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Analysis of Residual Solvents in Pharmaceutical Base Materials by Purge and Trap Gas Chromatographic technique

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□ ABSTRACT □

A purge and trap method was investigated for the determination of different types of residual solvents in pharmaceuticals in aqueous solutions. Samples were purged at room temperature, 40°C and 60°C and the analytes were trapped on activated carbon. The trap was extracted with CS_2 and then solution injected into a gas chromatograph equipped with a flame ionization detector. The method was validated for two groups of residual solvents (aromatic hydrocarbons and alcohols with acetone).

Key Words
Gas chromatography
Purge and trap
Residual solvents

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تحديد بقايا الأثر المتبقي في المواد الفعالة للأدوية بواسطة الاستخلاص الغازي والمصيدة واستخدام الكروماتوغرافية الغازية

الدكتور يوجف بالا *
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(قبل للنشر في 2002/10/15)

□ الملخّص □

استخدمنا تقنية الاستخلاص الغازي والمصيدة لتحديد أنواع مختلفة من بقايا المحلات العضوية في المحاليل المائية للأدوية، تم الإستخلاص الغازي (الذي هو عملية جرف المركبات من المحلول بواسطة غاز خامل مثل الهواء- النتروجين) في درجات حرارة مختلفة هي درجة حرارة الغرفة وفي الدرجات 40 و60 مئوية، حيث استخدمنا مصيدة من نوع الكربون الفعال.

تم اعادة الاستخلاص تلك المحلات بحل المصيدة في كمية معلومة من كبرتيد الكربون ثم حقنت الى جهاز الكروماتوغرافية الغازية المزودة بكاشف اللهب.

حققت هذه الطريقة من اجل مجموعتين من المحلات العضوية (بعض المركبات العضوية وبعض المركبات الكحولية والأستون الشائعة الاستخدام لدى تحضير المواد الفعالة صناعيا).

حددنا في البداية الزمن المثالي اللازم لجرف المحلات من محاليلها المائية باستخدام غاز خامل (نتروجين) وقد وجدنا أنه من أجل المحلات القطبية أن الزمن الجرف 40 دقيقة أقل ما يمكن، أما من أجل المحلات العضوية الأقل قطبية فإن الزمن الجرف 50 دقيقة أقل ما يمكن.

يمكننا الاستخلاص من النتائج بأن طريقة الاستخلاص الغازي والمصيدة مع استخدام الكروماتوغرافية الغازية هي طريقة جيدة لتحديد أثار (10 ppm) * المحلات العضوية في محاليل الأدوية المائية.

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Introduction:

The analysis of volatiles and semi-volatile organics, in soil [1], drinking and environmental water [2], [3], [4] has been made by purge and trap technique combined with gas chromatography. On this literature base we tried to use this one in the case of different pharmaceutical base materials.

The method consist of three steps as follows: The first step is the purge of residual solvents from aqueous solutions of pharmaceutical base materials, the second is the trapping on activated carbon, then the third step is removal of the trapped analytes by extraction with a small amount of a suitable solvent [2 cm^3 CS_2]. An aliquot of this solution is subsequently injected into a gas chromatography system for separation and identification of the analytes [5]. The purging process can be expressed for the i-th analyte by this expression:

$$\frac{dm_{i,g}}{dt} = - m_{i,g} \frac{F}{V_g + K_i V_l} \qquad (1)$$

after integration from $m_{i,g}$ until $m_{i,o}$ we can write this equation in the following:

$$m_{i,o} = m_{i,g}\, e^{- \frac{F\,t}{V_g + K_i V_l}} \qquad (2)$$

where $m_{i,o}$ is the total mass of the analyte in the liquid phase, $m_{i,g}$ is the mass of the analyte in the gaseous phase, F the volumetric flow of purge gas, V_l and V_g are the volumes of the liquid and gaseous phases and K_i a partition coefficient. We can write Eq. (2) in a simple form:

$$m_{i,o} = m_{i,g} e^{- Bt} \qquad (3)$$

where

$$B = \frac{F}{V_g + K_i V_l} \qquad (4)$$

The "purge time" can be calculated by the following equation:

$$t_{95\%} = \frac{3}{B} \qquad (5)$$

Where $t_{95\%}$ is the time needed to purge 95% of sample.

