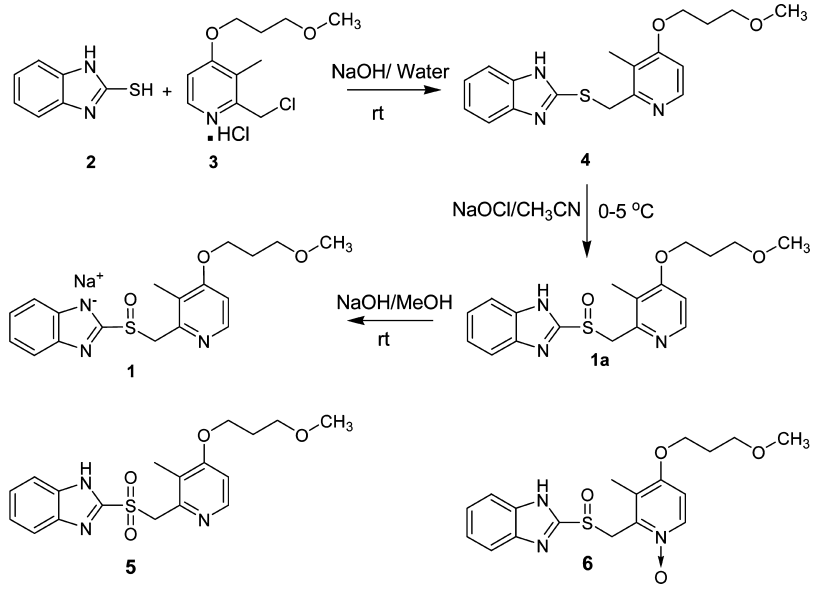

Table 1. **Effect of mole equivalents of sodium hypochlorite on quality**

				purity by HPLC		
entry	NaOCl (equiv)	sulfide (**4**) (equiv)	*T* (°C)[a]	purity (**1a**)[b] (%)	sulfide (**4**) (%)	sulfone (**5**) (%)
1	0.9	1.0	0−5	97.94	0.30	0.02
2	1.0	1.0	0−5	99.12	0.18	0.03
3	1.1	1.0	0−5	99.73	0.03	0.05
4	1.3	1.0	0−5	99.55	0.03	0.20

[a] Temperature of reaction mass. [b] Rabeprazole.

0.02−0.9%. Purification in ethyl acetate subsequent to oxidation and isolation of rabeprazole **1a** as rabeprazole sodium **1** helped in removing the sulfone impurity **5** and unknown impurities. Cost effectiveness as well as greenness of the process (sodium chloride is the byproduct) made this sodium hypochlorite-mediated oxidation an attractive alternative.

No other relevant references disclosed rabeprazole sodium **1** with sulfone impurity **5** at a level of less than 0.10% and all other unknown impurities at less than 0.10%, which is an essential criterion of a bulk drug substance. Hence, there is a call for development of an efficient, impurity-free, cost-viable, robust, and plant-friendly process for the preparation of rabeprazole sodium **1**. The optimization of various parameters involved in the oxidation step resulted in a dramatic improvement in the purity and yield of **1a** when using sodium hypochlorite as the oxidizing agent. Various parameters such as mole equivalents of the sodium hypochlorite, temperature of the reaction, workup conditions, and purification process were studied thoroughly. The details of the optimization and various parameters are discussed below in this article.

During the process optimization, we paid great attention to optimize the equivalents of NaOCl. When we use 0.9 and 1.0 equiv of NaOCl, reaction did not complete; 1.1 equiv of the sodium hypochlorite was found to be the most ideal for getting the required compound **1a** with high purity and good yield (Table 1). The results of the experiments are depicted in the form of a graph (Figure 1).

