



Improve Acid Stability of Pantoprazole Sodium by Cocrystal Technique

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Accepted on: 24-08-2013; Finalized on: 31-10-2013.

ABSTRACT

Pantoprazole inhibit the H⁺/K⁺ ATPase enzyme system at the secretory surface of the gastric parietal cell. It's an acid labile drug. The rate of degradation of pantoprazole shows direct relationship with H⁺ ion, as the pH value increases, the rate of degradation decreased. The purpose of this work is to improve the acid stability of pantoprazole sodium. It was characterized by using PXRD and SEM which suggested the formation of new crystalline phase. The acid stability profile by using HPLC method revealed the acid degradation of pantoprazole sodium pure drug was 87.11 % while that of its co crystal degradation was only up to 9.08 %.

Keywords: Acid stability, Co-crystal, Co-former, Pantoprazole sodium, Sodium carbonate.

INTRODUCTION

Cocrystal formation has gained recent interest in application to pharmaceuticals. The ability to tailor the physicochemical properties of a drug substance via complexation is highly desirable for dissolution rate, bioavailability, stability and processing consideration.^{1,4} Co-crystals can be defined as crystalline complexes of two or more neutral molecular constituents bound together in the crystal lattice through non-covalent interactions, primarily hydrogen bonding.⁵ The formation of a pharmaceutical co-crystal involves incorporation of an API with a pharmaceutically acceptable molecule in the crystal lattice. The resulting multicomponent crystalline phase maintains the intrinsic activity of the parent API.⁶

Co crystal former employed in co crystallization may be an excipient or another drug.⁷ A number of pharmaceutical co crystals have been reported to date with co crystal formers selected from the list of GRAS (generally recognized as safe) compounds which includes various food additives, preservatives and pharmaceutical excipients.⁸

Pantoprazole sodium belong to a class of antisecretory compounds, the substituted benzimidazoles that suppress gastric acid secretion by specific inhibition of the H⁺/K⁺ ATPase enzyme system at the secretory surface of the gastric parietal cell.⁹ It is used for the treatment of acid-peptic diseases such as duodenal, gastric and oesophageal ulceration.¹⁰ It's an acid labile drug. The rate of degradation of pantoprazole shows direct relationship with H⁺ ion, as the pH value increases, the rate of degradation decreased.¹¹

Pantoprazole sodium is available in enteric coated solid dosage and for emergency intravenous dosage forms are available in the market. It's a great challenge to formulate simple compression solid dosage form of these drugs with considerable stability and efficacy. Co crystallization of pantoprazole with sodium carbonate (GRAS candidate)

has been found to be useful for preventing the acid degradation of pantoprazole sodium in the acidic medium.

MATERIAL AND METHODS

Material

Pantoprazole sodium was obtained as a gift sample from Vasudha Pharma Chem Ltd, Ahmadabad, India. Sodium carbonate and sodium hydroxide purchased from Merck Ltd, Mumbai, India. Methanol (HPLC grade), Water (HPLC grade), Acetonitrile (HPLC grade) and Potassium dihydrogen phosphate (AR grade) were obtained from SD fine chem. Ltd. Mumbai, India.

Sample preparation

Pharmaceutical co crystal of the drug Pantoprazole sodium was prepared with the co-former sodium carbonate using slow evaporation method. Pantoprazole sodium (2gm) and sodium carbonate (2gm) were dissolved in equal amount of water. The solution was covered with perforated aluminum foil and agitated it by using magnetic stirrer for 24 hour under ambient condition.

Scanning electron microscopy (SEM) analyses

Electron-micrographs of crystal habit of co crystalline phase were examining using SEM (JEOL 5400, Japan). SEM analyses were carried out using an accelerating voltage of 20 kV after gold sputtering.

Powder x-ray diffraction spectroscopy (PXRD)

PXRD profile was taken with an X-ray diffractometer (BRUKER D8 ADVANCE, Germany). It was performed after sealing the samples in aluminum pans. Scanning parameter Range was 2-40° 2θ: continuous scan, Rate: 3 deg/min.

Acid stability study using high performance liquid chromatographic method (HPLC)

HPLC is probably the most powerful and versatile tool for quantitative determination of many individual components in a mixture in one single procedure.¹² It has many applications in the field of pharmaceuticals which include; stability and pharmacokinetic studies, separation of impurities, enantiomeric purity and drug monitoring in biological fluid.¹³⁻¹⁴ In this work, HPLC was chosen as comparative acid stability study of pantoprazole sodium and its co crystal.

Chromatographic condition

The column used was C₁₈ (Grace), 5 μm, 4.6 x 250 mm HPLC cartridge column. The mobile phase was a mixture of 5:3:2 (v/v/v) 0.05 M potassium dihydrogen phosphate, methanol and acetonitrile (pH adjusted to 7.0± 0.2 with potassium hydroxide) filtered through a 0.45μm Teflon membrane. The flow rate was 1 ml/min. injection volume was 20μl. The separation was monitored at a wavelength of 280 nm.

