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Analytical Method Development to Determine Residual Solvents in Esomeprazole by Gas Chromatography (GC/FID) with Head Space



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ABSTRACT

Residual solvents in pharmaceuticals are termed as organic Volatile Impurities. These are the chemicals that are used in the manufacture of drug substance or excipients or use in the preparation of final formulation. Analysis of organic volatile impurities is of key importance for Active Pharmaceutical Ingredients (API). Most of the available methods use liquid chromatography which could be expensive and time consuming. Hence, an analytical method for the quantification of residual solvents in Esomeprazole was established using a headspace gas chromatography (HSGC) coupled with a flame ionization detector (FID). Methanol, Acetone, Isopropyl alcohol, Methylene dichloride, Toluene as residual solvents were determined in Esomeprazole. Analysis was performed by headspace GC/FID method on Agilent GC 7820A system. Nitrogen was used as a carrier gas with constant flow rate of 4.2 mL/min and the separation of residual solvents was achieved on DB-624 column. The thermostat temperature was 105°C for 30 minutes for each vial and after the equilibration, the vials were pressurized and injected on GC column. The % RSD for six injections obtained in acceptance criteria. The percentage recovery ranges obtained from 92.49 and 106.69%. The correlation coefficient R² obtained greater than 0.99. The method parameters were validated included specificity, limit of detection and quantification, accuracy, linearity, precision, and robustness. A new, simple, specific, accurate and precise method was validated according to the International Conference on Harmonization (ICH) guidelines.



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INTRODUCTION

Esomeprazole is a proton pump inhibitor which is used in the treatment of dyspepsia, peptic ulcer disease, gastroesophageal reflux disease, and Zollinger-Ellison syndrome (1). Esomeprazole is the S-isomer of omeprazole, which is a mixture of the S- and R- isomers. Its molecular formula is $(C_{17}H_{18}N_3O_3S)_2 Mg \times 3 H_2O$ with molecular weight of 767.2 as a trihydrate and 713.1 on an anhydrous basis. The magnesium salt is a white to slightly colored crystalline powder. It contains 3 moles of water of solvation and is slightly soluble in water. The stability of esomeprazole magnesium is a function of pH; it rapidly degrades in acidic media, but it has acceptable stability under alkaline conditions. At pH 6.8 (buffer), the half-life of the magnesium salt is about 19 hours at 25°C and about 8 hours at 37°C. The structure of Esomeprazole is shown in figure 1.

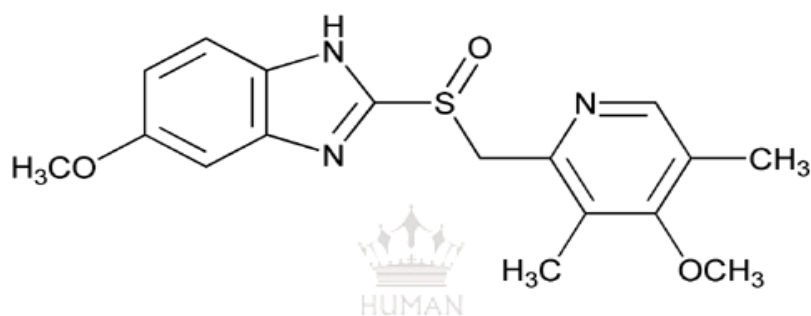


Figure 1: Esomeprazole

The side effects of the drug includes dizziness, confusion, fast or uneven heart rate, jerking muscle movements, jittery feeling, diarrhea that is watery or bloody, muscle cramps, muscle weakness or limp feeling, cough or choking feeling or seizure (convulsions) (2). Esomeprazole is marketed under the brand name of Nexium which is a magnesium salt of the drug and is a blockbuster in the US and Europe. Each packet of Nexium for Delayed-Release Oral Suspension contains 2.5 mg, 5 mg, 10 mg, 20 mg, or 40 mg of esomeprazole, in the form of the same enteric-coated granules used in Nexium Delayed-Release Capsules, and also inactive granules. In India, Esomeprazole is available under various brand name as shown in table 1 (3).

MATERIALS AND METHODS

Sample and standards

Reagents: Methanol, Acetone, Isopropyl alcohol, Methylene Dichloride, Toluene and Dimethyl sulfoxide (DMSO) were obtained from Sigma Aldrich-Mumbai. Esomeprazole was obtained from AB Pharmaceuticals (Mumbai).

Diluent: Dimethyl Sulfoxide (DMSO).