After the optimization of mole equivalents of sodium hypochlorite, the next task was to study the effect of temperature on the reaction. It was found that the temperature at which the reaction was carried out also proved to be a very important factor in controlling the levels of sulfone impurity **5**. The percentage of sulfone **5** was found to be increasing with reaction temperature (Table 2). The reaction proceeded very well at lower temperatures, as low as 0−5 °C, and this minimized the formation of sulfone **5**. Thus, oxidation carried out at temperatures of 0−5 °C produced a compound with minimal levels of sulfone **5** (entry 1, Table 2).

To control further the sulfone **5** and other unknown impurities in the active pharmaceutical ingredient (API), the following workup process was developed. The workup process involved quenching the reaction mass with a solution of sodium thiosulfate, so that unreacted sodium hypochlorite was quenched completely. If the reaction mass was not quenched with hypo solution, then the impurity **5** was enhanced up to 0.27% (entries

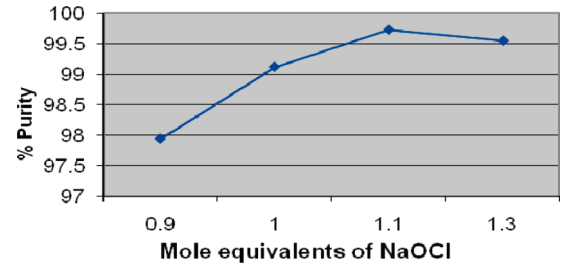

Figure 1. **Effect of mole equiv of NaOCl on % of purity.**

Table 2. **Effect of temperature on purity of rabeprazole**

				purity by HPLC	
entry	*T* (°C)[a]	NaOCl (equiv)	sulfide (**5**) (equiv)	purity (**1a**)[b] (%)	sulfone (**5**) (%)
1	0−5	1.1	1.0	99.69	0.05
2	10−15	1.1	1.0	99.61	0.11
3	25−30	1.1	1.0	99.30	0.29

[a] Temperature of reaction mass. [b] Rabeprazole.

Table 3. **Effect of the sodium thiosulphate solution on formation of impurity 5**

				purity by HPLC	
entry	T (°C)[a]	NaOCl (equiv)	10% of hypo solution	purity (**1a**)[b] (%)	sulfone (**5**) (%)
1	0−5	1.1	used	99.56	0.05
2	0−5	1.1	used	99.69	0.06
3	0−5	1.1	not used	99.36	0.25
4	0−5	1.1	not used	99.25	0.27

[a] Temperature of reaction mass. [b] Rabeprazole.

Table 4. **Effect of isolation in mixture of DCM and MTBE on yield**

					purity by HPLC	
entry	batch size (kg)	T (°C)[a]	NaOCl (equiv)	yield (%)	purity (**1a**)[b] (%)	sulfone (**5**) (%)
1	0.050	0−5	1.1	63	99.61	0.04
2	5.0	0−5	1.1	50	99.71	0.03
3	5.0	0−5	1.1	46	99.73	0.04

[a] Temperature of reaction mass. [b] Rabeprazole.

3 and 4, Table 3) during the workup process, and the results are tabulated in Table 3.

Initially, one process was developed using DCM for extraction and MTBE as an antisolvent for isolating the compound. When three batches were executed with the same process in the pilot plant, what we observed is inconsistency in the yield (varied from 46−63%). An alternative process was developed to get consistency in the yield using water and acetonitrile. The results are tabulated in Table 4.

An alternative workup process involves, after completion of the reaction (monitored by thin layer chromatography), adjustment of the pH to 8.0−8.5 using acetic acid, and then compound **1a** was isolated from the mixture of acetonitrile and water (3:10) at temperature 0−5 °C. The purity was 98%, and two unknown impurities were observed with this process at 1.7 relative retention time (RRT) (ranges from 0.02−0.30%) and 5.0 RRT (ranges from 0.60−0.80%). Therefore, a purification process was developed in ethyl acetate to remove these two unknown impurities, but the yield loss was 70−90% (entries 1 and 2, Table 5) due to the solubility of compound **1a** in ethyl acetate in the presence of water when the compound **1a** was purified without drying the crude material. Once compound **1a** is filtered, it should be dried thoroughly because it contains 30−40% of water content. Thus, the drying process has to be efficient to remove the entrained water. Hence, a study was carried out to decrease the water content of compound **1a**. Water content and purity of the compounds were obtained at regular intervals, and the results are tabulated in Table 5.

