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Gas chromatographic methods for residual solvents analysis

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ABSTRACT

Gas chromatographic methods were developed and validated for the routine analysis of residual solvents in pharmaceuticals. Methods were compared for the simultaneous estimation of 6 residual solvents viz; methanol, ethanol, acetone, isopropyl alcohol, dichloromethane and toluene. The column of intermediate polarity BP-624 (6% cyanopropyl phenyl and 94% polysiloxine) eluted all six solvents within 8 min. The method has been compared by non polar column EC-5 (5% phenyl and 95% dimethyl polysilixone) column has elutedwithin 5 min and compared. Results indicated for simultaneous residual solvent analysis of solvents than, both column showed good resolution between the separated peaks. Methods were validated as per ICH method validation guidelines. The validation data of both the methods was compared and indicates both methods are sensitive, specific, precise and rugged for simultaneous residual solvents analysis of methanol, ethanol, acetone, isopropyl alcohol, dichloromethane and toluene

Key words: Optimization, residual solvents, organic volatile impurities, gas chromatography.

INTRODUCTION

The determination of residual solvents in the drug substances, excipients or drug products is known to be one of the 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. Organic impurities[1-3] may arise during the manufacture or storage of new substance. They may be identified or unidentified, volatile or non volatile; include starting materials, by-products, intermediates, degradation products, reagents, ligands and catalysts. Apart from the use of solvents in the manufacture of drugs substance, large quantities of organic solvents are frequently used to dissolve the film coating materials such as methyl cellulose and ethyl cellulose to facilitate application on to compressed tablets. Hence evaluation of organic volatile impurities (OVI's) is considered as an important tool in the quality control of pharmaceuticals. Presently in the pharmaceutical industries, special importance given for residual solvent testing. As these residual solvents are potentially undesirable substances, they either modify the properties of certain compounds or are hazardous to the health of the individual. OVI's also affect physico- chemical properties of bulk drug substances. Crystallinity[4-7] of the bulk drug can be affected, as difference in the crystal structure of the bulk drug may lead to change in dissolution properties and problems with formulations of the finished product. Finally, residual solvents can create odour problem and colour change in the finished products.

Two fundamental issues of drug therapy are safety and efficacy of pharmaceuticals. The safety of the drug is determined by its pharmacological, toxicological profile and adverse

effects. The residual solvents in APIs possess toxicological effects, so ICH has prescribed acceptable limits for residual solvents in APIs[1]. The content of residual solvents in APIs analyzed by gas chromatography. GC applications include analysis of APIs to comply with good laboratory and good manufacturing practices as well as in process testing of residual solvents[2]. Over the last decade, several GC methods to monitor residual solvents have been reported in the literature.

EXPERIMENTAL

Instruments and materials

Gas Chromatograph Shimadzu 17A version 3 was used in the development and validation of GC method. Gas chromatograph was equipped with standard oven for temperature ramping, split/split less injection ports and flame ionization detector. The comparative studies were carried out using BP 624 column (30m × 0.53mm i.d. × 0.25µm coating thickness, 4% cyanopropyl phenyl and 96% dimethyl polysiloxane stationary phase, intermediate polar column) and non polar column EC-5 (5% phenyl and 95%-di methyl poly siloxane), with nitrogen as carrier gas in the split mode by direct injection method. Analytical grade solvents methanol, ethanol, acetone, isopropyl alcohol, dichloromethane, toluene and dimethyl sulphoxide (DMSO) were purchased from Thomas Baker, Mumbai, India.

Temperature programming

Initial temperature maintained at 40° C for five min and then increased at a rate of 10° Cmin-1 to 55° C min 1 and maintained for 5min, finally increased at the rate of 10° Cmin-1 to reach the final temperature of 200° C and maintained for 5 min for BP-624 column. For EC-5 column, initial temperature was maintained at 35°C for 3 min and then increased at a rate of 3°Cmin-1 to 55°C min 1 and maintained for 3 min, finally increased at the rate of 25°C min-1 to reach the final temperature of 200°C and maintained for 2 min.

Standard stock preparation

Volume 0.1ml of pure methanol, ethanol, acetone, isopropyl alcohol, dichloromethane and toluene were taken separately in 10 ml volumetric flask and diluted using dimethyl sulphoxide. 1µl of these solutions were injected separately into the gas chromatograph, the retention time was observed with the same chromatographic conditions using BP-624 and EC-5.