Standard Preparation: Weigh accurately 0.5gm of methanol, 0.5gm of acetone, 0.5gm of isopropyl alcohol, 0.1gm of methylene dichloride and 0.1gm of toluene into a clean dry volumetric flask. Dissolve and dilute to the mark with dimethyl sulfoxide (DMSO). Transfer 1 ml of above prepared solutions into 100 ml volumetric flask and dilute to the mark with same solvent and marked as Standard solution.

Test Preparation: Weigh accurately 0.2 gm each of the test samples into two different HSS vials, and add 2 ml of DMSO solvent and seal the vials with aluminum closure.

Procedure:



Transfer the above prepared standard solutions each 2 ml into six different HSS vials and sealed with an aluminum closure. Each of the vials contains 500 ppm of methanol, 500 ppm of isopropyl alcohol, 500 ppm of acetone, 100 ppm of methylene dichloride and 100 ppm of toluene with respect to the sample. The vials have a DMSO solution containing solvents at different concentrations, the vials are kept at 40°C. The headspace sampler was equipped with a 1-mL sample loop. Since a sufficient flow must be maintained through the system to avoid excessive peak broadening.

The analysis was performed on Agilent GC 7820A FID detector and Chem station software. The injection temperature was 190°C and detector temperature was 290°C. Column was DB-624m (30m long, 0.53mm internal Diameter coated with 3.0um film of 6% Cyanopropylphenyl 94% Dimethyl polysiloxane). Split ratio of injection 1:4, Oven temperature was maintained at 40°C for 5 min, and then raised at rate of 10°C/min to 170°C, maintained for 7min. Total run time was 25 min. Nitrogen was used as a carrier gas at a constant flow rate of 4.2 mL/min [9-19].

RESULTS AND DISCUSSION

The chromatogram of Esomeprazole with mixture of solvents is shown in figure 2 (I, II AND III). The Ramping rate of 5°C/min prolonged the total run time to 54 minutes with an average separation of 3 minutes in between 2 peaks hence a faster ramping rate made sense. At 10°C/min although the overall run time was brought down to 34 minutes there was an overlap of Peak of Methanol and Acetone. Hence a ramping rate of 7°C/min was chosen as an optimum rate to get perfect separation of solvents. The retention times of the solvents are as below followed with their chromatograms. The developed method had a ramp rate of 7°C/min with headspace conditions mentioned in Table 3 (II) and 4. This method was further validated using ICH guidelines.

