Environmental Benign and Facile Process for the Synthesis of Pantoprazole Sodium Sesquihydrate: Phase Transformation of Pantoprazole Sodium Heterosolvate to Pantoprazole Sodium Sesquihydrate

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§Supporting Information

ABSTRACT: A cost-effective, scalable, and environmentally benign process is herein reported for the synthesis of pantoprazole sodium sesquihydrate: 5-(difluoromethoxy)-2-[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole. It is a proton pump inhibitor used to treat ulcers, gastroesophageal reflux disorder, erosive esophagitis, and Zollinger–Ellison syndrome. Pantoprazole sodium (1) was disclosed for the first time in European patent application EP0166287. The process comprised the condensation of 5-difluoromethoxy-2-mercaptobenzimidazole (2) with 2-chloromethyl-3,4-dimethoxypyridinium hydrochloride (3) to get the sulfide intermediate (4), which is oxidized with m-chloroperbenzoic acid (MCPBA) in dichloromethane, yielding pantoprazole. The main disadvantages are the formation of sulfone impurity (6), which is difficult to remove, use of costly reagent (MCPBA), and the generation of m-chlorobenzoic acid as a byproduct during the reaction, which affects the purity of the product. Several other oxidizing agents, namely, tert-BuOCl, tert-butylhydroperoxide, oxone, H₂O₂, Na₂CO₃, NaOH, 4H₂O, NaNBO₃, 1.5H₂O, CH₃CO₂H, H₂SO₄, N-chlorosuccinimide, and C₆H₅OCl, are well reported for the preparation of pantoprazole from its corresponding sulfide intermediate by oxidation. However, the major drawbacks of these methods are the formation of oxidative impurities, high cost, difficulty in scale-up, longer reaction time (1–2 days), and low yields, as well as use of expensive transition-metal catalysts, such as sodium tungstate, ammonium molybdate, and VO(acac). A key step in the synthesis of this largest-selling drug is the oxidation of sulfide (4) to the corresponding sulfoxide (5). A critical issue is to avoid unwanted further oxidation (over-oxidation) of the sulfoxide (5) to the corresponding sulfone derivative (6) and the formation of pantoprazole N-oxide (7). Due to the structural similarity of sulfoxide and sulfone, the removal of the sulfone impurity is very difficult, and even the application of high-performance liquid chromatography (HPLC) at an industrial scale has been mentioned, which is an expensive procedure. Different approaches, as well as their combinations, have been described to prevent overoxidation of 5: application of different, sometimes for industrial use, and even somewhat extraordinary oxidizing agents, working with diluted oxidizing agents, working at low, sometimes even extremely low, temperatures, optimization of molar ratio of the sulfide oxidizing agent, and use of mild oxidizing agents, such as magnesium monoperoxyphthalate. All of these oxidation process modifications are indirect in their approach.

1. INTRODUCTION

Pantoprazole is the active ingredient of a pharmaceutical product that is marketed as sodium salt in the United States by Wyeth Pharmaceuticals Inc. and sold under the brand name Protonix. Pantoprazole is chemically known as 5-(difluoromethoxy)-2-[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole. It is a proton pump inhibitor used to treat ulcers, gastroesophageal reflux disorder, erosive esophagitis, and Zollinger–Ellison syndrome. Pantoprazole sodium (1) was disclosed for the first time in European patent application EP0166287. The process comprised the condensation of 5-difluoromethoxy-2-mercaptobenzimidazole (2) with 2-chloromethyl-3,4-dimethoxypyridinium hydrochloride (3) to get the sulfide intermediate (4), which is oxidized with m-chloroperbenzoic acid (MCPBA) in dichloromethane, yielding pantoprazole. The main disadvantages are the formation of sulfone impurity (6), which is difficult to remove, use of costly reagent (MCPBA), and the generation of m-chlorobenzoic acid as a byproduct during the reaction, which affects the purity of the product. Several other oxidizing agents, namely, tert-BuOCl, tert-butylhydroperoxide, oxone, H₂O₂, Na₂CO₃, NaOH, 4H₂O, NaNBO₃, 1.5H₂O, CH₃CO₂H, H₂SO₄, N-chlorosuccinimide, and C₆H₅OCl, are well reported for the preparation of pantoprazole from its corresponding sulfide intermediate by oxidation. However, the major drawbacks of these methods are the formation of oxidative impurities, high cost, difficulty in scale-up, longer reaction time (1–2 days), and low yields, as well as use of expensive transition-metal catalysts, such as sodium tungstate, ammonium molybdate, and VO(acac). A key step in the synthesis of this largest-selling drug is the oxidation of sulfide (4) to the corresponding sulfoxide (5). A critical issue is to avoid unwanted further oxidation (over-oxidation) of the sulfoxide (5) to the corresponding sulfone derivative (6) and the formation of pantoprazole N-oxide (7). Due to the structural similarity of sulfoxide and sulfone, the removal of the sulfone impurity is very difficult, and even the application of high-performance liquid chromatography (HPLC) at an industrial scale has been mentioned, which is an expensive procedure. Different approaches, as well as their combinations, have been described to prevent overoxidation of 5: application of different, sometimes for industrial use, and even somewhat extraordinary oxidizing agents, working with diluted oxidizing agents, working at low, sometimes even extremely low, temperatures, optimization of molar ratio of the sulfide oxidizing agent, and use of mild oxidizing agents, such as magnesium monoperoxyphthalate. All of these oxidation process modifications are indirect in their approach.
and mostly result in complicated isolated procedures and reaction conditions that are noncompetitive at industrial scale. Attempts to scale up some of the laboratory procedures reported in the literature showed very poor reproducibility and scalability. Therefore, the prior art teaches that the reaction can only be controlled by taking extreme care to find the precise reaction conditions and by repeating the process many times to validate the ideal conditions. This makes the reaction extremely inflexible in terms of transferring the process to new facilities or scaling up the production capacity by moving the process to larger reactors.

