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PREPARATION OF AMORPHOUS FORM OF ANTI ULCER DRUGS

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ABSTRACT

*Rabeprazole sodium (**1**, Achiphex), Pantoprazole potassium (**2**) Pantoprazole sodium (**3**, Protonix), Omeprazole magnesium (**4**, Prilosec) are gastric proton pump inhibitors. The prazoles exist in different polymorphic forms. Amorphous form is one of the polymorph in almost all the prazoles. The amorphous form in rabeprazole sodium, pantoprazole potassium, pantoprazole sodium, and omeprazole magnesium are prepared in commercial scale by an agitated thin film dryer (ATFD) in high yields. The process involves solvent evaporation under vacuum in agitated thin film dryer and the product is taken out from reactor directly. Powder X-ray diffraction spectroscopy data confirms the amorphous form.*

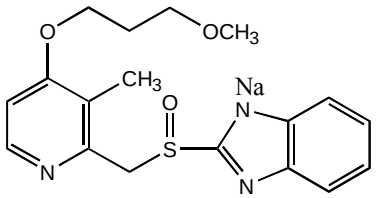
Key Words: *Rabeprazole, Pantoprazole, Omeprazole, amorphous, polymorph, ATFD*

INTRODUCTION

Prazoles are belong to the class of 2-[[(2-pyridinyl) methyl] sulfinyl]-1*H*-benzimidazoles. In general, prazoles are used for the prevention and treatment of gastric acid related diseases and in the treatment of gastroesophageal reflux disease (GERD) ulcers.[1] Polymorphism is the occurrence of different crystalline forms of a single compound and it is a property of some compounds and complexes. Thus, polymorphs are distinct solids sharing the same molecular formula, yet each polymorph may have distinct physical properties. Therefore a single compound may give rise to a variety of polymorphic forms where each form has different and distinct physical properties, such as different solubility profiles, different melting point temperatures and/or different X-ray diffraction peaks. Since the solubility of each polymorph may vary, identifying the existence of pharmaceutical polymorphs is essential for providing pharmaceuticals with predictable solubility profiles. It is desirable to investigate all solid forms of a drug, including all polymorphic forms, and to determine the stability, dissolution and flow properties of each polymorphic form. The value of amorphous form is high due to its high solubility than the crystalline form.

A comprehensive study was undertaken to synthesize and characterize the amorphous form in commercial scale-up by isolating it using agitated thin film dryer technique. The aim is to prepare amorphous form of prazoles[2] consistently in a novel route and high yield. In this technique the

solid isolation does not take much time for crystallization, hence the product obtained is essentially an amorphous form.



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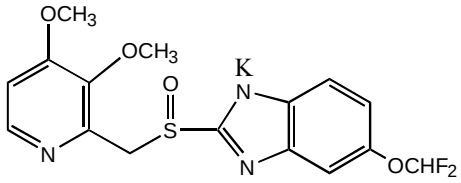

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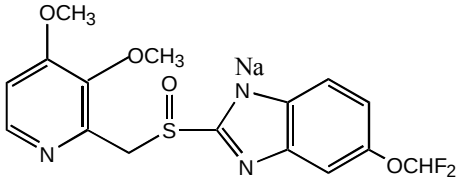

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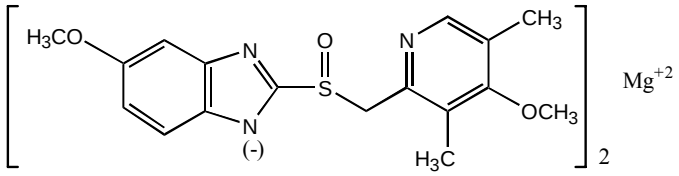