Preparation of mixture of six solvents

Dimethyl sulphoxide (DMSO) was selected as the standard and sample diluent, based on its ability to dissolve wide variety of substances and high boiling point that does not interfere with more volatile solvents analyzed by GC. Standard stock of each solvent methanol, ethanol, acetone, isopropyl alcohol, dichloromethane and toluene was prepared by diluting with DMSO. Working standard

Table 1: Retention time of 6 solvents

S. No.	Solvent	Column BP-624		Column EC-5	
		Retention time of separate injection (min)	Retention time of mixture(min)	Retention time injection (min)	Retention time of mixture(min)
1.	Methanol	3.77	3.72	2.38	2.31
2.	Ethanol	5.19	5.26	2.73	2.62
3.	Acetone	6.02	5.96	2.93	2.87
4.	Iso propyl alcohol	6.21	6.28	3.00	2.92
5.	Dichloromethane	7.09	6.68	3.40	3.27
6.	Toluene	7.61	7.30	2.91	4.67
7.	Dimethyl sulfoxide	7.53	7.41	4.73	4.75

of each solvent ranging from concentration 100ppb to5600 ppm was prepared with DMSO in 10 mL volumetric flasks. 1µL of each working standard was injected in to gas chromatograph and standard calibration curve.

Method Validation

The analytical method validation was carried out as per ICH method validation guidelines[9]. The validation parameters addressed were specificity, precision, linearity, limit of detection, limit of quantitation, ruggedness and system suitability.

RESULTS AND DISCUSSION

Development of method

Gas chromatographic methods were developed for the analysis of 6 residual solvents with BP-624 (Intermediate polar) and EC-5 (non polar) columns. Both methods were showed good separation and resolution between the peaks of 6 solvents in 8 min (Fig. 1) and EC-5 has shown

