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Residual solvent analysis by headspace gas chromatography

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Abstract

An automated headspace GC method was developed and validated for the analyses of eight common process solvents and the five solvents whose quantification is required by the US Pharmacopeia. The sample is dissolved in dimethylformamide solvent and the equilibrium headspace gas formed at 60°C is analyzed using a megabore capillary column. Quantification is performed by the standard addition technique to eliminate any possibility of matrix effects. This method is sensitive, precise, accurate and linear in the range of interest.

1. Introduction

The quality and stability of a pharmaceutical drug substance, product and excipient could be affected by the presence of volatile impurities. Volatile impurities are often residual solvents used in the synthesis and crystallization which escape drying. Solvents can be bound to the drug substance with varying strengths depending on the mechanism. Solvates contain the solvent molecules as a part of the crystal lattice. This type of solvent cannot be analyzed without first releasing it in a homogeneous solution. Solvents are best analyzed by gas chromatography [1–4]. Direct injection, purge-and-trap and headspace injections are common ways of introducing the sample in GC. Direct injection of a solution of a non-volatile drug substance could be detrimental to the performance of the injection system of the gas chromatograph and also to high-performance capillary columns. Further, interaction between the solvents and the sample in the injection port could lead to recovery problems [5]. For reliable results, it is important that the chromatographic flow path is clean and free from residues and contaminants at all times. Built-up charred material in the injector from multiple injection of a non-volatile sample requires frequent and time-consuming cleaning procedures.

We describe here a general GC method that employs equilibrium headspace injection to eliminate the above problems associated with direct injection. The method utilizes a megabore capillary column for the separation of thirteen process solvents including benzene, methylene chloride, chloroform, 1,4-dioxane and trichloroethylene whose testing is required by the US Pharmacopeia (USP). The USP method IV describes the analysis of these solvents by headspace chromatography using manual injection [6]. This method is fully automated, sensitive, precise, accurate and linear over the range 30–300% of the target concentration of 30 ppm for all of the solvents. Quantification was performed

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by the method of standard additions to eliminate any possible drug matrix effect.

2. Experimental

2.1. Reagents and materials

Drug samples were obtained from the Chemical Process Research Department of Rhône-Poulenc Rorer Central Research. Solvents used were of ≥99% purity and were purchased from the following sources: acetone, acetonitrile, ethyl acetate, methanol, methylene chloride, 2-propanol, ethanol, chloroform, benzene, trichloroethylene, toluene, 1-propanol, 1,4-dioxane and methane from Fischer Scientific (Malvern, PA, USA), tetrahydrofuran from Fluka (Buchs, Switzerland) and dimethylformamide (DMF) of Omni-Solv grade, used as the solvent to dissolve the sample and to prepare a standard of the above thirteen solvents, from VWR Scientific (Bridgeport, NJ, USA). DMF was purged with helium for 2 h to free it from trace-level volatiles prior to use.

2.2. Chromatographic system

Experiments were performed on a Hewlett-Packard Model 5890 Series II gas chromatograph equipped with a Model 19395A automated headspace unit. Flame ionization detection was used. Chromatographic data were collected and handled via the in-house Waters ExpertEase chromatographic data management system.

2.3. Chromatographic method

A Supelco Nukol, acid-modified, bonded polyethylene glycol capillary column (60 mm × 0.53 mm I.D.) with a 0.50-μm film thickness was utilized for chromatographic separation of the solvents. The carrier gas was helium at a total flow-rate of 4.2 ml/min. A minimum helium flow-rate of 0.2 ml/min from the GC injector was used to avoid any sample backup in the latter during injection from the headspace autosampler. The remainder of the gas flow was obtained from the headspace autosampler. Injections were made in the splitless mode through a packed-column injector adapted for megabore operation. The injector was maintained at 150°C and the detector temperature was 250°C. Helium, at a flow-rate of 20 ml/min, was used as make-up gas. The temperature program involved an initial oven temperature of 35°C for 10 min, increased at 2°C/min to 50°C and then at 3°C/min to 80°C. In order to remove the solvent DMF, the ramp rate was then increased to 20°C/min up to 190°C and held there for 5 min. Headspace autosampler conditions were as follows: servo air pressure, 3.0 bar; auxiliary pressure, 1.2 bar; bath temperature, 60°C; injection loop temperature, 100°C; sample thermal equilibration time, 15 min; sample vial pressurization for 10 s; headspace vent opened for 15 s; and inject time, 18 s. These headspace events were all separated from each other by a 3-s delay time.