In order to identify the suitable solvent for purification, we have tried in various ICH class three solvents and chosen ethyl acetate. With this purification in ethyl acetate, impurities at RRT 1.7 and RRT 5.0 in compound **1a** were come down to 0.10% and 0.24%, respectively. These two unknown impurities were further washed out in the next step of sodium salt formation to less than 0.05%. The results are tabulated in Tables 6 and 7.

When we executed one 25 kg batch in pilot plant, sulfone **5** and other two unknown impurities were observed at the level of 0.2%. but these impurities were reduced to less than 0.1% after converting to sodium salt (**1**). The results are tabulated in Table 7.

Table 5. **Effect of drying before purification in ethyl acetate**

					purity by HPLC after purification in ethyl acetate			
entry	experiment	T (°C)[a]	water content (%)	yield (%)	purity (**1a**)[b] (%)	sulfone (**5**) (%)	U imp[c] (%)	U imp[d] (%)
1	without drying	−	31	29.6	99.76	0.07	0.01	ND[e]
2	without drying	−	42	13.1	99.64	0.17	0.02	0.04
3	with drying	45	0.3	87.9	99.56	0.05	0.009	0.06
4	with drying	45	3.0	86	99.47	0.02	0.01	ND

[a] Temperature of drying. [b] Rabeprazole. [c] Unknown impurity at RRT 1.7. [d] Unknown impurity at RRT 5.0. [e] Not detected.

Table 6. **Effect of purification in ethyl acetate to eradicate unknown impurities at RRT 1.7 and RRT 5.0**

	purity by HPLC before purification (**1a**)				purity by HPLC after purification (**1a**)			
entry	purity (**1a**)[a] (%)	sulfone (**5**) (%)	U imp[b] (%)	U imp[c] (%)	purity (**1a**)[a] (%)	sulfone (**5**) (%)	U imp[b] (%)	U imp[c] (%)
1	98.21	0.05	0.24	0.70	99.49	0.05	0.10	0.03
2	98.57	0.07	0.09	0.72	99.56	0.07	0.03	0.03
3	98.29	0.08	0.14	0.67	99.28	0.08	0.10	0.13

[a] Rabeprazole. [b] Unknown impurity at RRT 1.7. [c] Unknown impurity at RRT 5.0.

Table 7. **U imp[c] Comparison of quality between rabeprazole base and rabeprazole sodium after execution in pilot plant**

	quality of rabeprazole base (**1a**)					quality of rabeprazole sodium (**1**)				
entry	batch size (kg)	purity (**1a**)[a] (%)	sulfone (**5**) (%)	U imp[b] (%)	U imp[c] (%)	batch size (kg)	purity (**1**)[d] (%)	sulfone (**5**) (%)	U imp[b] (%)	U imp[c] (%)
1	25	99.51	0.20	0.05	0.03	40	99.84	0.06	0.03	0.02
2	25	99.28	0.12	0.06	0.15	40	99.79	0.07	0.05	0.02
3	25	99.14	0.06	0.10	0.24	40	99.77	0.08	0.03	0.02

[a] Rabeprazole. [b] Unknown impurity at RRT 1.7. [c] Unknown impurity at RRT 5.0. [d] Rabeprazole sodium.

