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Research Article

METHOD DEVELOPMENT AND VALIDATION FOR THE DETERMINATION OF RESIDUAL SOLVENTS IN OMEPRAZOLE API BY USING HEADSPACE GAS CHROMATOGRAPHY

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ABSTRACT

Residual solvents in pharmaceutical samples are monitored using gas chromatography with head space. Based on good manufacturing practices, measuring residual solvents is mandatory for the release testing of all active pharmaceutical ingredients (API). The analysis of residual organic solvents (methanol, ethanol, acetone and toluene) in Omeprazole API was investigated. Omeprazole is a potent reversible inhibitor of the gastric proton pump H+/K+-ATPase. The Head space gas chromatography (HSGC) method described in this investigation utilized a DB - 624, 30 m long x 0.32 mm internal diameter, 1.8 µm thick column. Since Omeprazole is a thermally labile compound, the selection of the proper injector temperature is critical to the success of the analysis. The injector temperature was set at 180°C to prevent degradation. The initial oven temperature was set at 50°C for 10 min and programmed at a rate of 30°C min^{-1} to a final temperature of 200°C for 10 min. Nitrogen was used as a carrier gas and flame ionization detector was used. N,N-dimethyl formamide was selected as a diluent. The method was validated according to ICH guidelines and found to be specific, linear i.e.,C.C is 0.998, precise, %RSD of each analyte is less than 8% , sensitive, rugged and showed excellent recovery.

Keywords: : Headspace-gas chromatography, Omeprazole, Method validation, Residual solvents

INTRODUCTION

Organic solvents are routinely applied during synthesis of drug substances, excipients, or during drug product formulation. They are not desirable in the final product, mainly because of their toxicity, influence on the quality of crystals of the drug substance, and their odor or taste, which can be unpleasant for patients. To remove them, various manufacturing processes or techniques (usually under increased temperature or/and decreased pressure) are in use. Even after such processes, some solvents still remain, albeit in small quantities. These small quantities of organic solvents are commonly known as organic volatile impurities (OVIs) or residual solvents (RS). The determination of residual solvents in drug substances, excipients or drug products is known to be one of the most difficult and demanding analytical tasks in the pharmaceutical industry. Furthermore, the determination of polar residual solvents in pharmaceutical preparations continues to present an analytical challenge mainly because these compounds are difficult to remove from water or polar solvents1

The manufacturing of active pharmaceutical ingredients (API) under GMP (good manufacturing practice) conditions requires adequate control of the quality of the different ingredients involved in the synthesis. Organic residual solvents must therefore be controlled and their purity determined, before any GMP synthesis.

Inadequate attention has been paid during pharmaceutical investigations. Headspace gas chromatography (HSGC) is a technique where the liquid or solid sample is set in a closed vessel until the volatile components reach equilibrium between the sample and the gas volume above i.e. the so called "headspace". An aliquot of the headspace is sampled and introduced into a gas chromatographic (GC) column for analysis. Regulatory agencies and pharmacopoeias suggest headspace gas chromatography as the most suitable technique for residual solvent testing for active substances and formulations soluble in water. Residual solvent specification limits, set in accordance with the toxicity of solvents, vary from a few ppm to thousands of ppm. HSGC determination of residual solvents is nowadays a mature technique (Grodowska *et al.*, 2010; Puranik *et al.*, 2009; Groman *et al.*, 2008; Alzaga, 2007; Camarasu, 2006; Michulec *et al.* 2005; Rocheleau *et al.*, 2004; Klick, 2004; Snow, 2002; Hymer *et al.*, 2003; Iofer *et al.*, 1984). Direct injection of analytes evaporated through equilibration between liquid (or solid) phase and gas phase into a GC system minimized the contamination of the GC system and the deterioration of the GC column (Kolb *et al.*, 1997). In addition, the automation of equilibrium and injection procedure reduced analysis time and improved reproducibility in the injection procedure.

Omeprazole is a potent reversible inhibitor of the gastric proton pump H^+/K^+-ATPase. The molecular structure of omeprazole is illustrated in Figure 1.

