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# Scalable Process for the Premix of Esomeprazole†

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**Abstract:**

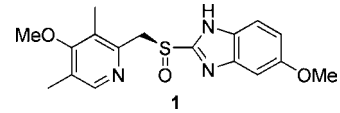
**An efficient, scalable process for the premix of unstable esomeprazole base is described that allows accessibility to the stable amorphous form of esomeprazole 1.**

## Introduction

Prazoles are known as proton pump inhibitors that mechanistically inhibit gastric acid secretion and are thus used as antiulcer agents.[1,2] The new proton pump inhibitor (PPI), esomeprazole Mg (Nexium), developed by AstraZeneca is the *S*-isomer of omeprazole, the first PPI developed as a single optical isomer and used for the treatment of acid-related diseases.[3]

Esomeprazole **1** as shown in Figure 1 is found to be a more effective PPI than omeprazole[4] due to the fact that it has superior pharmacokinetic properties and less variability in effectiveness as compared to omeprazole. Esomeprazole shares a similar mechanism of action, side-effect profile, and precautions with currently available proton-pump inhibitors. The better efficacy of esomeprazole may be attributed to the active moiety that is the enantiomerically pure (*S*)-isomer of omeprazole.

Earlier we have reported a resolution process for the synthesis of the magnesium salt of *S*-omeprazole through a transition metal complex using a combination of D-(−)-diethyl tartrate, $Ti(O^iPr)_4$, and L-(+)-mandelic acid as resolving agents.[5] In continuation of our work, we opted to stabilize an unstable




1

***Figure 1.*** **Structure of esomeprazole 1.**

form of esomeprazole base to achieve a pharmaceutically acceptable formulation.

Certain pharmaceutically active ingredients are acid labile, and thus, they create a myriad of problems during *in vivo* absorption. Therefore, formulating such an acid-labile compound in the oral pharmaceutical dosage form to allow compatibility to the acidic environment of the stomach imposes a great challenge. For example, a few substituted benzimidazole derivatives have poor stability. In particular, these compounds tend to decompose rapidly and acquire color under moist or acidic to neutral conditions. When these compounds are formulated for oral administration, they require specific coating to avoid exposure to the gastric acid of the stomach. In order to achieve effective enteric coating, granulation or pellet formation techniques are practiced that prohibit the active pharmaceutical ingredient (API) from being soluble in water under acidic or neutral conditions and allow the API to be soluble in alkaline conditions. However, the material used in enteric coatings is often acidic, which can cause the decomposition of the acid-labile compounds. Such decomposition occurs even during the enteric coating process, which results in the coloration of the surface of the core. In order to avoid such problem, an inert sub coating, which is not acidic, is often required between the core and enteric coating, which brings the intricacy and adds the cost of the formulation in the manufacturing process of acid-labile compounds.

For substances that are labile in acidic media, but have better stability in neutral to alkaline media, it is often advantageous to add alkaline as the inactive constituents in order to increase the stability of the active compound during manufacturing and storage. In particular, substituted benzimidazole derivatives such as omeprazole and esomeprazole are not only unstable in acidic condition but also in neutral solid state. Thus, in order to enhance the storage stability, an alkaline base such as sodium bicarbonate is added to the formulation, and/or the substituted benzimidazole derivatives are converted to their alkaline salts, which are usually more stable than the free species. It is also known that such alkaline base has adverse effects on patients who suffer from hypertension, heart failure, etc.

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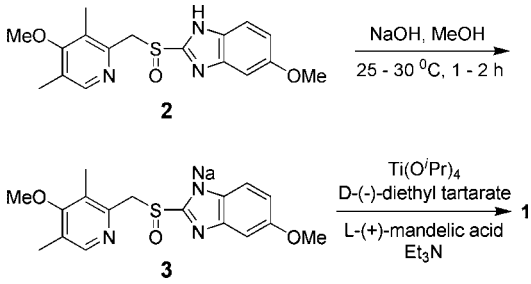
***Scheme 1.*** **Synthesis of esomeprazole starting from omeprazole**




Various stabilizing agents are disclosed for benzimidazole derivatives in the core tablets.[6] The findings also show that such compounds are stable in the presence of basic inorganic salts of magnesium, calcium, potassium, and sodium. The stability is further consolidated by separating the acid-labile prazoles from the acidic components of the enteric coat by an intermediate coating (subcoating).

At our end, we have unsuccessfully attempted to formulate the amorphous form of the free base of **1** by employing the basic, or neutral or acidic coating or subcoating excipients. This observation prompted us to embark on studies of preparation of premix to stabilize the amorphous form of **1**.

Premix is a well-defined mixture of API and a set of additives that help in retaining the stability of the formulated drug product. The premix process of esomeprazole base is not yet reported. Herein, we describe an efficient, scalable, unprecedented process for the premix of unstable esomeprazole base by understanding the role of water which was not studied in detail in earlier disclosures[6h] and employing organic base and neutral components that allows us to stabilize the esomeprazole base **1**.