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RESULTS AND DISCUSSION

In the preparation of amorphous form of prazoles in the laboratory, the isolation of solid is complicated owing to the hygroscopic nature of the amorphous form. The amorphous polymorph form of any compound is prepared by dissolving the compound in a solvent particularly methanol or ethanol. Then evaporating the solvent completely and isolating the solid in polar or non-polar solvents, particularly in non-polar solvents. At the time of isolation of a polymorph in a solvent, the compound is in contact with solvent for more time hence the solid obtained is not amorphous consistently. To overcome this problem we developed a process to prepare the amorphous polymorph consistently by using a technique called agitated thin film dryer (ATFD, Fig.1).[3] Agitated thin film dryer is used to convert liquids, slurries, and pastes to free-flowing solids in continuous, single-pass operation. Agitated thin film dryers have a short residence time and are especially useful for processing heat sensitive products, due to low 'hold-up' and self-cleaning heating surfaces.

This technique is used in commercial scale for preparation of amorphous polymorph of rabeprazole sodium (**1**), pantoprazole potassium (**2**), pantoprazole sodium (**3**), and omeprazole magnesium (**4**). In this process the compound is dissolved in methanol and feed the solution into moving hinged blades spread over a heated wall. The thickness of the layer is defined by the clearance between the blade and the heated wall. A highly agitated blow wave is formed in front of the rotating blades. The turbulence increases as the product passes through the clearance before entering a calming zone situated behind the blades. The volatile component evaporates continuously under vacuum (600-700 mm/Hg). The product layer is a few millimeters in thickness. The hinged pendulum blades are designed to give a minimum clearance with the dryer wall to prevent fouling of the heating surface by product. However, the blades do not themselves

contact the heated wall. The solid obtained is pushed to the receiver where the solid can be taken out as amorphous form consistently.

EXPERIMENTAL

Preparation of amorphous polymorph in Rabeprazole sodium (1), Pantoprazole potassium (2), Pantoprazole sodium (3), and omeprazole magnesium (4).

General procedure: A mixture of sodium hydroxide/potassium hydroxide/magnesium and methanol were stirred for dissolution at 25-30 ^{o}C, followed by addition of corresponding prazole and stirred for 1 h. The reaction mass was filtered through hyflow for particle free and was passed through agitated thin film dryer at 40^{o}C under vacuum (600-700 mm/Hg). The separated solid was collected form the reactor. The yields were obtained in the range from 93-96%.

^{1}H NMR (CDCl$_3$+DMSO) *of Rabeprazole sodium (**1**): δ 2.1 (m, 2H –CH$_2$-), 2.2 (s, 3H, -CH$_3$), 3.3 (s, 3H, -OCH$_3$), 3.6 (t, 2H, -OCH$_2$-), 4.1 (t, 2H,-CH$_2$-OCH$_3$), 4.5 (d, Ha, -CH$_2$-pyridine), 4.7 (d, Hb, -CH$_2$-pyridine), 6.6 (d, 1H, 1H-pyridine), 7.1-7.6 (m, 4H, Ar-H), 8.2 (d, 1H, pyridine).*

^{1}H NMR (CDCl$_3$+DMSO) *of Pantoprazole potassium (**2**) and Pantoprazole sodium (**3**): δ 3.7 (s, 3H –OCH$_3$-), 3.9 (s, 3H, -OCH$_3$), 4.5 (d, Ha, -CH$_2$-pyridine), 4.7 (d, Hb, -CH$_2$-pyridine), 6.7 (d, 1H-pyridine), 6.9 (m, 1H, Ar-H), 7.3 (s, 1H, -OCHF$_2$), 7.6 (m, 2H, Ar-H), 8.0 (d, 1H, pyridine).*

^{1}H NMR (DMSO) *of Omeprazole magnesium (**4**): δ 2.1 (s, 3H –CH$_3$-), 3.3 (s, 3H, -CH$_3$), 3.6 (s, 3H, -OCH$_3$), 3.8 (s, 3H, -OCH$_3$), 4.6 (d, Ha, CH$_2$-pyridine), 4.7 (d, Hb, CH$_2$-pyridine), 6.9-7.4 (m, 3H, Ar-H), 8.1 (s, 1H-pyridine).13.3 (s, 1H, NH).*

Table 1: TGA Data

Product	TGA
Rabeprazole sodium (**1**)	10.42 %
Pantoprazole Potassium (**2**)	7.318 %
Pantoprazole Sodium (**3**)	5.774 %
Omeprazole magnesium (**4**)	8.065 %

Samples: The investigated samples of rabeprazole sodium (1), pantoprazole potassium (2), pantoprazole sodium (3), and omeprazole magnesium (4) were synthesized in Dr.Reddy's laboratories Ltd., Bulk Actives-III, Hyderabad, India.