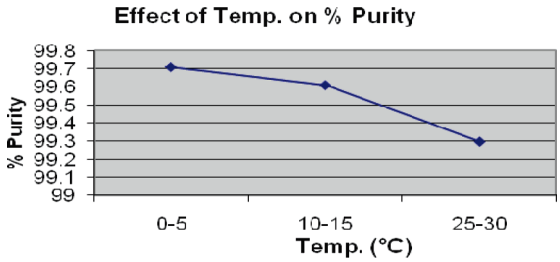

Figure 2. **Effect of temperature on purity %.**

Conclusion

In conclusion we have developed an efficient and plant-friendly process by improving the original process for the preparation of **1** substantially free from sulfone impurity **5** and all other unknown impurities. The oxidizing reagent, *m*-CPBA, was replaced by NaOCl, and we have examined various possibilities to reduce the identified/unidentified impurities and optimized several parameters such as temperature, usage of sodium thiosulphate for quenching the reaction mass, and amount of oxidant. The purification process in ethyl acetate was developed, and this process ensures the production of rabeprazole sodium **1** with sulfone **5** less than 0.10% and all other impurities less than 0.05%. This improved process was implemented at the commercial scale with 25 kg batch size of rabeprazole **1a** and 40 kg batch size of rabeprazole sodium **1**.

Experimental Section

Rabeprazole sodium and its impurities were analyzed (Agilent with empower software, 1100 series, G1312A Binary pump, G1314A variable wavelength detector, Waldbronn, Germany) with an Inertsil ODS-3 V column, 250 mm × 4.6 mm, 5 μm (GL Sciences Inc., Japan), with mobile phase A consisting of 0.01 M KH_2PO_4, with the pH adjusted to 6.0 with diluted potassium hydroxide and acetonitrile in the ratio of 65:35, mobile phase B consisting of acetonitrile and water in the ratio of 90:10 with a flow rate of 1.0 mL/min, and UV detection at 280 nm was used with a timed gradient program. This LC method was able to detect all these impurities. The solvents and reagents were used without further purification.

2-[[[4-(3-Methoxypropoxy)-3-methyl-2-pyridinyl]methyl]-sulfinyl]-1*H*-benzimidazole (1a). To a solution of sodium hydroxide (7.5 kg, 187.5 mol) in water (30 L) and acetonitrile (75 L) was added compound **4** (25 kg, 72.8 mol) at 25−30 °C. The contents were cooled to 0 °C, and sodium hypochlorite (47.5 L, 79.3 mol, assay 12.45%) was added at 0−5 °C for 1 h, and the reaction mass was stirred for 45 min. After completion of the reaction (*vide* TLC) the reaction mixture was quenched with a solution of sodium thiosulfate (10 kg in 212.5 L of water). The resulting mixture was cooled to 0 °C, and the pH of the solution was adjusted to 8.3 with acetic acid. The precipitated solid was stirred at 0−5 °C for 2 h, filtered, and washed with water (25 L) followed by drying under suction. The wet solid was dried in a vacuum oven at 40−45 °C to get the moisture content less than 5%. The dried solid was purified in ethyl acetate (125 L) to give a cream-colored powder **1a**: yield 19 kg (72%).

Purification. Compound (**1a**, 19 kg) was added into ethyl acetate (95 L) and then stirred at 25−30 °C for 1 h. The heterogeneous solution was cooled to 5 °C and stirred for 45 min. The solid was filtered at 0−5 °C, and the solid was dried in a vacuum oven (550 mm/Hg) for 5 h at 45−50 °C to yield **1a**. Yield 17.05 kg (90%).

2-[[[4-(3-Methoxypropoxy)-3-methyl-2-pyridinyl]methyl]-sulfinyl]-1*H*-benzimidazole Sodium (1). To a solution of sodium hydroxide (4.673 kg, 116.85 mol) in methanol (80 L) was added compound **1a** (40 kg, 111.42 mol), and the mixture was stirred for 1 h. The reaction mass was filtered through hyflow to remove particulates; the resulting filtrate was concentrated to dryness. *n*-Butanol (20 L) and MTBE (400 L) were added to the crude product, and the contents were stirred at 25−30 °C for 5 h. The precipitated solid was stirred at 0−5 °C for 1 h, filtered, and washed with MTBE (80 L). The solid was dried at 85 °C under vacuum to yield **1**. Yield 40.32 kg (95%). NMR, mass, IR of the compounds **1a** and **1** are matching with the reported values.[8]

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