## Result and Discussion

During formulation, it was found that esomeprazole base can undergo degradation due to its unstable nature at ambient conditions as well as at lower temperatures. To overcome this problem, we decided to make the API more stable at 2−8 °C, by mixing it with additives such as mannitol **4** and meglumine **5** in the preparation of esomeprazole **1** premix. This innovative approach provides a stabilized premix for the pharmaceutical formulations of acid-labile APIs.

Esomeprazole base **1** as an oily residue is prepared by following the novel resolution process published earlier by us[5] and shown in Scheme 1.

Esomeprazole **1** generates many impurities under acidic conditions. In our early attempts, we prepared the esomeprazole base **1** as a solid amorphous polymorph from its oily residue by employing acetone and water (1:2). In this experiment the chiral purity was enhanced from 97% to 99.8%. However, we encountered difficulty in drying the wet solid at less than 30 °C, as the compound started changing its color from off white to cream, and simultaneously the material also changes its morphological behavior as it turned out to be a sticky mass instead of free-flowing powder.

***Table 1.*** **Different ratios of 1, 4, 5 and various solvents used for premix preparation**

| **1** (%) | **4** (%) | **5** (%) | solvent | result |
|---|---|---|---|---|
| 15 | 85 | − | $(CH_3)_2CO$ and cyclohexane | unstable |
| 25 | 75 | − | $(CH_3)_2CO$ and cyclohexane | unstable |
| 50 | 50 | − | $(CH_3)_2CO$ and cyclohexane | unstable |
| 61.5 | 30 | 8.5 | $(CH_3)_2CO$ and cyclohexane | unstable |
| 97 | − | 3 | $(CH_3)_2CO$ and cyclohexane | gummy |
| 50 | 47 | 3 | $(CH_3)_2CO$ and cyclohexane | stable[a] |
| 50 | 47 | 3 | MeOH and cyclohexane | gummy |
| 50 | 47 | 3 | $CH_2Cl_2$ and cyclohexane | gummy |
| 50 | 47 | 3 | EtOAc and cyclohexane | gummy |
| 50 | 47 | 3 | $(CH_3)_2CO$ | gummy |
| 50 | 47 | 3 | MeOH | gummy |
| 50 | 47 | 3 | EtOAc | gummy |
| 50 | 47 | 3 | $CH_2Cl_2$ | gummy |
| 50 | 47 | 3 | cyclohexane | gummy |

[a] ∼49% **1**, ∼48% **4**, ∼3% **5**.

In order to prepare premix, we have screened different pharmaceutically acceptable water-soluble sugar derivatives such as mannitol, lactose, fructose, sorbitol, xylitol, maltodextrin, dextrates, dextrins, and lactitol, and we found that the sugar derivative alone is not sufficient to obtain the stable premix (Table 1). In fact ingredients **4** and **5** with other additives were employed in the formulation of commercialized batches of omeprazole tablets.[7] Thus, **4** and **5** were considered to be nontoxic and clinically safe to use in our premix preparation of **1**.

By considering the first principle of acid/base reaction it can be visualized that the use of base may enhance the stability; therefore, we screened different pharmaceutically acceptable water-soluble bases, such as meglumine, lysine, *N*,*N*′-dibenzylethylenediamine, chloroprocain, choline, diethanolamine, ethylenediamine, procaine (except meglumine **5**; results with other bases are not included) along with mannitol **4** as the structures are shown in Figure 2.

Interestingly, stable esomeprazole premix was obtained with meglumine base along with mannitol in appropriate solvents. We have tried different combinations of meglumine and mannitol along with esomeprazole to get the stable premix. Noticeably, a 50:47:3 ratio of esomeprazole, mannitol, and meglumine offered a stable premix. Interestingly, it was observed that the dry esomeprazole base is fragile under the conditions that we applied for the preparation of premix of **1**. However, in the presence water the isolation of stable premix of **1** was possible. This observation prompted us to investigate the role of water in the premix formation event. At first, we attempted the preparation of premix by using dried material (dried under vacuum at 25−30 °C) **1** at lower temperatures

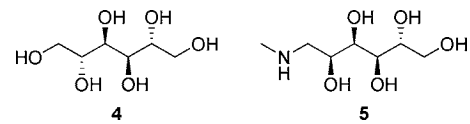



***Figure 2.*** **Structures of mannitol 4 and meglumine 5.**

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***Table 2.*** **Assessment of the stability of the premix of 1**

| duration of analysis | color description | HPLC purity (%) | % of esomeprazole base in premix of **1** |
|---|---|---|---|
| initial | light-yellow solid | 99.82 | 49.2 |
| 1st month | no change | 99.86 | 47.1 |
| 2nd month | no change | 99.85 | 47.3 |
| 3rd month | no change | 99.80 | 47.6 |
| 6th month | no change | 99.82 | 47.9 |
| 9th month | no change | 99.83 | 47.6 |
| 12th month | no change | 99.82 | 47.7 |
| 18th month | no change | 99.81 | 47.4 |
| 24th month | no change | 99.78 | 47.0[a] |

[a] There is no change in the amorphous nature of the premix of **1** after the 24th month as is evident in the powder-XRD experiment.