2.4. Sample and standard preparation, quantification and calculations

A standard containing 1000 μg/ml of each of the thirteen solvents was prepared by first partially filling a 50-ml volumetric flask with the solvent DMF, weighing it with the stopper, injecting 0.050 g of each solvent into the flask and weighing it again after replacing the stopper. This solution was then diluted to volume with DMF and stored in a refrigerator after use.

Sample solution was prepared by weighing accurately 100 mg of the drug substance in a 10-ml volumetric flask and dissolving it in the same batch of DMF followed by dilution to volume. Four 1.0-ml aliquots of this solution were placed in four separate 10-ml capacity headspace vials. Standard additions were made in three of these vials by introducing 10, 20 and 30 μl of the standard solution. All four of the vials were sealed properly with a crimper before placing them in the headspace.

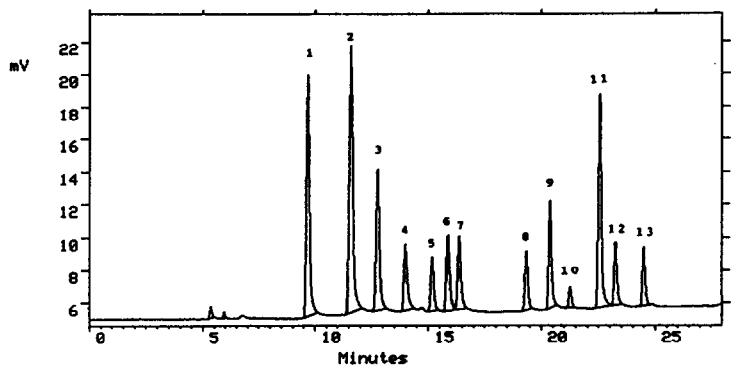


Fig. 1. Headspace GC of a 10 ppm standard solution containing thirteen solvents. Peaks: 1 = acetone; 2 = tetrahydrofuran; 3 = ethyl acetate; 4 = methanol; 5 = methylene chloride; 6 = benzene or 2-propanol; 7 = ethanol; 8 = trichloroethylene; 9 = acetonitrile; 10 = chloroform; 11 = toluene; 12 = 1-propanol; 13 = 1,4-dioxane.

3. Results and discussion

In a sealed vial, an equilibrium is reached between a liquid and its vapor. The composition of the vapor phase is the same as that of the liquid at a given temperature and pressure. By analyzing the vapor phase, the content of the solvents in the solution can be determined.

The use of wide-bore capillary columns in GC determinations has specific advantages owing to the capacity and the efficiency characteristics of these columns. Columns of 0.53 mm I.D. have become popular for headspace analysis because they can be operated in a range of carrier gas flow-rates which is suitably high to reduce peak broadening due to the dead volumes in headspace autosampler components [7]. We employed a 60 m × 0.53 mm I.D. Nukol column, which provided the selectivity required for the separation of the thirteen solvents contained in the standard solution described above. The choice of DMF as the solvent was based on its solvent strength and retention on the Nukol column, which allows its elimination from the system after the peaks of interest but within a reasonable analysis time of 35 min. Fig. 1 shows a chromatogram resulting from a headspace injection of the standard solution. Under these chromatographic conditions, 2-propanol coelutes with benzene. These two solvents can be analyzed by this method if they are not present together.

The concentration of a solvent in the headspace is dependent on the temperature of the solution. We selected 60°C as the lowest temperature that was required to obtain a sufficient signal from an injection made under the given headspace conditions from a 10.0-ml capacity headspace vial containing 1 ml of a 10 ppm standard solution. Higher temperatures provide better sensitivity but the possibility of thermal degradation will also increase.