Sodium hypochlorite (NaOCl) has attracted much interest in the synthesis of pantoprazole owing to its potential to control the sulfone impurity. Sodium hypochlorite is a commercially available, nonhazardous, and inexpensive reagent, which is easy and safe to handle, and its use in an industrial scale requires neither specific reactors nor safety devices and procedures. Besides, NaOCl and its byproduct are less polluting and allow to easily recover the resulting pantoprazole in highly pure form, without the need for cumbersome and costly purification processes. Furthermore, it has been found that the use of NaOCl as an oxidizing agent allows to predict and control the kinetics of the oxidation reaction, thereby avoiding the formation of byproducts with different oxidation degrees, such as N-oxides and/or sulfonyl (−SO2−) derivatives and/or dangerous accumulations of oxidizer. In contrast, such accumulations take place with other known oxidizing agents, for example, with peracetic acid, H2O2, or acetic acid aqueous solution, which contains about 15% of active oxygen. Therefore, the oxidation reaction can be easily carried out by using NaOCl on a large scale without particular hazards. Bajic et al. reported the use of 16.9% sodium hypochlorite solution (active chlorine assay) for oxidation; however, the commercial availability of higher assay NaOCl is limited, which makes the process less attractive. They have also reported process improvement to avoid overoxidation impurities, which involves

Table 1. Comparison of the Results of Present Reagent System (NaOCl/NaOH/H2O) with the Literature Precedents of Some Recently Published Oxidative Systems for the Conversion of 4 to 5 in the Synthesis of Pantoprazole

| entry | reagent system | solvent | temp (°C) | time (h) | yield (%) | HPLC purity (%) |
|-------|----------------|---------|-----------|----------|-----------|-----------------|
| 1     | H2O2/Na2WO4·2H2O | MeOH    | 25−30     | 1        | 85a       | >95             |
| 2     | tert-BHP/VO(acac)2 | EtOH    | 16−17     | 3        | 79a       | 98.1            |
| 3     | oxone/NaHCO3 | aq. MeOH | −2 to 0   | 5.5      | 98.1      | 98.1            |
| 4     | Na2CO3·1.5H2O2/(NH4)2MoO4 | MeOH/DCM | 5        | 4        | 88a       | 99.71           |
| 5     | e-phthalimidoperhexanoic acid (70%) | IPA     | 25       | 1−2 days | 84.4a     | 99.98           |
| 6     | peracetic acid | DCM     | −10 to −5 | 2.5      | 86a       | 99.98           |
| 7     | NCS/NaOH | MeCN    | 25−30     | 2        | 86a       | 99.98           |
| 8     | H2O2/Na2CO3/(NH4)2MoO4 | MeOH     | 0−5      | 1−2 days | 83.5a     | 99.98           |
| 9     | tert-ButOCl/NaOH | IPA     | 0−5      | 1        | 68a       | 99.98           |
| 10    | peracetic acid/NaHCO3 | DCM/IPA | 0−5      | 3        | 85a       | 99.98           |
| 11    | NaOCl/NaOH | DCM     | 5−8      | 6        | 79.6b     | 99.5            |
| 12    | NaOCl/NaOH | EtOAc/MTBE | −10 to 25 | 3        | 71b       | 99.98           |
| 13    | NaOCl/NaOH | DCM     | −20 to −5 | 4        | 78b       | 99.98           |
| 14    | NaOCl/NaOHF | water   | 0−5      | 3        | 85b       | 99.98           |