RESULTS AND DISCUSSION

Scanning electron microscopy (SEM) analyses

Optical and electron microphoto of pantoprazole and its co crystal was shown in figure 1 and 2, respectively. It was identified and confirms the difference in the shape of pantoprazole sodium and its co crystal. It was obtained that co crystal was irregular shaped as compare to that of pure drug.

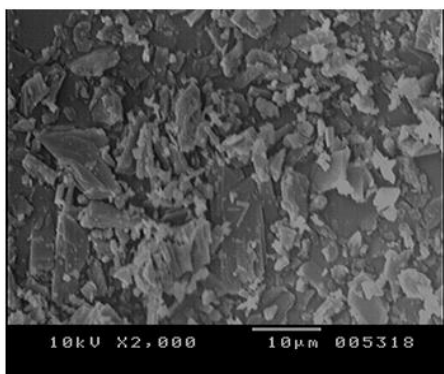


Figure 1: SEM microphoto crystal habit of pure drug at 2,000X

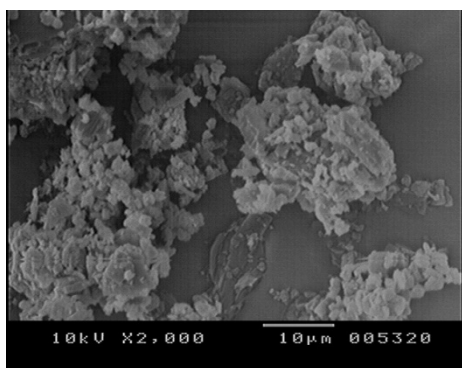


Figure 2: SEM microphoto crystal habit of co crystal at 2,000X

Powder x-ray diffraction spectroscopy (PXRD)

Powder XRD is useful method for fast identification of new crystalline phase in solid state. A different pattern for the co crystal from those of the individual components confirms the formation of a new phase. The PXRD pattern of pantoprazole sodium and its co crystal have been depicted in figure 3 and 4, respectively. The co crystal had several characteristic interference peaks at $2\theta = 10.1, 10.6, 20.9, 20.1, 30.1, 30.5$ and also absent of many unique peaks (figure 4) in it, as compare to pure drug. Co crystal showed a different PXRD pattern and the result suggested that those formed from sodium carbonate.

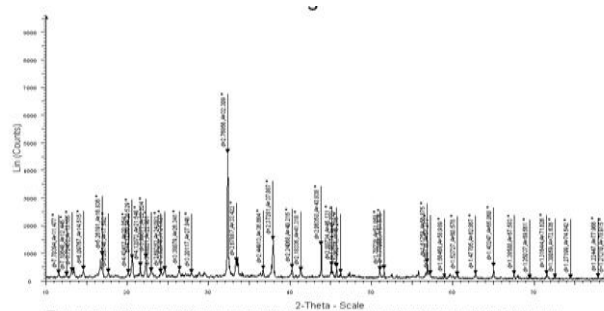


Figure 3: PXRD pattern of pure drug

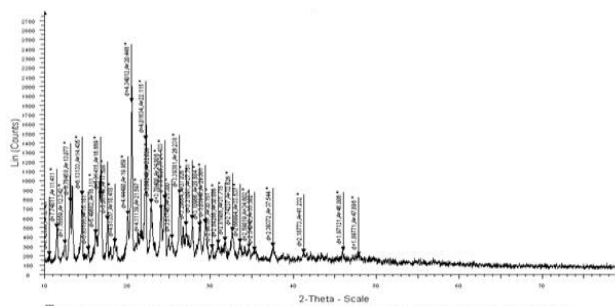


Figure 4: PXRD pattern of co crystal

Acid stability study using high performance liquid chromatographic method (HPLC)

Preparation of acid degradation product of pure drug

20 mg of the pantoprazole was transferred into a 50 ml conical flask; 25 ml of 0.1 M hydrochloric acid were added. As soon as the drug dissolved in 0.1 M HCl withdraw the first sample immediately and next sample after half an hour from it for the comparative studies. Neutralized it with 0.1 M sodium hydroxide solution then quantitatively transferred into 100 ml volumetric flask and completed to 100 ml with methanol.

The chromatogram of first sample showed that the percentage area of pantoprazole sodium was 100.00% at its retention time 4.3667 min (figure 5) respectively while the next sample after half an hour showed the percentage area was 22.12% at its retention time 4.1500 min (figure 6) respectively which revealed that pantoprazole sodium's degradation was up to 87.11%. The remaining percentage areas (1.16%, 30.62% and 47.10% at its retention time 4.0167 min, 4.8000 min and

4.9667 min, respectively) were indicated the degradation products of pantoprazole sodium in 0.1 M HCl.