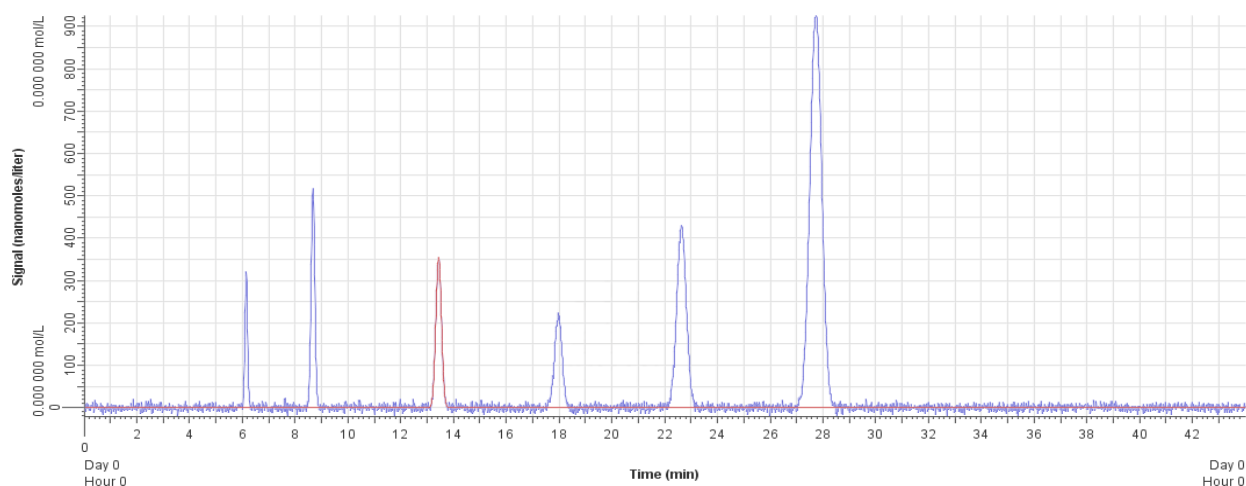


FIGURE 2 (I): CHROMATOGRAM OF ESOMEPRAZOLE WITH MIXTURE OF SOLVENTS AT 5°C/MIN

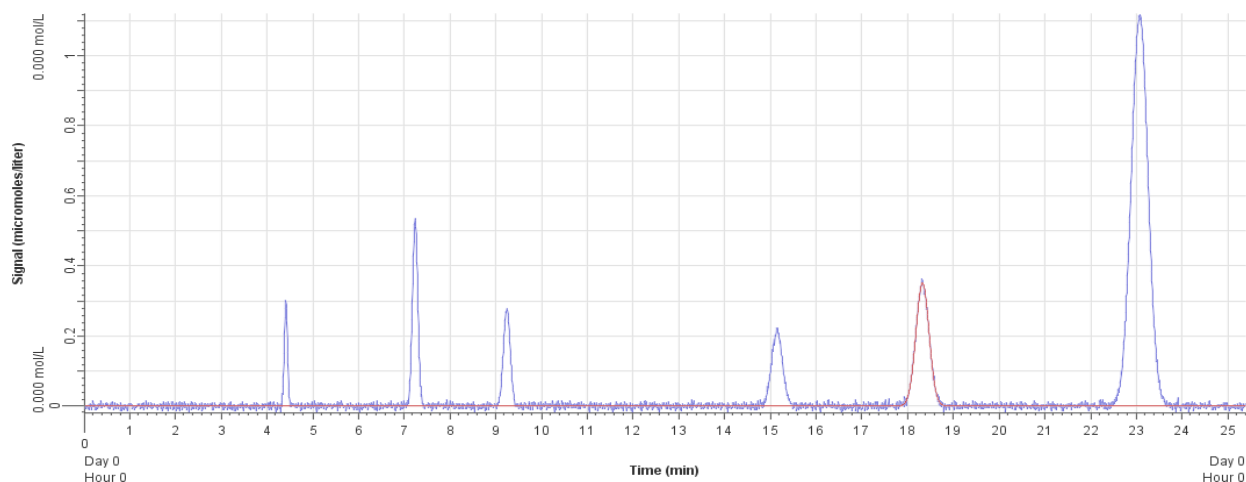


FIGURE 2 (II): CHROMATOGRAM OF ESOMEPRAZOLE WITH MIXTURE OF SOLVENTS AT 7°C/MIN

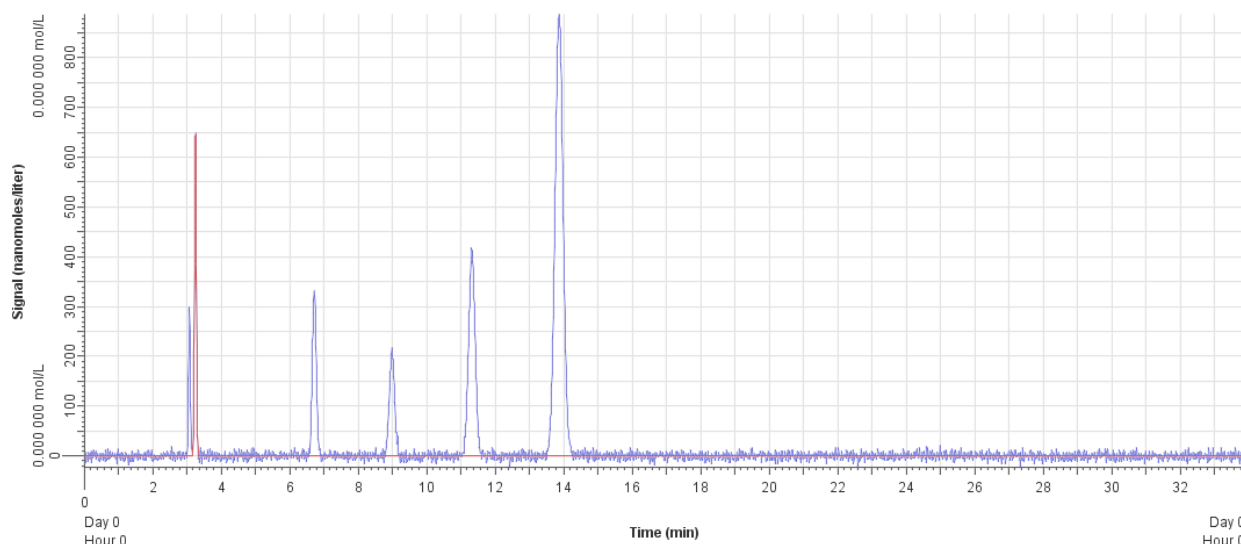


FIGURE 2 (III): CHROMATOGRAM OF ESOMEPRAZOLE WITH MIXTURE OF SOLVENTS AT 10°C/MIN

CONCLUSION

A simple, rapid and economical method to detect the residual solvents in Esomeprazole was developed and validated.

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