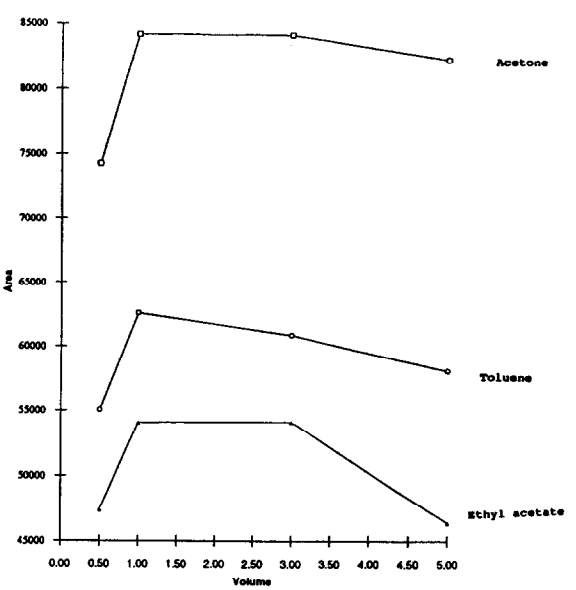
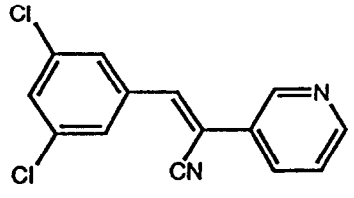


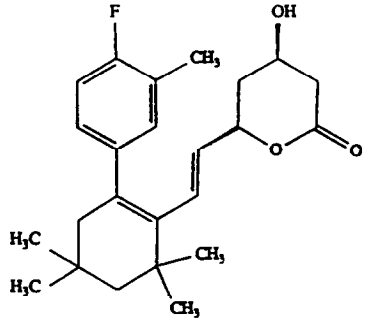
Fig. 2. Effect of sample solution volume on the peak areas of three solvents for an equilibration time of 15 min.

The choice of a 1-ml volume of the sample solution (10 mg/ml) in a 10-ml capacity vial was based on choosing a ratio of solution-phase and gas-phase volumes which provides the best sensitivity. We studied the effect of varying the ratios of liquid- to gas-phase volumes on the sensitivity of three different solvents. Fig. 2 shows that the best sensitivity is achieved with a sample volume of 1 ml contained in a 10-ml vial for a 15-min equilibration time.

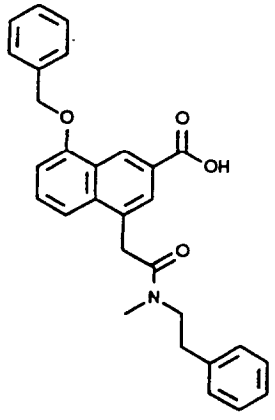
For solubility reasons, the minimum concentration to achieve the desired sensitivity will be desirable. Lower concentrations are also preferable to minimize any possible matrix effects. Solute–solvent interaction in the sample solution can influence the activity of an analyte solvent [8]. In the presence of such a matrix effect, quantification by an external standard method may provide misleading results. We therefore decided to employ the standard additions method for quantification. In this standard additions method, a sample is analyzed alone and after addition of three incremental levels of a standard solution. The detector response from the four vials is plotted on the ordinate against the amount (ppm) of standard added. A standard plot is thus obtained for each sample. The x-intercept can be determined by dividing the y-



(1)
Basic



(2)
Neutral



(3)
Acidic

Fig. 3. Structures of the three compounds used to demonstrate recovery and linearity from acidic, basic and neutral matrices.

intercept of the fitted line by the slope. The amount of solvent (ppm, w/w) in the sample was calculated as follows:

$$\text{solvent (ppm)} = \frac{x}{y} \cdot 1000$$

where x is the x-axis intercept (ppm) and y is the mass of the sample in nanograms.