aIsolated yields of pantoprazole free base (5). bIsolated yields of pantoprazole sodium sesquihydrate (1). cConditions: pantoprazole sulfoxide wet cake (in situ; corresponds to benzimidazole (2), 1 equiv); NaOH (1.5 equiv); NaOCl (1.05 equiv, 9%); water (5 vol); temp (0−5 °C); time (3 h).
controlling the molar ratio of oxidizing agent versus sulfide intermediate by providing an initial inadequate amount of oxidizing agent into the process and adding further appropriate amount(s) of oxidizing agent sufficient to substantially complete the reaction but inefficient to produce any over-oxidation impurities. However, such techniques are tedious and cumbersome from commercial point of view.

In the present work, we have found that by the use of sodium hypochlorite, the oxidation of 4 to 5 is readily achievable, giving a reproducible and easily scalable process having sulfone impurity and sulfide below quantification limits by HPLC. The concentration of sulfide impurity is not critical for the final quality of the product because it can be efficiently removed as it has no inclination toward sodium salt formation. The present process produces the pantoprazole containing not more than 0.2% (w/w by HPLC) of total impurities.

Compared to the reported procedures, our main aims were to develop a green, cost-effective, scalable, and economic process to conduct the mass production of pantoprazole in a more concentrated fashion to increase throughput and minimize cost and waste. Although we are mindful of the diversity of methods available for the oxidation of sulfide to sulfoxide, in the present work, we have explored the conditions for the industrial synthesis of pantoprazole taking into account all of the aforesaid literature reports and reported, for the first time, the alkylation and oxidation reactions in aqueous reaction media, the key steps involved in the synthesis of pantoprazole (Scheme 1). A comparison of the results of present reagent system (NaOCl/NaOH/H2O) with the literature precedents of some recently published oxidative systems for the conversion of 4 to 5 in the synthesis of pantoprazole is reported in Table 1, which clearly indicates the advantages of the present system over existing methods.

2. RESULTS AND DISCUSSION

Herein, we described an improved, one-pot approach for the synthesis of pantoprazole free base as per the standards of European Pharmacopoeia. The present process involves the coupling of the key starting materials 2 and 3 in water using NaOH to yield pantoprazole sulfoxide (4) as a solid in the reaction mass. The obtained sulfoxide (4) is then subjected to oxidation in water using NaOCl as an oxidizing agent under organic-solvent-free conditions. The oxidant is added slowly to the alkaline aqueous solution of 4 over a period of 2–3 h at a temperature of 0–5 °C. After completion of reaction by HPLC, the residual hypochlorite was quenched using 5% Na2S2O5 solution, and the pH was adjusted between 7.5 and 8.0 to yield the corresponding pantoprazole free base (5), which was isolated as a red-brown residue by extraction of aqueous layer using DCM. The residue obtained after removal of solvent was then treated with ~46% w/w aqueous solution of NaOH in acetonitrile to afford the final API that meets all aspects as per the European Pharmacopoeia.

It is possible for the pantoprazole sulfoxide (4) to be isolated and dried before subjected to oxidation; however, this is not preferred, as it is possible to improve the yield and purity of the pantoprazole sodium by carrying forward the wet cake of pantoprazole sulfoxide in situ for the oxidation step by treating it with the hypohalite solution in water. Reported industrial processes involved the isolation of 4 in the form of a dried solid. Nevertheless, it is a low-melting compound, and a large amount of time is consumed for its drying to proceed to the next stage. Herein, the intermediates 4 and 5, as shown in Scheme 1, were not isolated during the process. In particular, they were not subjected to any purification.

Optimization of Ideal Reaction Conditions. Concomitant tests were carried out for the screening of best reaction conditions for the synthesis of 1. The main parameters of the reaction have been studied and determined as discussed herein.

2.1. Coupling of 2 and 3. The first step is the modest coupling of 2 and 3, in which equimolar amounts of 2 and 3 react in aqueous medium in the presence of NaOH to form 4 under organic-solvent-free conditions. The syntheses of 4 have been accomplished by various researchers; however, the drawbacks associated are reaction at high temperature (60–65 °C), use of organic solvent (isopropyl alcohol), and tedious and cumbersome workup procedures. As per the chemistry involved, 2 M equiv of NaOH will be required to affect the coupling. However, the volume of water plays an important role in the quality and yield of 4. Figure 1 describes that yield and quality of product are strongly dependent on the volume of water used. The yield of the product reduced to 94.18% with purity 98.81% when 5 vol water was used (Table 2, entry 1). However, if we increase the water volumes, the yield and purity profile of 4 gets increased. On the other hand, when the volume of water is less, the reaction mass increased viscosity, causing difficulty in stirring the solution. Therefore, it has been found that the optimum yield (99.80%) and the desired HPLC purity (99.91%) of 4 are obtained when 10 vol of water are used in the reaction of 2 and 3 in the presence of 2 mol equiv of NaOH in a reaction time of 3 h at 25–30 °C (Table 2, entry 4). The obtained 4 has been carried forward to the next stage as wet solid without drying.