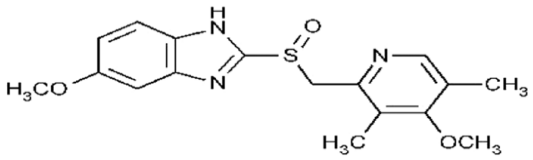

Fig.1: Structure Formula of Omeprazole

It is composed of a substituted pyridine ring linked to a benzimidazole by a sulfoxide chain. Chemically designed as 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2- pyridinyl)methyl]sulfinyl]-1*H*-benzimidazole. Omeprazole is a white powder, slightly soluble in water, but is highly soluble in alkaline solutions as the negatively charged ion. It is an ampholyte with pKa=4 (pirydinium ion) and 8.8 (benzimidazole). In solution, Omeprazole degrades rapidly at low pH values, and it is photo and heat sensitive (Sarisuta *et al.*, 1997). Its molecular formula and weight is C17H19N3O3S, and 345.4, respectively (Marzocchi *et al.*, 2001). Omeprazole is known for its high potential to interact with other drugs (United States Pharmacopoeia, 2006; Anderson, 1996; Mayer,1996). The aim of this study was to develop a HSGC method for analysis of residual solvents in omeprazole API. The residual solvents were compared to standard solvents and the ICH standard residual solvents limit.

EXPERIMENTAL

Material

Used Chemicals were obtained from the following suppliers: methanol, acetone, ethanol and toluene (Sigma- Aldrich, Mumbai India) *N,N*-dimethylformamide (DMF) GC grade (Spectrochem, Mumbai, India). Omeprazole API was obtained from Ranbaxy Research Laboratories, Gurgaon, India.

Instrumentation

A Gas chromatograph (Agilent technologies 6890N) equipped with a flame ionization detector, a Headspace sampler (Agilent technologies G1888) was used to load the sample. An analytical balance (XS 205 from Mettler Toledo) and autopippette (100 – 1000 µL from Eppendorf) were used.

Chromatographic conditions

For Gas chromatographic analysis, a DB – 624 column (30 m length, 0.32 mm internal diameter, and 1.8 µm film thickness) was used. Nitrogen was used as carrier gas. Flow rate was kept1.0 mL/ min (Linear velocity 26 cm/sec).Split ratio was 1:10, detector temperature was 270 °C, Oven temperature was initially kept 50 °C, held for 10 minutes and increased at 30°C/min to 200°C held at 220°C for 5 minutes. Headspace injector oven equilibrium was at

80 °C. Loop temperature was 90 °C. Transfer line temperature was 100 °C. GC cycle time was 35 min. Oven/vial equilibration time was 30 min and pressurization time was 0.5 min. Loop fill time and loop equilibration time were 1.0 min and 0.5 min respectively.

Preparation of standard and sample vial

N, N- DMF was selected as the standard and sample diluent because of its ability to dissolve a wide variety of substances. It has a high boiling point that does not interfere with more volatile solvents, analyzed by GC. A common standard stock solution in DMF containing all the known residual solvents of Omeprazole API (i.e., methanol, acetone, ethanol, and toluene) was prepared in such a way that it had a final concentration of 3000 ppm for methanol, 3000 ppm for acetone, 500 ppm of ethanol, 500 ppm for toluene. The standard vial was prepared with 1 mL of the standard solution and the sample vials were prepared with approximately 100 mg of sample with 1 ml N, N- DMF as diluent.

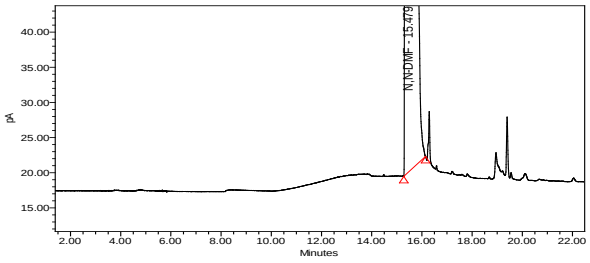

Fig.1: Chromatogram of blank

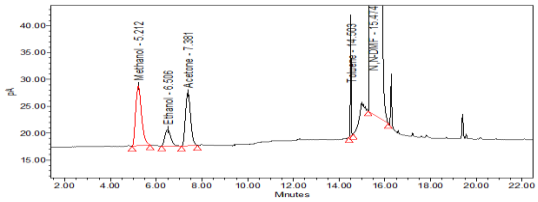

Fig.2: Chromatogram of standard

Method validation

The method validation was done by evaluating specificity, limit of detection (LOD) and limit of quantitation (LOQ), linearity, accuracy, repeatability, ruggedness, system suitability and method precision of residual solvents as indicated in the ICH harmonised tripartite guideline (1997, 2002).

