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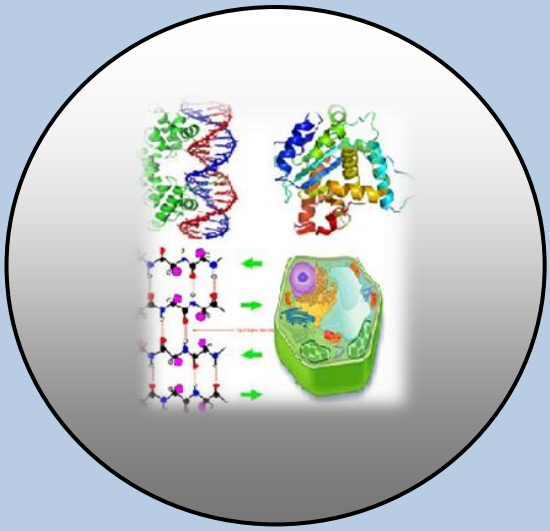

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Synthesis and Characterization of Polymorphic form of Esomeprazole Sodium

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ABSTRACT

Polymorphism is important in the development of pharmaceutical ingredients. Many drugs receive regulatory approval for only a single crystal form or polymorph. 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 esomeprazole sodium polymorphic form. Powder X-ray diffraction spectroscopy data confirms the polymorphic form N.
Key Words: Esomeprazole Potassium Salt, Polymorphic Forms and XRD.

INTRODUCTION

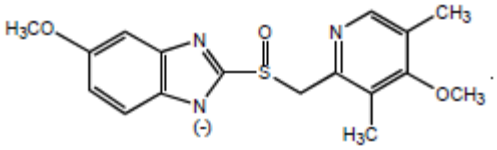
The first observation of polymorphism in organic materials is attributed to Friedrich Wöhler and Justus von Liebig when in 1832 they examined a boiling solution of benzamide: upon cooling, the benzamide initially crystallized as silky needles, but when standing these were slowly replaced by rhombic crystals (Wholer 1832).

Regulatory authorities throughout the world require that all possible crystalline forms of the same active drug compound be synthesized and characterized as completely as possible. There is thus a continuing need to prepare new polymorphic forms of pharmacologically active compounds of commercial interest such as esomeprazole or its salts, which provide the pharmaceutical formulation with a broader spectrum of crystalline forms of an active ingredient to choose from, based on their differing physiochemical properties (Andrew et al., 2004).

Proton-pump inhibitors (PPIs) are a group of drug compounds that has an acidic pKa value at 8-9 and basic pKa at 3-5 (Sacs et al., 2006).

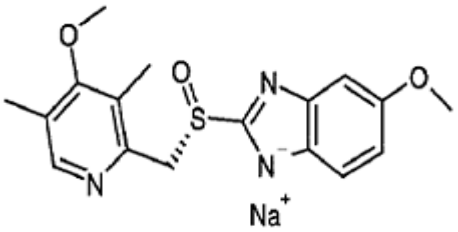
Omeprazole is a proton pump inhibitor (PPIs) and inhibits the action of hydrogen/potassium adenosine triphosphatase (H+/K+ATPase) in parietal cells. They are effective inhibitors of

gastric acid secretion and, therefore, are useful for the prevention and treatment of gastric acid-related disorders and inflammatory gastrointestinal diseases (Tavis et al., 1991).

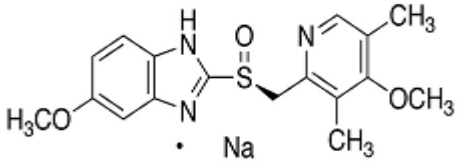


Omeprazole presents one of the most interesting cases in drug development. "Racemic" Omeprazole is a racemate with a central sulphur atom, which acts as a chiral centre; it contains two isomers, S and R shown in figure and normally exists as a racemic mixture (Kendall, 2003).

Esomeprazole sodium



(R)-Omeprazole Sodium



However, the S-isomer, esomeprazole, is metabolized more slowly and reproducibly than the R-isomer and omeprazole, and therefore produces higher plasma concentrations for longer and, as a result, inhibits gastric acid production more effectively and for longer.