XRD : Powder X – ray diffraction patterns were recorded on a D8 ADVANCE BRUKER axs model diffractometer equipped with vertical goniometer in θ / θ geometry. Copper K α (λ = 1.5406 A°) radiation was used, and the sample was scanned between 3 and 45° 2θ.3.4.

TGA: Thermo gravimetric analyzer (TGA Q500 V6.2 Build 187). The thermograms were recorded under nitrogen atmosphere at a heating rate of 5°C / minute.

NMR spectroscopy: The ^{1}H NMR was carried out on Gemini-2000 (Varian 200 MHz) FT-NMR spectrometer and Mercury Plus Varian 400 MHz FT-NMR spectrometer at 25

^{o}C in $CDCl_3$ + DMSO and ^{1}H chemical shifts are reported on the δ scale in ppm, relative to TMS (δ 0.00).

CONCLUSIONS

The results from the physicochemical techniques confirm the amorphous nature of the rabeprazole sodium (**1**), pantoprazole potassium (**2**), pantoprazole sodium (**3**), and omeprazole magnesium (**4**).

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REFERENCES

1. E. G.Giannini; V.Savarino,; R.Testa, *Dig Dis Sci.*, **51(9)**, 1602-6(2006).
2. a) T. Mahahiko,; M. Yukio. PCT WO 2004/085424 (2004), b) F. Nina,; K. Barnaba,; W. Shlomit, PCT WO 2004/080961 (2004).
3. http://www.technoforce.net/design/agited_dryers.htm.

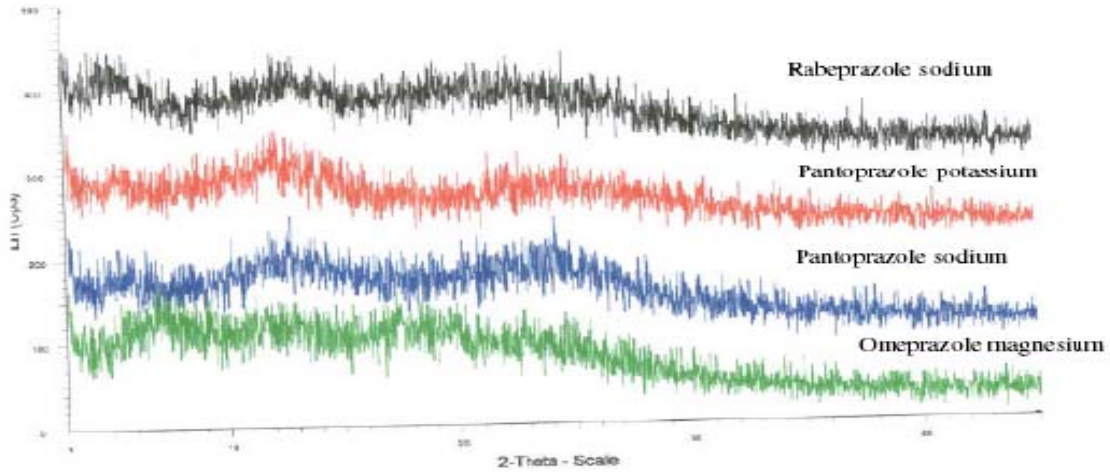

Fig. 2: The Powder XRD of amorphous polymorphic forms of Rabeprazole sodium (1), Pantoprazole potassium (2), Pantoprazole sodium (3), and Omeprazole magnesium (4)