2.2. Oxidation of 4 to 5. With the optimized synthesis of 4 in hand, we next explore the ideal reaction conditions of oxidation of 4 to 5. A detailed discussion of the main parameters is given below.

2.2.1. Effect of Solvent. Solvents ethyl acetate, acetonitrile, acetone, and DCM were tried to study the reaction rate of oxidation of 4 to 5 using NaOCl as an oxidant. Table 3 indicates that the HPLC conversion of 4 to 5 is good using ethyl acetate, acetonitrile, and DCM. However, using ethyl acetate and DCM, biphasic reaction mass was obtained, which leads to difficulty in the monitoring of reaction as 4 is soluble in organic solvent and 5 being sodium salt in the reaction mixture will remain soluble in aqueous phase. Acetone leads to poor conversion by exploiting the same reaction conditions. However, in case of acetonitrile, homogeneous reaction mass
was obtained throughout the reaction with 96.58% conversion by HPLC. Later, surprising to our results, almost same reaction profile was obtained when the reaction was carried out in neat water (Table 3, entry 5). The only difference between using water and organic solvents arises in the impurity profile of 5, wherein content of pantoprazole dimer impurity (8) (Scheme 2) was slightly high (0.45%) compared to that obtained in rest of the solvents (Table 3).

Scheme 2. Pantoprazole Dimer (8)

\[ \text{Scheme 2. Pantoprazole Dimer (8)} \]

2.2.2. Effect of Mole Equivalents of NaOCl. It is quite obvious from Table 4 that the quality of product is strongly dependent on the mole equivalents of NaOCl. It has been observed that the optimum conversion (98.29% by HPLC, Table 4, entry 3) and the desired purity profile were obtained when 1.05 equiv of NaOCl was utilized. The reaction conversion decreased to 97.78 and 96.52% with an increased content of 4 (0.08 and 0.49%, entries 1 and 2), if we decrease the mole equivalent of NaOCl to 1.0 and 0.95, respectively. On the other hand, if we increase the mole equivalent of NaOCl from 1.05 to 1.1 and 1.2, the conversion of 4 to 5 decreases comparatively with an increased sulfone content (0.07 and 0.10%, respectively, entries 4 and 5).

Table 2. Effect of Volume of Water on the Condensation of Benzimidazole (2) with 2-Chloromethyl-3,4-dimethoxypyridinium Hydrochloride (3)\(^a\)

| entry | solvent | pantoprazole sulfide (4) HPLC (%) | benzimidazole (2) | 2-chloromethyl-3,4-dimethoxypyridinium hydrochloride (3) | unknown impurity (%) | yield (%)\(^b\) |
|-------|---------|----------------------------------|-------------------|----------------------------------------------------------|---------------------|------------------|
| 1     | acetone | 96.58                            | 0.09              | 0.13                                                     | nd                  | 96.18            |
| 2     | water   | 99.95                            | 0.06              | 0.01                                                     | nd                  | 99.80            |

\(^a\)Reaction conditions: benzimidazole (2) (1 equiv); 2-chloromethyl-3,4-dimethoxypyridinium hydrochloride (3), (1 equiv); NaOH (2 equiv); temp (25–30 °C); time (3 h).

\(^b\)Refers to isolated yield.

2.2.3. Effect of Temperature. After optimization of mole equivalents of NaOCl, we explored the effect of temperature on the oxidation reaction. The temperature of reaction proved to be a very important factor in controlling the content of sulfone impurity (6). It was found that the oxidation of 4 to 5 carried out at temperatures of 0–5 °C produces high-quality compound (Table 5). The content of 6 was found to be increasing with the increase in temperature (Table 5, entries 2 and 3). The chances of formation of 6 also minimize at low temperature (−5 to 0 °C); however, the reaction conversion was slightly slow.