Method of Quantitative Analysis

The use of chromatographic method for quantitative analysis of analyte is based on the fact that the peak area is proportional to the amount (alternatively to the concentration

in the case of constant volume injections) of the analyte injected. Detectors do not always produce signals proportional to the amount of the analytes in all instances. The range in which the detector response is directly proportional to the amount of the analyte is known as the linear dynamic range of the detector. Thus it is necessary that the concentration of the analyte fall into this linear response region of the detector. In the linear range the concentration (amount) of the analyte is directly proportional to the area under the peak. We have used in this work the internal standard method (**ISTD)** in quantitative gas chromatographic analysis. The most important advantage of the internal standard method is that the volumetric measurement error of sample preparation and introduction (using micro-syringes) can be eliminated [5]. The basis of the internal standard method is the determination of the relative sensitivity (relative response factor). The ratio of the response factors of two analytes in the same environment is a constant if the experimental conditions are practically the same. The areas of a given analyte peak and of the internal standard peak (A_s and A_i, respectively) are obtained from the chromatogram of a reference sample and are then used to calculate the relative sensitivity by the following formula:

$$\mathbf{f_i} = \frac{\mathbf{m_s\ A_i}}{\mathbf{m_i\ A_s}} \text{ or } \mathbf{f_i} = \frac{\mathbf{C_s\ A_i}}{\mathbf{C_i\ A_s}} \qquad (6)$$

where m_i (C_i) is the mass (concentration) of a given analyte to be measured and m_s (C_s) is the mass (concentration) of the internal standard. In the main experiment we mix the known quantity of the unknown sample to be analysed (G) and the internal standard (m_s^*) and take some measurements. From these chromatograms we can calculate the concentration of unknown residual solvents ($C_{i,x}$ **,** analyte):

$$\mathbf{C_{i,x}} = \frac{\mathbf{m_s^*\ A_i^*}}{\mathbf{f_i\ A_s^*\ G}}\ \mu g/g \qquad (7)$$

where the ratio $\frac{A_i^*}{A_s^*}$ is obtained from the chromatogram of an unknown sample, m_s^* (mg) is the mass of internal standard which is added to the purged unknown sample, G (g) is the mass of sample (pharmaceutical base material).

Experimental
Instrumentation and Condition

Gas chromatographic measurements were performed on a Shimadzu GC-14A gas chromatographic system, using a 15m x 0.32mm i.d. SPB^{TM}-1 fused-silica column (Supelco catalog no. 2-4295; maximum operating temperature 320 ^oC) with 5 □m of film thickness. Nitrogen was used as a carrier gas at a linear flow of 20 cm s^{-1}. The injected volume was 1 ml. Two column oven temperature programmes were used: 1 from 40 ^oC, held isothermal for 2 min, to 150 ^oC at 10^{o}min^{-1} (programme 1., Figure 4.), 2. from 80 to 200 ^oC at 20^o min$^-$

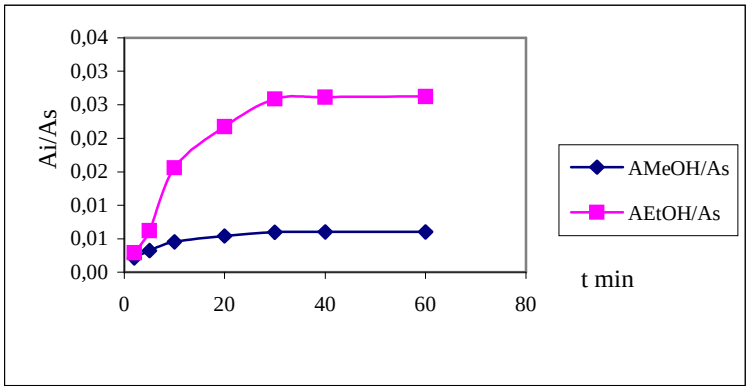
[1] (programme 2., Figure 5.). Flame ionization detection (FID) was performed with range 10 and attenuation 2; data were integrated with a Shimadzu C-R4AX Chromatopac devise. The injector and detector temperatures were both 200 ^{o}C. The sampler trap was packed with active carbon and the vessel was attached to the sampler purged with nitrogen at 15 min^{-1} for 30, 40 and 60 min. The purges were done at three different temperatures (room temperature, 40 and 60 ^{o}C).