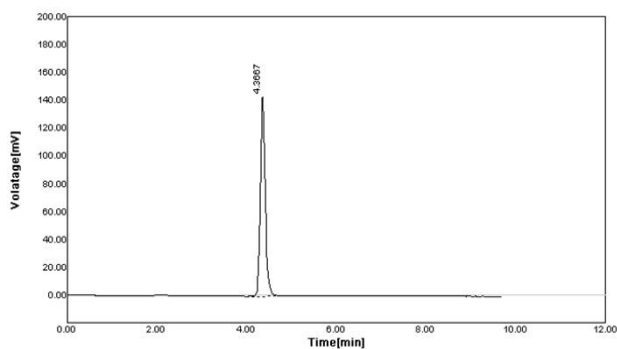


Figure 5: HPLC chromatogram of pure drug (Retention Time= 4.3667 Min)

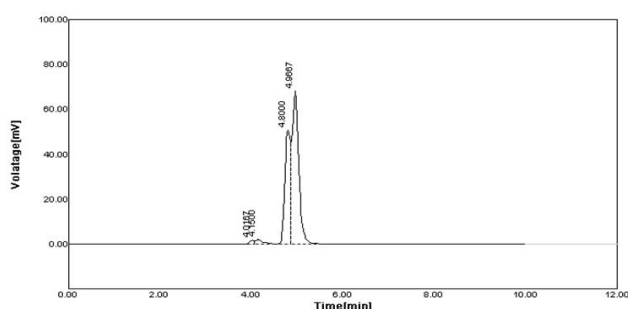


Figure 6: HPLC chromatogram of pure drug (Retention Time= 4.1500 Min)

Preparation of acid degradation product of co crystal

An amount of co crystal equivalent weight to 20 mg of pantoprazole sodium was transferred into a 50 ml conical flask; 25 ml of 0.1 M hydrochloric acid were added. As soon as the co crystal dissolved in 0.1 M HCl withdraw the first sample immediately and next sample after half an hour from it for the comparative studies. Neutralized it with 0.1 M sodium hydroxide solution then quantitatively transferred into 100 ml volumetric flask and completed to 100 ml with methanol.

The first sample chromatogram showed that the percentage area of co crystal was 100.00% at its retention time 4.3333 min (figure 7) respectively while the next sample after half an hour showed the percentage area was 90.92% at its retention time 4.4167 min (figure 8) respectively which revealed the co crystal degradation only up to 9.08%. The remaining percentage areas (9.08% at its retention time 3.5000 min, respectively) was indicated the degradation products of co crystal in the 0.1 M HCl.

CONCLUSION

To improve the acid stability of pantoprazole sodium and its co crystal was prepared with the co-former sodium carbonate (GRAS status) by using slow evaporation method. Its characterization by using SEM and PXRD revealed the formation of new crystalline phase. The acid stability profile by using HPLC method strongly suggested

the increased acid stability of pantoprazole sodium in the presence of co-former sodium carbonate.

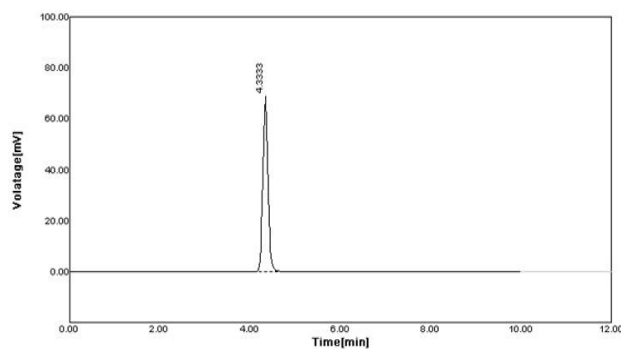


Figure 7: HPLC chromatogram of co crystal (Retention Time= 4.3333 Min)

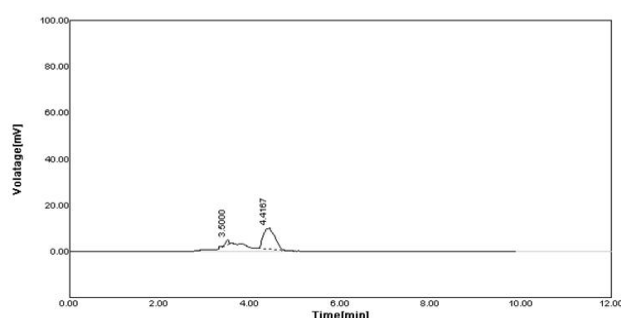


Figure 8: HPLC chromatogram of co crystal (Retention Time= 4.4167 Min)

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Source of Support: Nil, **Conflict of Interest:** None.