Table 4. Effect of Mole Equivalent of NaOCl on the Oxidation of Sulfide (4) to Sulfoxide (5)\(^a\)

| entry | NaOCl (equiv) | pantoprazole sulfoxide (5) HPLC (%) | pantoprazole sulfone (6) HPLC (%) | pantoprazole dimer (8) HPLC (%) | yield (%)\(^b\) |
|-------|--------------|-----------------------------------|----------------------------------|--------------------------------|------------------|
| 1     | 0.95         | 96.52                             | 0.49                             | 0.02                          | 0.29             |
| 2     | 1.0          | 97.78                             | 0.08                             | nd                            | 0.32             |
| 3     | 1.05         | 98.29                             | nd                               | 0.03                          | 0.38             |
| 4     | 1.1          | 96.02                             | 0.03                             | 0.07                          | 0.41             |
| 5     | 1.2          | 93.26                             | 0.02                             | 0.10                          | 0.48             |

\(^a\)Reaction conditions: pantoprazole sulfoxide wet cake (in situ; corresponds to benzimidazole (2) 1 equiv); NaOH (1.5 equiv); NaOCl (1.05 equiv, ~9%); solvent (5 vol); temp (0–5 °C); time (3–4 h).

\(^b\)nd = not detected.

Table 5. Effect of Temperature on the Oxidation of Sulfide (4) to Sulfoxide (5)\(^a\)

| entry | temp (°C) | pantoprazole sulfoxide (5) HPLC (%) | pantoprazole sulfone (6) HPLC (%) | pantoprazole dimer (8) HPLC (%) | yield (%)\(^b\) |
|-------|----------|-----------------------------------|----------------------------------|--------------------------------|------------------|
| 1     | rt       | 30.30                             | 68.68                            | 0.01                           | 0.29             |
| 2     | 5 to 10  | 98.72                             | 0.01                             | 0.28                           | 0.53             |
| 3     | 5 to 10  | 98.66                             | 0.02                             | 0.46                           | 0.42             |
| 4     | 0 to 5   | 98.29                             | nd                               | 0.03                           | 0.38             |
| 5     | 0 to 5   | 97.27                             | 0.14                             | 0.05                           | 0.45             |
| 6     | −5 to 0  | 97.23                             | 0.43                             | 0.03                           | 0.31             |

\(^a\)Reaction conditions: pantoprazole sulfoxide wet cake (in situ; corresponds to benzimidazole (2) 1 equiv); NaOH (1.5 equiv); NaOCl (1.05 equiv, ~9%); water (5 vol); temp (3–4 h).

\(^b\)nd = not detected.
isolation of the compound by pH adjustment in water alone proved problematic. The nature of the solid obtained after pH adjustment was found to be gummy; therefore, a suitable solvent for the isolation of 5 from aqueous layer was required. From the economic point of view and the solubility of 5, the best possible solvent was DCM. Thus, extraction of the aqueous layer using DCM followed by its removal gives the sulfoxide (5) free from the contamination of parent sulfide (4) and sulfone impurity (6).

### 2.3. Formation of Sodium Salt of 5

Next, we explore the formation of sodium salt of pantoprazole free base (5) using NaOH in a suitable solvent. Solvents acetonitrile, DCM, ethyl acetate, and acetone were tried (Figure 2). Table 6 concludes that quality (99.92% HPLC purity, Figure 3) and other parameters as per international standards and the optimal yield (85%) of 1 were accomplished using acetonitrile as solvent. DCM leads to off-white product with an increased content of dimer impurity (8). However, using ethyl acetate, yield was low and the product fails with respect to description.

#### 2.3.1. Acetone–Water Solvate of Pantoprazole Sodium

An almost white powder with good yield (82%) was obtained using acetone as solvent; however, the product fails with respect to assay by potentiometry (90.43% w/w), which is not adequate as per the international standards. The residual solvent analyses of the product by GC revealed that acetone has been trapped in the molecule up to 90 ppm even after drying at 45 °C up to 15 h. These observations led to the conclusion that both water molecules and acetone molecules get involved in the formation of crystal lattice, which is in turn resulted in the formation of a pantoprazole sodium heterosolvate (acetone–water solvate of pantoprazole sodium), which was further supported by 1H NMR, 13C NMR, powder X-ray diffraction (PXRD), thermogravimetric analysis (TGA), and differential scanning calorimetry (DSC) techniques. The acetone content in the product was found to be 20.37% from 1H NMR spectrum, which shows a singlet at 2.083 ppm (δ value), which is further supported by signals at 30.71 ppm (−CH3) and 206.58 ppm (−CO) in the 13C NMR spectrum. The PXRD patterns of pantoprazole heterosolvate and pantoprazole sesquisquhydrate are shown in Figure 4, which clearly illustrates that both sesquisquhydrate and heterosolvate exhibit distinct peaks. The TG thermograms of heterosolvate and sesquisquhydrate shown in Figure 5 disclosed that the weight loss of sesquisquhydrate was 6.19%, which is consistent with both the theoretical water content (6.67%; lit.28 between 5.9 and 6.9%) and water content (6.56%, Table 6), as determined by KP titrator. However, heterosolvate shows two weight-loss steps, corresponding to release of solvent twice. The weight loss is 12.49% in the first step and 2.79% in the second step. It can be inferred that the first-step weight loss corresponds to the removal of one water molecule and one acetone molecule, whereas the second-step weight loss corresponds to the removal of another water molecule. Figure 6 depicts the DSC thermograms of heterosolvate and sesquisquhydrate of pantoprazole. Only one endothermal peak was observed when water is removed in case of sesquisquhydrate, whereas heterosolvate shows two endothermic peaks, the first one being of removal of acetone molecules. Because acetone molecules with low boiling points form channels and connect with water molecules by hydrogen bonding (between O-atom of carbonyl group of acetone and H-atom of water) in the lattice, the desolvation begins at low temperature and water molecules are removed together with acetone molecules. Another water molecule is removed subsequently, which is the same with monohydrate. To date, no reports have been found regarding the conversion of heterosolvate to sesquisquhydrate utilizing DCM as solvent, a well-known drawback encountered in various reports.

