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Residual Solvents Determination by HS-GC with Flame Ionization Detector in Omeprazole Pharmaceutical formulations.

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Abstract: Residual process 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.In this paper demonstration a method of determination of residual solvents in Omeprazole bulk drug using gas chromatography with a head-space injention system has been developed. The chromatographic conditions and parameters of the injenction system were optimized to enable the quantification by external standardization of most common solvents Methanol, Acetone, Isopropyl alcohol (IPA), Methylene dichloride (MDC) and Toluene in concentrations from a few to a few percent.

Kew words: Headspace-gaschromatograpy, Method validation, Residual solvents, Omeprazole.

Introduction

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 quite difficult to remove from water or polar solvents.[1,2,3]
Many pharmaceutical products must be analyzed for residual solvents at different stages of their development (raw materials, intermediate products, and final product).
Organic solvents such as methanol, acetone, dichloromethane, isopropyl alcohol and toluene are frequently used in the pharmaceutical industry. The manufacturing of new active pharmaceutical ingredients (APIs) under GMP conditions commands to control adequately the quality of the different ingredients happening in the synthesis. Organic residual solvents have therefore to be controlled and their purity has to be determined before any GMP synthesis.
Headspace gas chromatography (HS-GC) method has been used for the determination of residual solvents in pharmaceutical compounds[4-11]. Direct injection of analytes evaporated through equilibration between liquid (or solid) phase and gas phase to GC system minimized the contamination of GC system and the deterioration of GC column[12] . Volatile residual solvents are accumulated prior to analysis[13, 14].
Omeprazole is a potent reversible inhibitor of the gastric proton pump H^+/K^+-ATPase. The molecular structure of Omeprazole illustrated in Fig1. It is composed of a substituted pyridine ring linked to a benzimidazole by a sulfoxide chain[15]. Chemically designed as 5-methoxy-2-[[(4-methoxy-3, 5-dimethyl-2-pyridinyl) methyl] sulfinyl]-1H-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[16], and it is photo and heat sensitive[17]. Its molecular formula and weight $C_{17}H_{19}N_3O_3S$, 345.4 respectively[18]. Omeprazole is known for its high potential to interact with other drugs[19-20]
The aim of this study is to develop HS-GC method for analysis of residual solvents in Omeprazole pharma. The residual solvents compared to standard solvents and the ICH standard residual solvents limit.

Experimental

Headspace gas chromatography.

The analysis was performed on Shimadzu Gas Chromatography; Japan equipped with model no Shimadzu-GC-2010 head-space AOC 5000 autosampler and a flame-ionization detector. The injector temperature was 100^{C}C and detector temperature was 250^{o}C. Column was DB-624 with serial no-US7109941H (100% dimethylpolysiloxane 30.0 m × o.53 mm ID, 3.0 µm d.f. Capillary). Split ratio of injection 1:10. Oven temperature

was maintained at 40°C for 5 min, and then raised at rate of 7°C/min to 220°C, maintained for 10 min. Total run time was 40 min.Nitrogen was used as a carrier gas at a constant flow rate of 2.10 mL/min.The headspace and detector conditions used for the analysis are outlined in Tables 1 and 2 respectively.

Table: 1 Head space Conditions.

Incubation temperature	100°C
Incubation time	1800 Sec
Syringe temperature	110°C
Agitator speed	500 rpm
Fill speed	1000 µl/s
Pullup Delay	100 ms
Injection speed	1000 µl/s
Pre inject delay	100 ms
Post inject delay	1000 ms
Flusn time	180 Sec
GC Runtime	2880 Sec

Table: 2 Detector Channel 1 (Flame Ionization Detector)

Temperature	250°C
Signal Acquire	Yes
Sampling rate	40 Sec
Stop time	40.71 min
Delay time	0.00 min
Makeup gas	Nitrogen/Air
Makeup flow	30.0 mL/min
Hydrogen Flow	50.0 mL/min
Air flow	450.0 mL/min

Sample and standards.