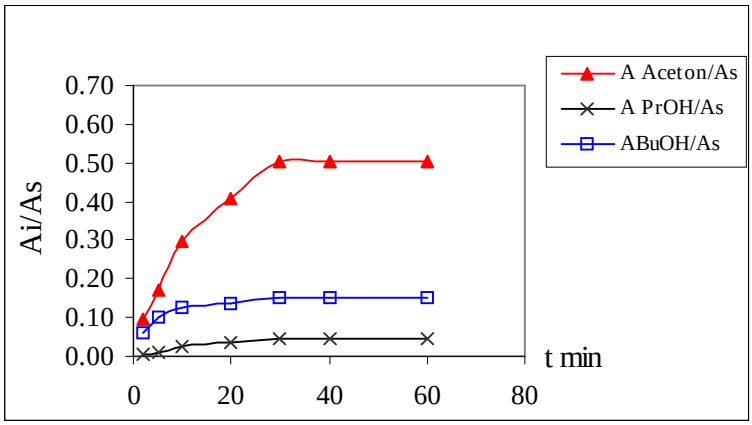
Results and Discussion

We have used off-line "purge and trap" sample preparation and gas chromatographic analysis for the determination of residual technological solvent impurities in pharmaceutical base material. We wanted to show the possibilities of this method in this special field of application. (Now in the analytical practice the head-space analysis is mach more frequently used for this purpose.)

The determination of optimum "purge time" is very important to get a well repeatable result using this technique. On **Fig.1**. are shown the results of these measurements. This purge time means that time when the concentration of purged volatile compounds do not increase more in function of the time, these curves on the Fig.1. reach a constant value. (Beside the concentrations the ratio of the measured peak areas are given.) It can be seen that the optimal "purge time" is more than 40 minutes in the case of polar residual solvents (Methanol: MeOH, Ethanol: EtOH, Acetone, n-Propanol: PrOH and n-Buthanol: BuOH) and more than 50 minutes for non-polar residual solvents (Benzene, Toluene and o-Xylene). The relative responses factors (relative sensitivity) for each residual solvents, as defined by Eq. (6) are shown in **Table I-VI**. at different temperatures. The linearity of relative sensitivities of standard within the range of 20-50 ppm are shown in **Fig. 2.** and **3.**

We have investigated two different types of solvents in two pharmaceutical base materials **A** and **B** at different temperatures. **A** contained polar (MeOH, EtOH, Acetone, PrOH and BuOH) and **B** non-polar (Benzene, Toluene and o-Xylene) residual solvents. The results are given in the **Table VII**. and **VIII.** Data in these tables were calculated from 5 consecutive measurements. We have concluded from the results two important facts: the first was that the RSD% (relative standard deviation) was small at room (23 ^{o}C) temperature for both types of solvents (polar and non-polar), see Tables VII., VIII. The loss of analyte at higher temperature explained the increasing value of RSD%, and the higher temperature did not help to increase the LOD for residual solvents as shown in **Table XI.** The second fact was that there was no matrix effect at this technique. The repeatability and the accuracy of the measurement were practically the same in both type of base material. Finally we could conclude that this off-line purge and trap GC technique was quite god in range of 10 and same hundreds of ppm for analysis of residual solvent impurities in pharmaceutical base material.





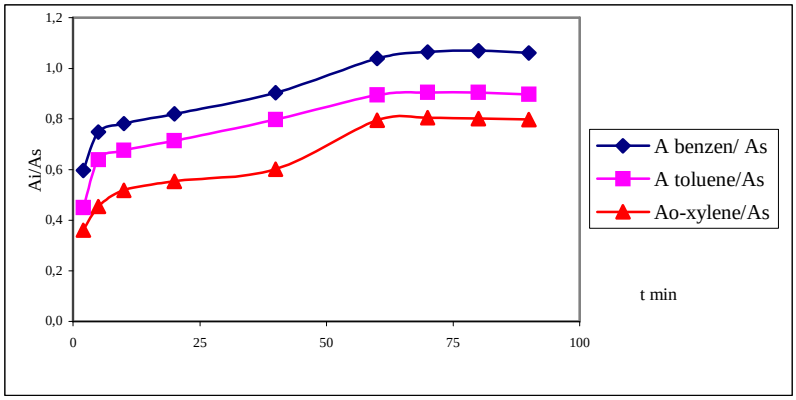


Fig. 1.
Optimum "purge time" of the residual solvents from aqueous solution (standard sample)