#### Table 6. Effect of Solvent on the Formation of Pantoprazole Sodium Sesquisquhydrate (1) from Pantoprazole Free Base (5)\(^a\)

| entry | parameters | solvent | as per EP monograph\(^b\) |
|-------|------------|---------|-------------------------|
| MeCN  | DCM        | ethyl acetate | acetone | acetone/DCM | white or almost white powder |
| 1     | appearance | almost white | off-white | off-white | almost white | almost white |
| 2     | water content (% w/w by KF) | 6.72 | 6.9 | 6.71 | 7.38 | 6.56 |
| 3     | hydrate/solvate | sesquisquhydrate | sesquisquhydrate | sesquisquhydrate | heterosolvate | sesquisquhydrate |
| 4     | assay by potentiometry (% w/w) | 100.45 | 100.55 | 99.99 | 90.43 | 100.57 |
| 5     | purity by HPLC | nd\(^c\) | 0.01 | nd\(^c\) | nd\(^c\) | nd\(^c\) |
| (a) pantoprazole | 99.92 | 99.63 | 99.85 | 99.79 | 99.87 | 1 (NLT \(^c\) 99.5) |
| (b) sulfide | 0.02 | 0.02 | 0.02 | 0.08 | 0.08 | 6 (NMT \(^d\) 0.2) |
| (c) sulfoxide | nd\(^c\) | 0.14 | 0.03 | 0.10 | 0.08 | 6 (NMT \(^d\) 0.2) |
| (d) dimer imp | 0.04 | 0.14 | 0.03 | 0.10 | 0.08 | dimer (NMT \(^d\) 0.1) |
| 6     | yield (%) | 85 | 83 | 77 | 82 | 80 |

\(^a\)Reaction conditions: pantoprazole free base (in situ; corresponds to benzimidazole (2) 1 equiv); NaOH (1.0 equiv); water (0.2 vol); solvent (5 vol); temp (0–5/20–25 °C); time (4–5 h). \(^b\)nd = not detected. \(^c\)NLT = not less than. \(^d\)NMT = not more than.
remove acetone from wet solid of 1 after its isolation by filtration of reaction mass. After several investigations, we discovered that next to the preparation of sodium salt of S in acetone as solvent, the wet solid obtained after filtration of reaction mass shall not be subjected to drying. Instead, the wet solid was given DCM slurry in a reactor to remove the traces of acetone. This technique works well, and the solid obtained after filtration of DCM slurry was pantoprazole sodium sesquihydrate (1). To confirm the transformation, the PXRD data were recorded, which proved that the heterosolvate has been converted to sesquihydrate.

3. CONCLUSIONS

The present process has a number of advantages compared to those of the known ones, for example, inexpensive and commercially available reagents (NaOH/NaOCl/H2O) and most of the reaction steps were carried out in water. High product purity with good yield was achieved by controlling the impurities after optimizing the main parameters. This makes the synthesis economical and scalable, thus rendering this process highly amenable to the synthesis of this important and largely consumed generic pharmaceutical. The problem of heterosolvate was successfully resolved by exploiting the DCM washing to the wet solid.
Figure 5. TGA curves of sesquihydrate and heterosolvate of pantoprazole sodium.