Reagents: Methanol, acetone, isopropyl alcohol, methylene dichloride, toluene and dimethyl sulfoxide (DMSO) were obtained from Merck-Mumbai.

Standard Preparation: Weighed accurately 500 mg of methanol, 500 mg of acetone, 500 mg of isopropyl alcohol, 100 mg of methylene dichloride and 100 mg of toluene into a clean dry volumetric flask. Dissolved and dilute to the mark with dimethyl sulfoxide. Transferred 1 ml of above prepared solutions into 100 ml volumetric flask and dilute to the mark with same solvent and marked as Stanadard solution.

Test Preparation: Weighed accurately 200 mg each of the test sample 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 aluminum closure. Each of the vials contains 500ppm of methanol, 500ppm of isopropyl alcohol, 500ppm of acetone, 100ppm of methylene dichloride and 100ppm 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.

Results and Discussion

The results for the residual solvents in omeprazole by using the following calculation:

$$\frac{\text{Average area of relevant solvent in test} \times \text{Conc in mg of relevant solvent in Std} \times 10^6}{\text{Average area of relevant solvent in Std} \times \text{Wt in mg of test sample}}$$

The linear range and correlation coefficients were determined between 10 ppm and 1500 ppm. The results for the 2-ml sample volume are documented in table-3.

Table 3. Linearity and Repeatability for Residual solvents using 2-ml liquid sample Volume

Solvents	Obtained values in Omeprazole	Repeatability at 50 ppm (%RSD)
Methanol	273 ppm	5.20
Acetone	165 ppm	4.22
IPA	150 ppm	5.30
MDC	25 ppm	5.38
Toluene	24 ppm	4.20

Method Validation: The method validation was done by evaluating specificity, limit of detection and quantitation, linearity, accuracy, repeatability, and method precision of residual solvents as was indicated in the International Conference on harmonization (ICH) guideline Q2B "Validation of Analytical Procedures: Methodology[21].

The accuracy of the method was determined by recovery experiments.Accuracy parameter was verified across five concentration levels ranging from 0.01% to 0.05% of the sample weight. % recovery at each concentration level was verified with an acceptance criteria 100±5%. Each concentration was carried out three times. The percentage recovery and standard deviation of the percentage recovery were calculated and presented in Table-1. From the data obtained indicates the accuracy of the method

For the specificity, methanol, acetone, IPA, MDC and toluene were used as residual solvents. The baseline separation of residual solvents was done by the HS-GC conditions.

The limits of detection (LOD) of residual solvents in Omeprazole were determined based on signal-to-noise ratio of 3:1: methanol, acetone, IPA 0.02 %(w/w), MDC 0.01% and toluene 0.05%.

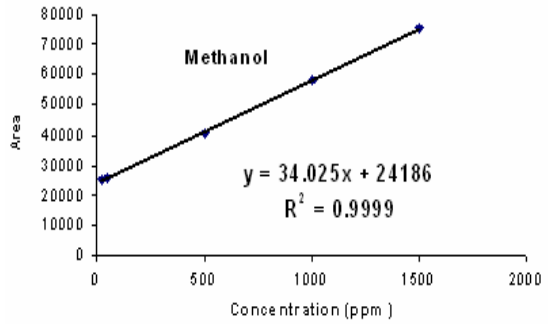
Table 3 shows limits of quantitations (LOQs), linearity and accuracy. LOQs of residual solvents were determined based on signal-to-noise ration 10:1. The linearity was determined at six levels in the range between LOQ and 8.0%(w/w). Three replicates were performed at each level. The calibration curves were obtained with the average of peak area ratios of three replicates (Figure 2). All of the correlation coefficients (R^2) were higher than 0.9995. The accuracy was evaluated by the recoveries of residual solvents spiked in sample solution without residual solvents. The recoveries of residual solvents were ranged between 95.2 and 102.6%.