RESULT AND DISCUSSION

Specificity

The omeprazole API sample was spiked with methanol, ethanol, acetone and toluene individually and each sample was chromatographed to examine interference, if any, of the residual solvent peaks with each other. The retention time for standard methanol, ethanol, acetone and toluene was found to be 6.705, 8.610, 10.060 and 15.912 min respectively.

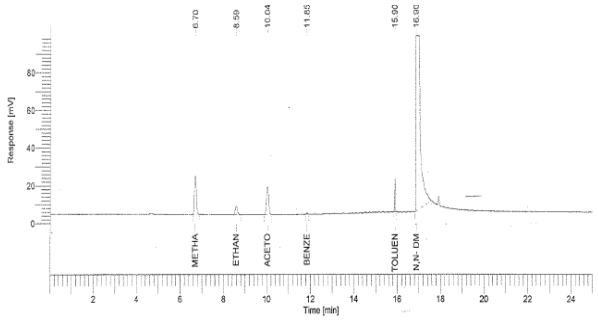

Fig 2: Chromatogram of Specificity

Linearity

The linearity of the method was determined by making injections of each residual solvent over the range 25-200% of specification limit. Two replicates were performed at each level. The calibration curves were obtained with the average of peak area ratios of two replicates. The correlation coefficient (r^2) values for all residual solvents were found to be higher than 0.997 and the calibration curves were linear within the range. Table II shows the linearity values for the residual solvents.

Limit of Detection (LOD) and Quantitation (LOQ)

The LOD and LOQ were calculated by instrumental and statistical methods. For the instrumental method, LOD is determined as the lowest amount to detect and LOQ is the lowest amount to quantify by the detector. The LODs of residual solvents in Omeprazole API were determined based on a signal-to-noise ratio of 3:1. The LOQs of residual solvents were determined based on a signal-to-noise of ratio 10:1. The values for the LOD and LOQ for methanol, ethanol, acetone and toluene are shown in Table II.

Accuracy (recovery)

A known amount of sample (100 mg) was taken separately in five different vials and spiked with known quantities methanol, ethanol, acetone and toluene at three different levels (50, 100 & 150 % of Quantization Limit) in triplicate. The results are presented in Table III. From accuracy data, the % recovery of residual solvents was found within the limits (80-120%) and % RSD for area did not exceed 10.0 for each solvent as per the ICH guideline. Results indicate that the method has an acceptable level of accuracy.

Precision

For the system precision, a single injection of blank and six replicate injections of standard solution were observed. The % RSD for each solvent was found to be less than 10 and system suitability was passed.

System suitability

The system suitability criterion was taken to be the resolution between the critical pairs i.e., ethanol and acetone. The system suitability was evaluated by injecting the standard solution on various days before starting any exercise during the validation study. The criterion for system suitability was that the resolution between the above-mentioned critical pair should not be less than 1.5 and it was found to be well above the minimum passing limit (Table IV).

Table 2: Validation results for residual solvents

Solvent	Specificity RT (min)	Linearity (r^2)	(LOD) (ppm)	LOQ (ppm)
Methanol	6.705	0.99989	1.00	3.00
Ethanol	8.610	0.99973	1.00	5.00
Acetone	10.060	0.99984	0.40	1.20
Toluene	15.912	0.99989	1.00	3.00

Table 3: Accuracy data for different residual solvents

Accuracy (Avg.)	Methanol	Ethanol	Acetone	Toluene
50 %	91	103	104	110
100 %	93	101	105	108
150 %	95	96	106	108

Table 4: System suitability

Experiment	Resolution between ethanol and acetone
Specificity	1.843
Precision	1.839
Accuracy	1.841
Linearity	1.811
LOD/LOQ	1.849

CONCLUSION

A single, rapid and highly selective HSGC method was developed and validated for the quantification of residual solvents present in Omeprazole API through an understanding of the synthetic process, nature of solvents and nature of stationary phases of columns. The residual solvents methanol, ethanol, acetone and toluene were determined. The developed method is specific, accurate, precise and rugged as per ICH guidelines.

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