Linearity and recovery experiments were performed using three types of analytes including a basic, an acidic and a neutral drug substance (Fig. 3). The results of linearity experiments for the fourteen solvents using compound **2** (Fig. 3) as the sample matrix are given in Table 1. Comparable results were obtained for compounds **1** and **3**.

Recovery experiments were performed using compounds **1**, **2** and **3** at eight levels from 1 to 50 ppm. Table 2 gives typical recovery results for 10, 30 and 50 ppm levels obtained for compound **2**. The recovery results for compounds **1** and **3** were comparable.

An analysis time of 3 h is required for the standard additions method described here. This time is acceptable for bulk drug lot analysis as the method is fully automated. For higher throughput work, this method can easily be converted into one-point standard addition or external standard methods [2].

4. Conclusions

An automated headspace GC method was developed to analyze eight common process and five USP solvents. This method employs a high-

Table 1
Linearity data using compound **2** as the sample matrix
Linearity of detector response of all fourteen residual solvents

Solvent	Intercept (ppm)	Slope	r^2
Acetone	0.78	12288.12	0.9999
Tetrahydrofuran	0.47	15173.33	0.9999
Ethyl acetate	0.93	7207.32	0.9999
Methanol	1.74	3377.45	0.9998
Methylene chloride	0.55	2726.40	0.9999
2-Propanol	0.66	570.87	0.9998
(Benzene)	0.19	17342.11	0.9999
Ethanol	2.14	3688.07	0.9997
Trichloroethylene	0.75	2523.98	0.9999
Acetonitrile	2.00	4880.66	0.9994
Chloroform	2.78	770.10	0.9991
Toluene	0.99	8556.96	0.9995
1-Propanol	2.08	2253.50	0.9992
1,4-Dioxane	0.88	2362.54	0.9998

Typical residuals table depicting the solvent ethyl acetate

Concentration (ppm)	y Observed	y Predicted	Residual
9.52	$6.43 \cdot 10^4$	$6.18 \cdot 10^4$	2498.40
19.04	$1.29 \cdot 10^4$	$1.30 \cdot 10^4$	−1405.80
38.08	$2.68 \cdot 10^4$	$2.68 \cdot 10^4$	1118.78
47.60	$3.32 \cdot 10^4$	$3.36 \cdot 10^4$	−4012.92
76.16	$5.43 \cdot 10^4$	$5.42 \cdot 10^4$	1416.48
95.20	$6.78 \cdot 10^4$	$6.79 \cdot 10^4$	475.08

Table 2
Recoveries of the thirteen solvents spiked at 0.001%, 0.003% and 0.005% levels

Solvent	0.0001% spike (10 ppm)		0.003% spike (30 ppm)		0.005% spike (50 ppm)	
	Recovery (%)	r^2	Recovery (%)	r^2	Recovery (%)	r^2
Acetone	94.09	0.9997	98.27	0.9994	102.62	0.9994
Tetrahydrofuran	96.13	0.9998	95.71	0.9968	102.83	0.9994
Ethyl acetate	93.49	0.9998	97.84	0.9992	98.32	0.9991
Methanol	101.20	0.9999	99.17	0.9975	98.95	0.9991
Methylene chloride	95.98	0.9996	94.71	0.9945	100.38	0.9991
2-Propanol	92.80	0.9988	102.70	0.9973	95.48	0.9994
Ethanol	98.04	0.9984	93.53	0.9995	96.42	0.9998
Chloroform	94.25	0.9994	980.8	0.9999	101.38	0.9994
Acetonitrile	95.45	0.9999	99.32	0.9979	98.81	0.9994
Trichloroethylene	94.57	0.9999	99.44	0.9979	101.57	0.9997
Toluene	90.85	0.9997	99.00	0.9997	94.95	0.9982
1-Propanol	96.82	0.9992	99.79	0.9978	94.04	0.9946
1,4-Dioxane	94.99	0.9996	103.59	0.9988	98.94	0.9996

Percentage calculated on 10 mg of drug substance mass basis as described in Section 2.4.

performance megabore capillary column and standard additions for quantification. The method has been shown to be general, sensitive, precise, accurate and linear in the range of concentrations of interest.

5. References

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