(10−20 °C) which afforded degradation byproducts. In other experiments, water was removed by extracting the product in dichloromethane followed by evaporation of solvent, and eventually the base **1** was subjected to premix preparation that afforded the gummy mass. Considering the aforementioned observations, we proceeded to prepare the premix with wet solid, and surprisingly, we obtained esomeprazole premix as a free-flowing solid. As a result, we anticipate the hydrogen bonding between additives **4**, **5**, and **1** up to great extent. The typical procedure involves the dissolution of around 75% (water) wet **1** in acetone followed by addition of additives, distillation of solvent up to around 60−70% and codistillation with cyclohexane afforded the material as a free-flowing powder of premix of **1** (Table 1).

**Polymorphism Studies.** During the synthesis, we observed that amorphous nature of the esomeprazole base was retained. Interestingly the impression of 3% of meglumine in the premix was not detected in the PXRD. However, the mannitol XRD remained unchanged. The X-ray powder diffraction results have been obtained on a Rigaku D/Max-2200 model diffractometer equipped with horizontal goniometer in $\theta/2\theta$ geometry. The Cu K$\alpha$ ($1 = 1.5418$ Å) radiation was used, and the samples were scanned between 3−45° $2\theta$.

**Stability Studies.** Stability studies of esomeprazole premix were conducted under the following two different stability conditions: (1) Accelerated stability conditions at 40 °C ± 2 °C and relative humidity (RH): 75% ± 5%. (2) Cold storage stability conditions at 2−8 °C. We have observed that esomeprazole premix was stable at cold storage stability conditions (condition 2).

The stability was judged by color description, HPLC purity, esomeprazole base content in the premix, and XRD. The details are summarized in Table 2. The level of water content during the first month of the stability test was found to be slightly higher (1.73%) than the initial content (1.61% w/w). This amount of moisture intake did not affect the nature of sample since no extra peak in XRD has been detected, indicating that the esomeprazole base in the premix of **1** is amorphous in nature even after 2 years.

## Conclusion

We have developed a robust and scalable process for the preparation of the stable premix of **1** and successfully demonstrated with concurrent pilot-plant scale. The polymorphic study was performed to generate irrefutable evidence for the amorphous nature of the premix of **1** being identical to that of its free base. We have also conducted the stability studies to document the storage conditions for the premix of **1**, which was found to have a stability profile better than that of the free base of **1**, and it helped us to formulate the premix of **1** as tablets with a wide range of excipients.

## Experimental Section

**Preparation of Esomeprazole Base Wet Solid (1) (50−80% Water Content).** To a solution of esomeprazole residue (10 kg, 28.9 mol) in acetone (50 L) was added DM water (100 L), and the mixture was stirred for 30 min. The pH of the mass was adjusted to 12−13 with 40% caustic lye solution (1.2 L) at 25−30 °C, and the mixture was stirred for 30 min. Thereafter, activated carbon (1 kg) was charged, the solution stirred for 30 min, and the reaction mass was filtered through a leaf filter having a Celite bed. Moreover, the leaf filter was washed with a solution of acetone (13 L) and demineralized water (25 L). Subsequently, pH was adjusted slowly to 7.0−8.0 with acetic acid, and the mass was cooled to 0−5 °C. After stirring the solution for 2 h at 0−5 °C, the solid material was separated, filtered, washed with demineralized (DM) water (50 L), and spun dried for 4 h. The wet solid [15 kg; 99.9% (HPLC)][8] was used immediately for the next step.

**Preparation of Esomeprazole 1 Premixed with 4 and 5.** To a solution of esomeprazole base wet solid (15 kg, 70% water content) in acetone (22.5 L) was added activated carbon (0.5 kg). After stirring for 30 min, the mass was filtered through sparkler and online cartridge filters. Thereafter, the filter bed was washed with acetone (13.5 L), and a combined solution of mannitol **4** (3.88 kg) and meglumine **5** (0.27 kg) was added. After stirring for 30 min, cyclohexane (54 L) was added, and the solution was distilled up to 60−70% at 20−30 °C under vacuum. Subsequently, cyclohexane (45 L) was charged, the solution distilled again at 20−30 °C under vacuum followed by further addition of cyclohexane (27 L) and stirred for 30 min at 20−30 °C. A free-flowing material suspended in cyclohexane was filtered and washed with another lot of cyclohexane (13.5 L), and then dried at 30−35 °C under vacuum to afford **1** premix in 90% (over all 35%) yield (7.15 kg) and 99.85% purity (HPLC);[9] [water content: 1.0%, esomeprazole base content: ∼49% (that corresponds to 90% yield), ∼48% **4** and ∼3.0% **5**].

## Acknowledgment

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(7) Lundberg, P. J.; Lovgren, K. U.S. Patent 6,013,281, 2000.

(8) HPLC data: Chiral pack AD 50 mm × 4.6 mm or equivalent, flow rate 0.5 mL/min with a UV detector at 280 nm, load 20 $\mu$L, run time 30 min at 25−30 °C.

(9) HPLC Data: HI-CHROM TBB, flow rate 1.0 mL/min with a UV detector at 280 nm, load 22 $\mu$L, run time 50 min at 25−30 °C.