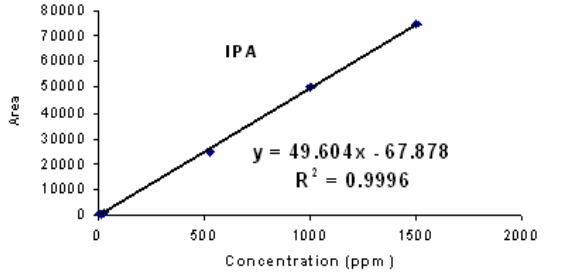
Repeatability was evaluated using 2.0% samle spiked with residual solvents. The relative standard deviations (RSDs) were: 5.20% for methanol, 4.0% for acetone, 5.30% for IPA, 5.10% for MDC and 4.205 for toluene.

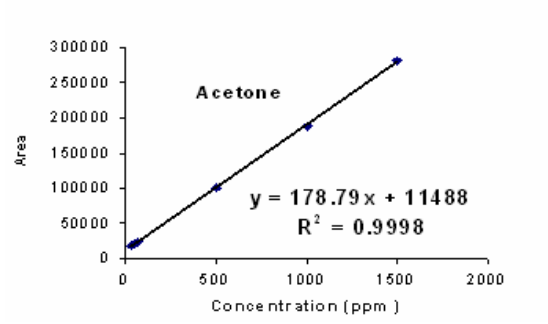
The method was found to be applicable for the routine analysis of the APIs like Omeprazole in pharma.

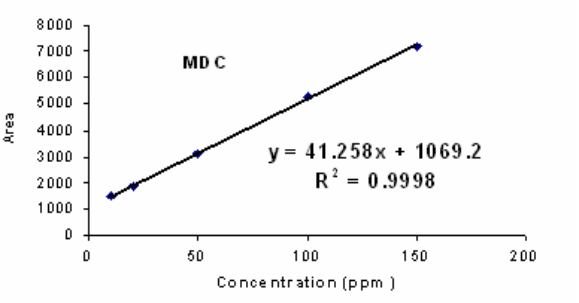
Table 4. Linearity and accuracy of residual solvents

	Linearity			Accuracy		
Solvents	Range (%)	R^2	Slope	Recovery (%)	Average	RSD (%)
Methanol	0.05-8.0	0.9999	34.02	95.2-101.1	98.7	5.25
Acetone	0.05-8.0	0.9998	178.79	97.6-102.6	99.4	4.29
IPA	0.05-8.0	0.9996	49.604	98.0-101.8	99.8	5.40
MDC	0.01-8.0	0.9998	41.25	97.8-102.0	99.6	5.41
Toluene	0.01-0.8	0.9988	190.42	98.6-101.5	99.7	4.24









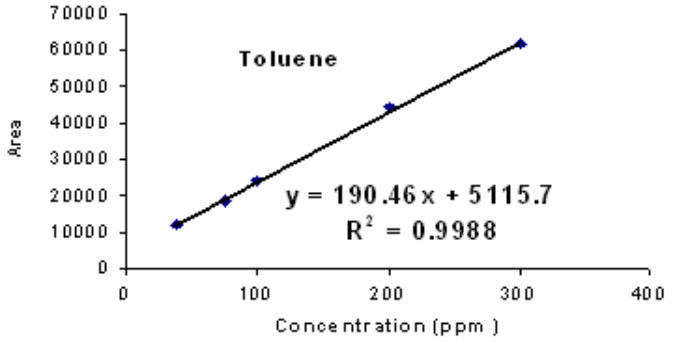


Figure-1. Calibration plots for residual solvents

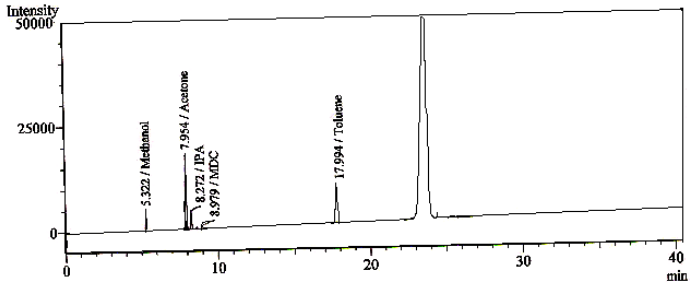


Figure-2. Chromatogram of Residual solvents

References

1. International Conference on Harmonization, Impurities in new drug substances, 2002.
Available from: http:// www.ich.org

2. **Hymer CB**,(2003) Residual solvent testing: A review of gas chromatographic and alternative techniques. *Pharm Res*; 23:337-44.