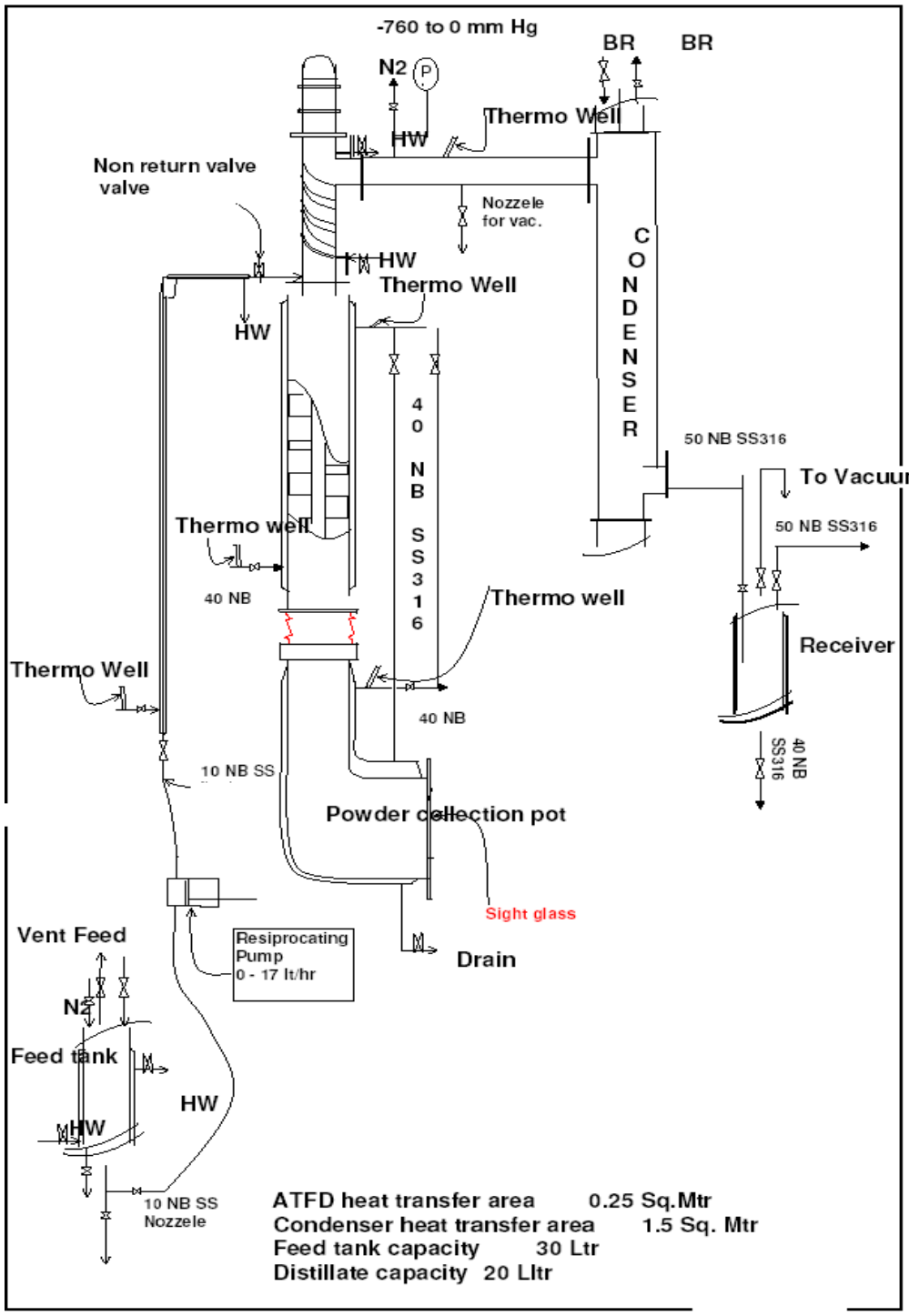

Fig. 1: Agitated thin film dryer (ATFD)

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