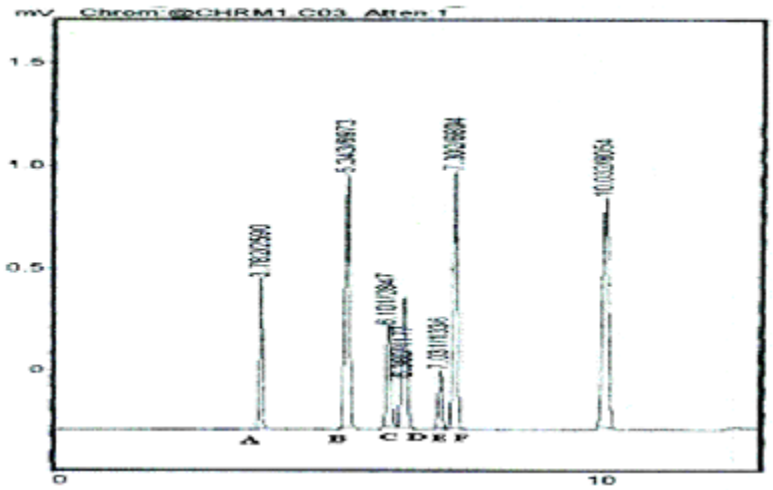

Fig. 1: Chromatograms for mixture of six solvents by BP-624 column

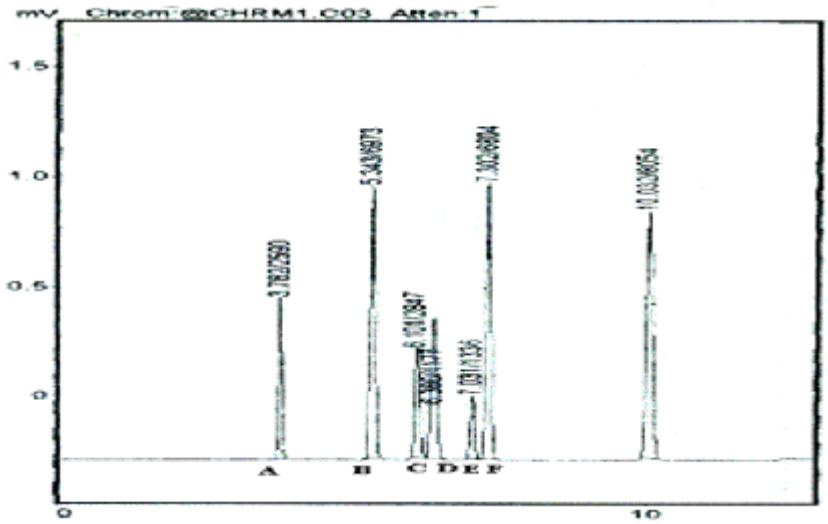

Fig. 2: Chromatograms for mixture of six solvents by EC-5 column

Table 2: Validation data for Column BP- 624 and EC-5

	LOD(ppm)/(ppb)	LOQ(ppm)/(ppb)		Linearity(ppm)/(ppb)		Linearity		Ruggedness(%) assay)		Precision (%RSD)	
		Visual	Stat	Visual	Stat	Regression	R2	Analyst 1	Analyst 2	Method	System
BP-625	Methanol	8	0.0033	200	0.0101	979.69x-16185	0.9997	94.89	95.12	0.16	0.65
	Ethanol	6	0.0003	100	0.0009	10386x-843897	0.9952	96.12	96.59	0.02	1.3
	Acetone	2	0.0015	10	0.0045	2149.4x-158807	0.9971	101.10	100.89	0.84	10.41
	Isopropyl alcohol	9	0.0027	100	0.0081	1214x-59559	0.9963	96.10	96.25	0.17	1.42
	Dichloro-methane	3	0.0049	40	0.0149	661.1x+35681	0.9995	98.25	98.45	6.97	1.36
	Toluene	10	0.0010	50	0.003	3256.2x-32571	0.9952	98.25	100.12	0.42	1.48
EC-5	Methanol	70	0.0057	100	0.0171	577.46x+11919	0.9988	95.15	95.69	15.63	10.21
	Ethanol	70	0.0028	100	0.0084	1172.4x-14170	0.9983	96.69	96.25	0.75	4.727
	Acetone	100	0.0051	300	0.0155	634.61x+29671	0.9986	100.65	100.10	3.51	9.24
	Isopropyl- alcohol	200	0.0546	300	0.1638	60.294x-846.85	0.9979	96.55	99.23	6.57	12.43
	Dichloro-methane	60	0.1052	100	0.3156	31.346x-640.66	0.9994	98.78	98.78	7.47	3.52
	Toluene	80	0.0028	150	0.0086	1147.8x+7147	0.9989	100.12	100.24	10.88	8.08