Figure 6. DSC thermograms of sesquihydrate and heterosolvate of pantoprazole sodium.
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4. EXPERIMENTAL SECTIONS

4.1. Reagents and Analytics. All of the starting materials used in the process were purchased from commercial suppliers with optimum purity and used without further purification. The reagents and solvents were supplied by manufacturers. NMR spectra were recorded on Bruker 400 MHz spectrometers with TMS as the internal standard. Chemical shifts are expressed in parts per million (δ, ppm). MS were recorded on Velos Pro from Thermo Scientific LC-Mass spectrometer. The IR spectra were recorded on a Shimadzu IR Affinity-1 FT-IR spectrophotometer (Shimadzu Corporation, North America) over the range of 4000–400 cm$^{-1}$ by pressed pellet method using KBr. HPLC analyses were conducted using Waters 2695 with UV detector, hypersil ODS column (125 mm × 4.0 mm, 5 μm), solvent system of acetonitrile and NaOH sol. (40 mg/L) in the ratio 1:1 (v/v), wavelengths of 290 and 305 nm, flow rate of 1.0 mL/min, and run time of 55 min. PXRD spectra were recorded on PANalytical, model: Empyrean. Melting points were determined on Buchi B-542 apparatus by an open capillary method and are uncorrected. TGA curves were recorded on PANalytical, model: Empyrean. Melting points were determined on Buchi B-542 apparatus by an open capillary method and are uncorrected. TGA curves were recorded on Mettler Toledo, model: TGA, software: STARe capillary method and are uncorrected. TGA curves were recorded on PANalytical, model: Empyrean. Melting points were determined on Buchi B-542 apparatus by an open capillary method and are uncorrected. TGA curves were recorded on Mettler Toledo, model: DSC, software: STAR$^\text{TM}$ system, method: 30–300 °C at 10 °C/min. DSC were recorded on Mettler Toledo, model: DSC, software: STAR$^\text{TM}$ system, method: 30–250 °C at 10 °C. Purified water by Milli-Q system (Millipore) was used for the preparation of samples, reference solutions, and mobile phases. Isolated yields refer to yields corrected for purity on the basis of HPLC assay using standards. The spectroscopic analysis data of API are well correlated with reported specifics.