It was first marketed by AstraZeneca as the magnesium salt of omeprazole under the trade names Losec and Prilosec and developed the chiral switch drug esomeprazole (which is the (S)-(-)-enantiomer of omeprazole) based on the premise that therapeutic benefit would be achieved by less inter-individual variation, (slow versus rapid metabolizers), and that average higher plasma levels would provide higher dose efficiency in patients. The benefits of esomeprazole have been extensively studied (Evangelos and Bjornsson, 2007). Due to the huge requirement of omeprazole in the market, it is very important to synthesize stable crystalline form of omeprazole to the customers. It is also important that the processes for the preparation of the polymorphic forms be robust and reproducible, so that the processes are easily scaled up in the plant. Other described polymorphic forms of esomeprazole sodium are less pure and less stable (Sonawane and Swati, 2013). Therefore it is need for preparation of highly pure polymorphic form N esomeprazole sodium by a repeatable process which guarantees stable physical form (Lindberg et al., 1990, Lindberg and Weidoff, 1999 and Olbe et al., 2003). The present work relates to stable esomeprazole sodium for injection has characteristics of good stability and high purity. A process for preparing esomeprazole sodium crystalline form N in physically stable and highly pure form (Pradhan et al., 2002 and Chong and Ensom, 2003).

MATERIAL AND METHODS

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.

EXAMPLE 1

300 gr esomeprazole Potassium salt, methylene dichloride 1000 ml and DM water. Neutralize with Glacial Acetic Acid upto 7-7.5 pH. Separate the MDC layer. Add this organic layer to 250 ml methanol containing 45 gr sodium methoxide. Maintain for 2 hours at Room temperature. Filter through hiflow bed. The solvent distilled atmospherically at 40° C. Add Isopropyl alcohol and cool to 10 ° C. The separated solid was filtered and washed with Isopropyl alcohol. The wet compound was dried at 60° C. for 4-6 hours to yield 197 g of the title compound. Purity by HPLC: 99.63%. R-isomer impurities: not detected.

Example 2

300 gr esomeprazole Potassium salt, methylene dichloride 1200ml and DM water. Neutralize with Glacial Acetic Acid upto 7-7.5 pH. Separate the MDC layer. Add this organic layer to 250 ml methanol containing 45 gr sodium methoxide. Maintain for 2 hours at Room temperature. Filter through hiflow bed. The mixture was then distilled atmospherically at 40° C to remove the solvents. Add diisopropyl ether and cool to 15 ° C. The separated solid was filtered and washed with diisopropyl ether. The wet compound was dried at 60° C. for 4-6 hours to yield 190 g of the title compound. Purity by HPLC: 99.59% R-isomer impurities: 0.01%.

RESULTS

We synthesized stable esomeprazole sodium for injection with high purity without R isomer impurity and having high chiral purity. A process for preparing esomeprazole sodium crystalline form N in physically stable and highly pure form.

DISCUSSION

Crystal form of esomeprazole sodium form N which is characterized by peaks at 2θ values of 6.46; 15.79; 19.58; in XRD diffractogram, respectively exactly or ± 0.2 degrees 2θ at the indicated 2θ values, preferably being characterized by an XRD diffractogram as shown in fig 1.

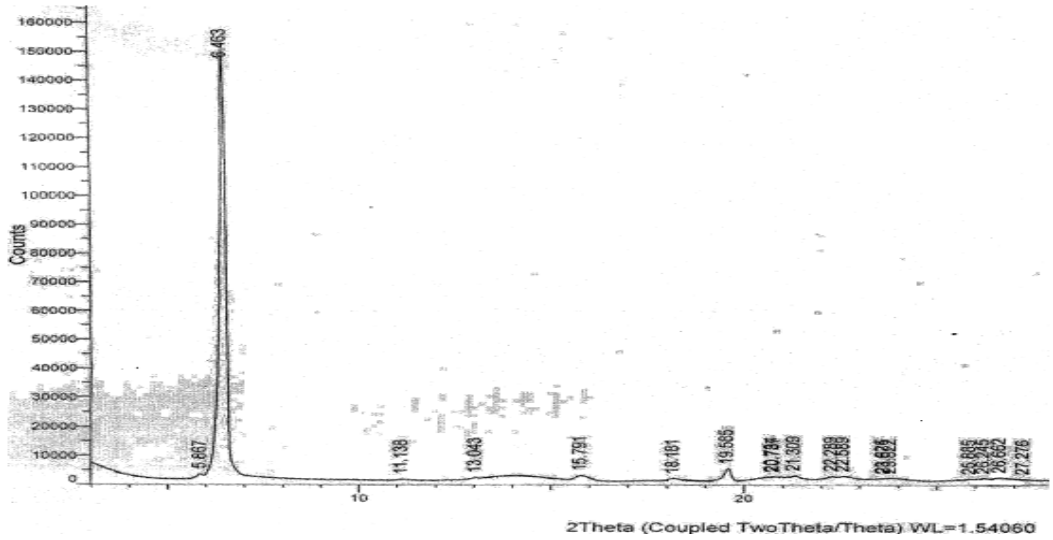


Figure 1. XRD diffractogram of esomeprazole sodium form N.

CONCLUSION

Significant advantages of the present method of synthesis reside in that polymorphic crystalline esomeprazole Sodium Form N can be provided repeatedly in pure form for injection have characteristics of good stability and high purity.

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