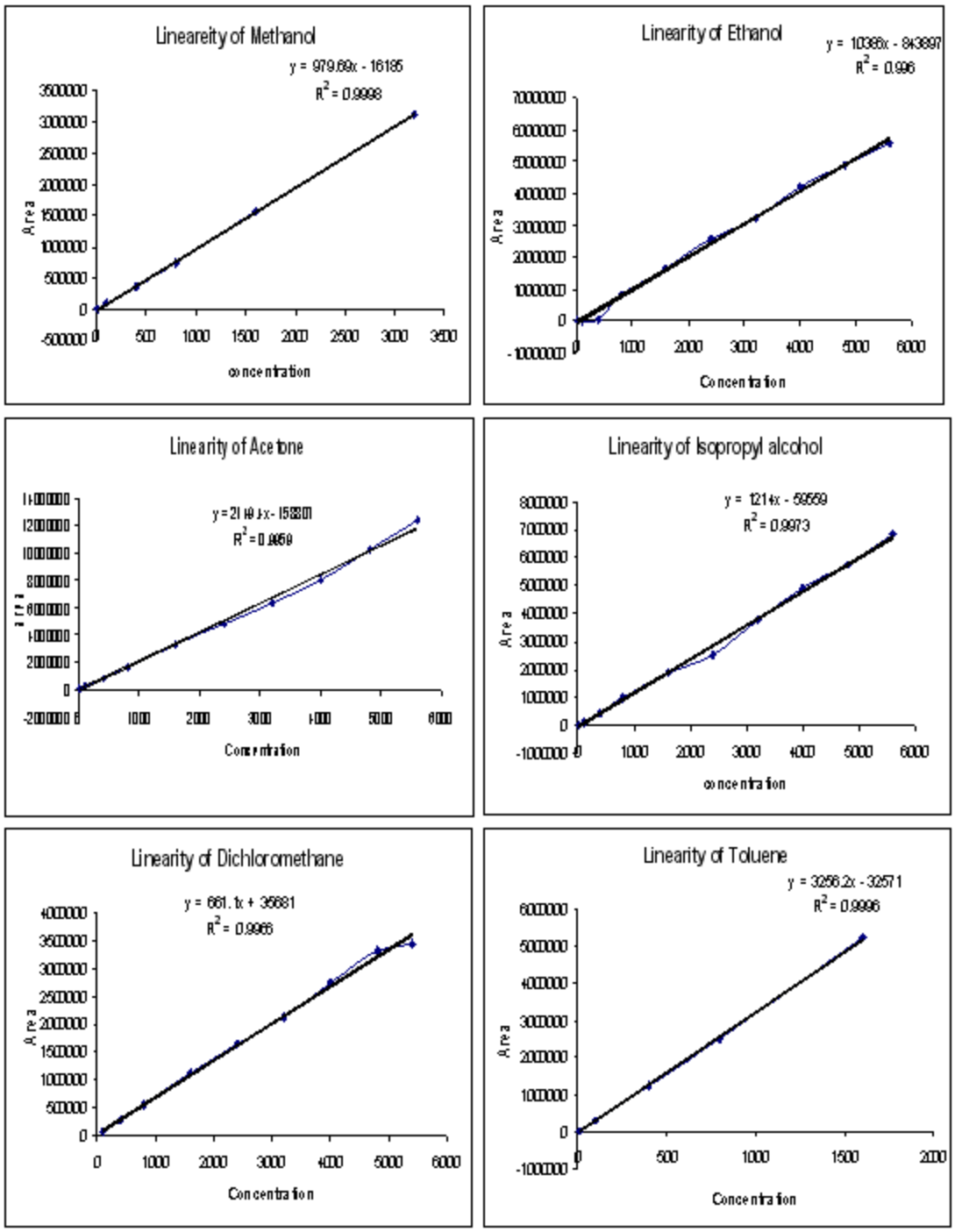

Fig. 3(A): Linearity of BP-624

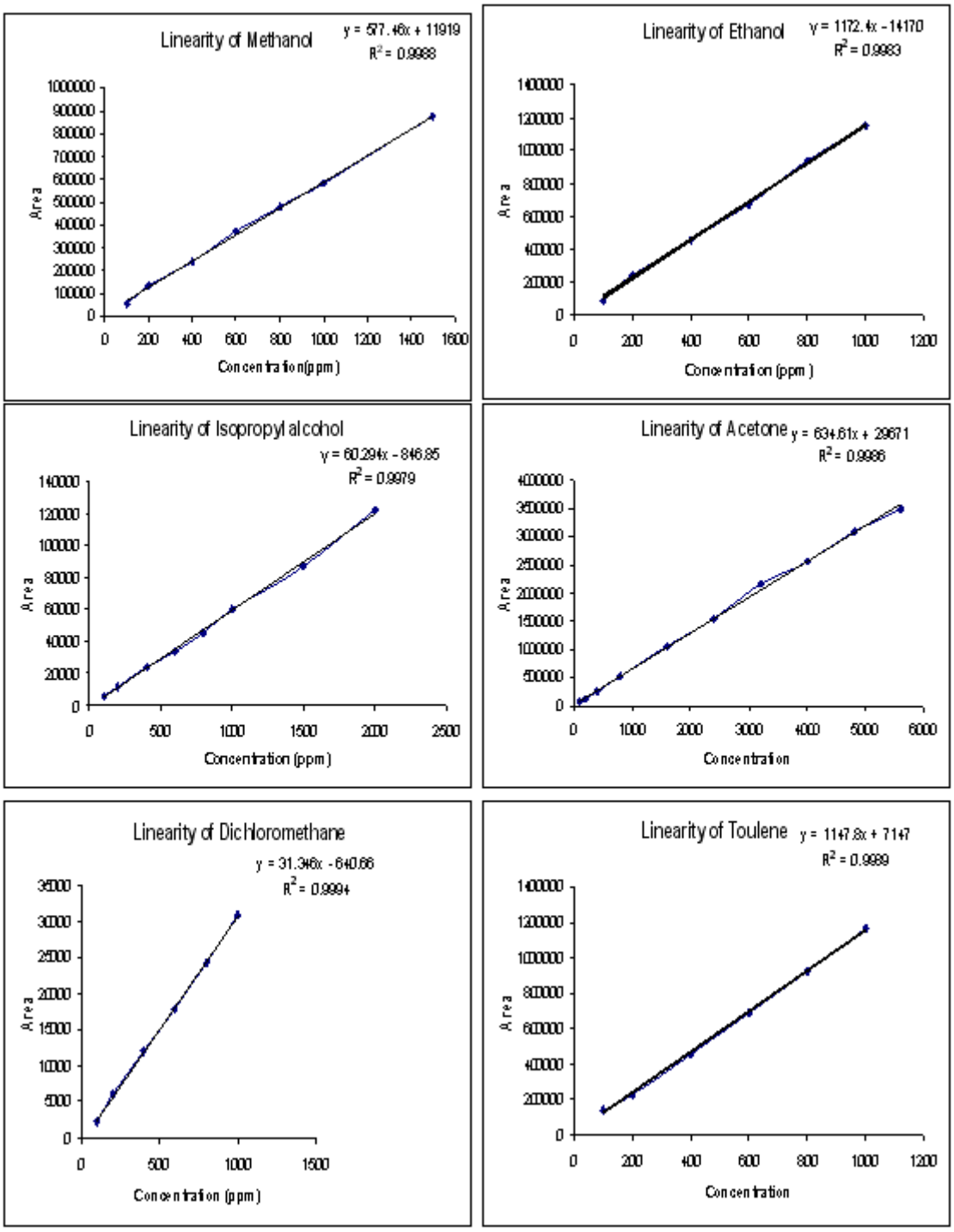

Fig. 3(B): Linearity of EC-5

elution of 6 solvents in 5 min. (Fig. 2). The peaks from the chromatogram were identified and standardized from the peak of the individual solvent chromatogram (Table 1).

Limit of Detection (LOD) and Limit of Quantitation (LOQ)

The LOD and LOQ were calculated by instrumental and statistical methods. In visualization method LOD is determined as the lowest amount to detect and LOQ is the lowest amount to quantify by the detector. For statistical method LOD and LOQ determined by statistical formula.

LOD = 3.3 R^2/Slope LOQ = 10 R^2/Slope

Values of LOD and LOQ for all six solvents by both columns were mentioned if Table 2.

Linearity and range

The linearity of solvent is its ability to elicit test results that are directly proportional to the concentration of analytes in samples within a given range.Linear regression equation and co-efficient of variance for all six solvents by both methods were mentioned in Table 2. Linearity graphs by BP-624 (Fig .3) and EC-5 column (Fig. 4).

Specificity

An injection of DMSO does not shown any peak in both columns s hence the proposed methods are specific for detection of methanol, ethanol, isopropyl alcohol, dichloromethane, acetone and toluene.

Ruggedness

The ruggedness for both methods were carried out by two analyst on different days the retention time and percentage assay for all six solvents were found to be within the acceptable criteria of 90-105% (Table 2-3)

Precision

Precision of the method and system expressed in terms of standard deviation and relative standard deviation. For the precision of method and system, six replicates of concentration of 100 ppm for each solvent of volume 1µL were injected. For the method precision %RSD of concentration for six solvents were calculated, for the system precision % RSD for peak areas were calculated. The % RSD for Precision of the method and system for all six solvents complies with the acceptance criteria of less than 15% (Table 4), hence the method and system is said to be précised.

CONCLUSION

By comparing all the datas and retention time of all the solvents it is conclude that non polar column EC-5 is best suited for the estimation of residual solvents because all the 16 solvents are resolved with in 15 minutes but in intermediate non polar column BP- 624 it took 30 minutes to resolve16 solvents, more over 8, 6, 2, 9, 3 and 10 ppm LOD, 200, 100, 10, 100, 40and 50 ppm LOQ was determined by BP-624,for EC-5 column 70,70,100, 200, 60, 80 ppb LOD and 100, 100, 300, 100 and 150 in ppb , hence EC-5 column is more selective and sensitive for the estimation of residual solvents in pharmaceuticals.

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