4.2. General Experimental Procedure for the Synthesis of Pantoprazole Sodium Sesquihydrate (1). A 3 L four-necked round-bottom flask equipped with a mechanical stirrer, a reflux condenser, a thermometer, and a pressure-equalizing funnel was charged with 5-difluoromethoxy-2-mercaptopen benzimidazole (2) (0.4625 mol, 10 g) in a mixture of water (1000 mL) and NaOH (0.925 mol, 37 g) under stirring. The reaction mass was stirred at 25–30 °C and an aqueous solution of 2-chloromethyl-3,4-dimethoxypyridinium hydrochloride (3) (0.4625, 103.64 g in 200 mL of water) was added dropwise over a period of 2–3 h. The stirring was continued for an additional 1 h at 25–30 °C. When the reaction was considered complete as determined by HPLC analysis, the precipitated solids were filtered under reduced pressure and washed with water, thus yielding the wet cake (466 g) of pantoprazole sulfide (4). The wet cake of pantoprazole sulfide (4) was charged into an aqueous solution of NaOH (0.6937 mol, 27.75 g dissolved in 500 mL of water) at 25–30 °C. The reaction mass was cooled to 0–5 °C, and an aqueous solution of 9% NaOCl (401.68 g) was added dropwise over a period of 2–3 h and then stirred for 1 h. Progress of the reaction was monitored by HPLC. After completion of the reaction, the reaction mixture was quenched with a 5% Na$_2$S$_2$O$_5$ solution (350 mL). DCM (500 mL) and water (400 mL) were charged into the reaction, and the pH of the reaction mass was adjusted between 7.5 and 8.0 using 2N-HCl solution. Layers were separated, and the aqueous layer was extracted with DCM (200 mL). The combined DCM layers were distilled off under vacuum at 30–35 °C to obtain a red-brown residue of pantoprazole free base (5). The residue was dissolved in acetonitrile (500 mL) and cooled to 20–25 °C. Aqueous solution of NaOH (18.5 g dissolved in 20 mL of water) was added dropwise, followed by addition of a seed crystal of pantoprazole sodium sesquihydrate. The contents were stirred for 2 h at 20–25 °C and then cooled to 0–5 °C for 3 h. The reaction mass was filtered, washed with chilled acetonitrile (50 mL), and the obtained solid was dried under vacuum at 35–40 °C; 170 g (85% yield and 99.92% w/w HPLC purity) of almost white powder of 1 having water content 6.72% (lit.$^{29}$ between 5.9 and 6.9%) was obtained; residual solvents by GC: acetonitrile (not detected), DCM (not detected); $^1$H NMR (400 MHz, D$_2$O): 6.7.95 (d, J = 5.6 Hz, 1H, Ar-CH), 7.49 (d, J = 8.8 Hz, 1H, Ar-CH). 7.30 (d, J = 1.6 Hz, 1H, Ar-CH), 6.87 (dd, J = 2.0, 8.4 Hz, 1H, Ar-CH), 6.82 (d, J = 6.0 Hz, 1H, Ar-CH), 6.64 (s, 1H, −OCH$_3$), 4.65 (d, J = 12.8 Hz, 1H, −CH$_2$), 4.45 (d, J = 12.8 Hz, 1H, −CH$_3$), 3.72 (s, 3H, −OCH$_3$), 3.54 (s, 3H, −OCH$_3$). $^{13}$C NMR (100 MHz, D$_2$O): 160.02, 159.45, 146.06, 144.65, 119.62, 118.03, 117.06, 108.78, 107.35, 104.15, 98.62, 96.55, 93.74, 83.71, 815.89, 806.25, 796.6, 775.38, 752.24, 709.8, 678.94, 644.22, 630.72, 582.5, 553.57, 524.64 cm$^{-1}$. MS mz calculated for C$_{16}$H$_{15}$F$_2$N$_3$O$_4$S, 383.37; found, 384.18 (M + H)$^+$, 382.20 (M − H)$^+$. 4.3. Procedure for the Synthesis of Pantoprazole Sodium Heterosolvate (9). The residue of pantoprazole free base (5) (equivalent to 5-difluoromethoxy-2-mercaptopen benzimidazole (2), 0.2312 mol, 50 g) as obtained by the process described in the above procedure was dissolved in acetone (250 mL) and cooled to 20–25 °C. Aqueous solution of NaOH (9.25 g dissolved in 10 mL of water) was added dropwise at 20–25 °C. The contents were stirred for 2 h at 20–25 °C and then cooled to 0–5 °C for 3 h. The reaction mass was filtered, washed with chilled acetone (25 mL), and the obtained solid was dried under vacuum at 35–40 °C; 82 g (82% yield and 99.79% w/w HPLC purity) of almost white powder of 9 having water content 7.38% was obtained as characterized by PXRD, TGA, and DSC; residual solvents by GC: acetone (90172 ppm), DCM (Not detected); $^1$H NMR (400 MHz, DMSO-d$_6$): 8.83 (d, J = 5.6 Hz, 1H, Ar-CH), 7.46 (d, J = 8.4 Hz, 1H, Ar-CH), 7.26 (d, J = 2.4 Hz, 1H, Ar-CH), 7.09 (d, J = 5.2 Hz, 1H, Ar-CH), 6.74 (dd, J = 2.4, 8.4 Hz, 1H, Ar-CH), 6.73 (s, 1H, −OCH$_2$F), 4.63 (d, J = 12.8 Hz, 1H, −CH$_2$), 3.89 (s, 3H, −OCH$_3$), 3.77 (s, 3H, −OCH$_3$), 2.08 (s, −CH$_3$, acetone). $^{13}$C NMR (100 MHz, DMSO-d$_6$): 206.58, 164.20, 158.37, 147.02, 144.60, 120.10, 117.56, 115.02, 111.08, 107.94, 60.96, 56.91, 55.94, 30.71. 4.4. Procedure for the Conversion of Pantoprazole Sodium Heterosolvate (9) to Pantoprazole Sodium Sesquihydrate (1). The residue of pantoprazole free base (5) (equivalent to 5-difluoromethoxy-2-mercaptopen benzimidazole (2), 0.2312 mol, 50 g) as obtained by the process described in the first procedure was dissolved in acetone (250 mL) and cooled to 20–25 °C. Aqueous solution of NaOH (9.25 g dissolved in 10 mL of water) was added dropwise at 20–25 °C. The contents were stirred for 2 h at 20–25 °C and then cooled to 0–5 °C for 3 h. The reaction mass was filtered and washed with chilled acetone (25 mL) to obtain the wet cake of pantoprazole sodium. Wet cake of pantoprazole sodium was charged into DCM (250 mL) in a cleaned and dried 1 L four-necked round-bottom flask equipped with a mechanical stirrer, a reflux condenser, and a thermometer. The reaction mass was stirred for 3 h at 25–30 °C and then filtered, washed
DCM (25 mL), and dried under vacuum at 35–40 °C; 80 g (80% yield and 99.87% w/w HPLC purity) of almost white powder of 1 having water content 6.56% (lit.15 between 5.9 and 6.9%) was obtained as characterized by PXRD, TGA, and DSC.

ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.7b00743.

REFERENCES

1H NMR, 13C NMR, IR, MS, PXRD, TGA, and DSC curves of 1, and 1H NMR, 13C NMR, PXRD, TGA, and DSC curves of 9 (PDF)

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Notes
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