3. International Conference of Harmonization, Impurities in new drug substances, 1997.Available from: http:// www.ich.org.

4. **Camarasu, C.C. Szjits, M.M., Varga, G.B**. Residual solvents in pharmaceutical Products by Gas chromatography headspace. *J. Pharm. Biomed. Anal*. **1998,** 18, 623

5. **Raghani, A. R**. High speed gas chromatographic analysis of solvents in pharmaceutical using solid phase microextraction.*J. Pharm. Biomed. Anal*. **2002**, 29.
507.

6. **Camarasu, C.C.** Unknown residual solvents identification in drug products by head space solid phase microextraction GC-MS. *J. Pharm. Biomed. Anal.***2000**, 23. 197.

7. **Coran, S.A., Giannellini, V., Furlanetto, S. Massimo. B.A., Pinzauti, S.** ImprovingGas chromatographicdetermination of residual solvents in pharmaceuticals by the
Combined use of head space solid-phase microextraction & isotopic solution. *J. Chromatogr. A.* **2001**, 915, 209.

8. **Rocheleau, M.J., Titley, M. Bolduc**, Measuring residual solvents in pharmaceutical
samples using fast gas chromatography techniques. J. *J.Chromatogr*. B. **2004**, 805, 77.

9. **Legrand, S., Dugay,** Use of **solid**-phase **microextraction** coupled with gas
Chromatography for the determination of residual solvents in pharmaceuticals in
pharmaceutical products. **J., Vial, J**. *J. Chromatogr. A.* **2003**, 999, 195.

10. **Klick, S., Skold, A.** Validation of generic analytical procedure for determination of
Residual solvents in drug substances. *J. Pharma. Biomed. Anal*. **2004**.36, 401.

11. **Shirey R**. Unknown residual solvents identification in drug products by headspace-
Gas chromatography-mass spectrometry, *J. High Resol chromatogr* 1995: 18: 495-9.

12. **Kolb, B: Ettre, L. S**. Static Headspace-Gas Chromatography: Theory and Practice:
Wiley-VCH: New York, **1997**; pp 3-4.

13. **Grote C, Pawliszyn**. Unknown residual solvents identification in drug products by
Headspace solid phase microextraction gas chromatography. J Anal Chem 1997. 69.
587-98.

14. **Page B, lacroix G.** Unknown residual solvents identification in drug products by
headspace solid phase microextraction gas chromatography-mass spectrometry. J
Chrmatogr. 1993. 648: 199-211.

15. **C.W. Howden**.(1990) Clinical pharmacology of omeprazole. Clin. Pharmacokinet,
20: 38-40.

16. **N. Sarisuta, T. Tourtip, and S. Chuarcharoern**. (1998), Chemical stability and
mechanism of degradation of omeprazole. *Thai. J. Pharm Sci.* 22:81-88.

17. **L. Marzocchi, J. R. Moyano, A. Rossi. P. Munoz, M. J. Arias, and F. Giordano**.
(2001).Current status of ATP-ase proton pump inhibitor complexation with
cyclodextrins. *Biolog. J. Armenia*. 53:176-193.

18. United States Pharmacopoeia (USP), (2006**)**, 1577-1578.

19. **Anderson, T**.(1996) Pharmacokinetics, metabolism & Interactions of acid pump
inhibitors. *Clinpharmacokinet.* 31. 2-98.

20. **Mayer, UA**, (1996) Interactions of proton pump inhibitiors with cytochromes p450,
consequences for drug interactions. *J. Biol. Med* 69-203-209.

21 **Rocheleau, M.J: Titely, M: Bolduc, J**.(2004) *J. Chromatogr. B.* 805, 77

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