Table I. Calibration data for determination of the relative sensitivity of residual solvents (methanol, ethanol, acetone, propanol and butanol) in their standard aqueous solution by purge and trap –GC (PT-GC) with the ISTD method (internal standard 1-hepthanol).

	C_i / C_s	A_i / A_s	f_i
MeOH	0.12	-	-
	0.23	0.13	0.055
	0.58	0.033	0.056
	1.16	0.075	0.065
	2.31	0.145	0.062
Mean			0.059
SD			0.004
RSD%			7.324
EtOH			
	0.23	0.054	0.236
	0.58	0.124	0.215
	1.15	0.301	0.261
	2.30	0.508	0.220
Mean			0.234
SD			0.018
RSD%			7.695
Acetone	0.12	0.374	3.233
	0.23	0.730	3.158
	0.58	1.590	2.750
	1.15	3.214	2.780
	2.30	7.074	3.059
Mean			2.907
SD			0.188
RSD%			6.450
PrOH	0.12	0.061	0.520
	0.24	0.124	0.527
	0.59	0.296	0.504
	1.17	0.686	0.584
	2.35	1.182	0.503
Mean			0.539
SD			0.039
RSD%			7.304
BuOH	0.12	0.071	0.598
	0.24	0.191	0.806
	0.59	0.429	0.726
	1.17	0.849	0.718
	2.35	1.704	0.721
Mean			0.761
SD			0.055
RSD%			7.263

Table II. Calibration data for determination of the relative sensitivity of residual solvents (methanol, ethanol, acetone, propanol and butanol) in their standard aqueous solution by PT-GC with the ISTD method (internal standard 1-hepthanol) at 40°C.

	C_i / C_s	A_i / A_s	f_i
Methanol	0.12	0.01	0.08
	0.23	0.02	0.08
	2.31	0.15	0.07
Mean			0.08
SD			0.01
RSD%			9.50
Ethanol	0.12	0.03	0.29
	0.23	0.007	0.29
	2.30	0.61	0.26
Mean			0.28
SD			0.02
RSD%			5.28
Acetone	0.12	0.29	2.48
	0.23	0.56	2.41
	2.30	5.03	2.17
Mean			2.35
SD			0.16
RSD%			6.82
Propanol	0.12	0.11	0.93
	0.24	0.21	0.88
	2.35	1.84	0.78
Mean			0.86
SD			0.07
RSD%			8.49
Butanol	0.12	0.13	1.07
	0.24	0.29	1.22
	2.35	2.78	1.18
Mean			1.15
SD			0.08
RSD%			6.74

Table III. Calibration data for determination of the relative sensitivity of residual solvents (methanol, ethanol, acetone, propanol and butanol) in their standard aqueous solution by PT-GC with the ISTD method (internal standard 1-hepthanol) at 60 ^{o}C

	C_i / C_s	A_i / A_s	f_i
Methanol	0.12	0.01	0.11
	0.23	0.02	0.09
	2.31	0.21	0.09
Mean			0.10
SD			0.01
RSD%			10.97
Ethanol	0.12	0.04	0.37
	0.23	0.09	0.38
	2.30	0.79	0.34
Mean			0.36
SD			0.02
RSD%			5.53
Acetone	0.12	0.31	2.70
	0.23	0.61	2.64
	2.30	5.42	2.34
Mean			2.56
SD			0.19
RSD%			7.49
Propanol	0.12	0.13	1.07
	0.24	0.23	0.99
	2.35	2.10	0.89
Mean			0.98
SD			0.09
RSD%			8.76
Butanol	0.12	0.13	1.13
	0.24	0.32	1.37
	2.35	2.97	1.26
Mean			1.25
SD			0.12
RSD%			9.51

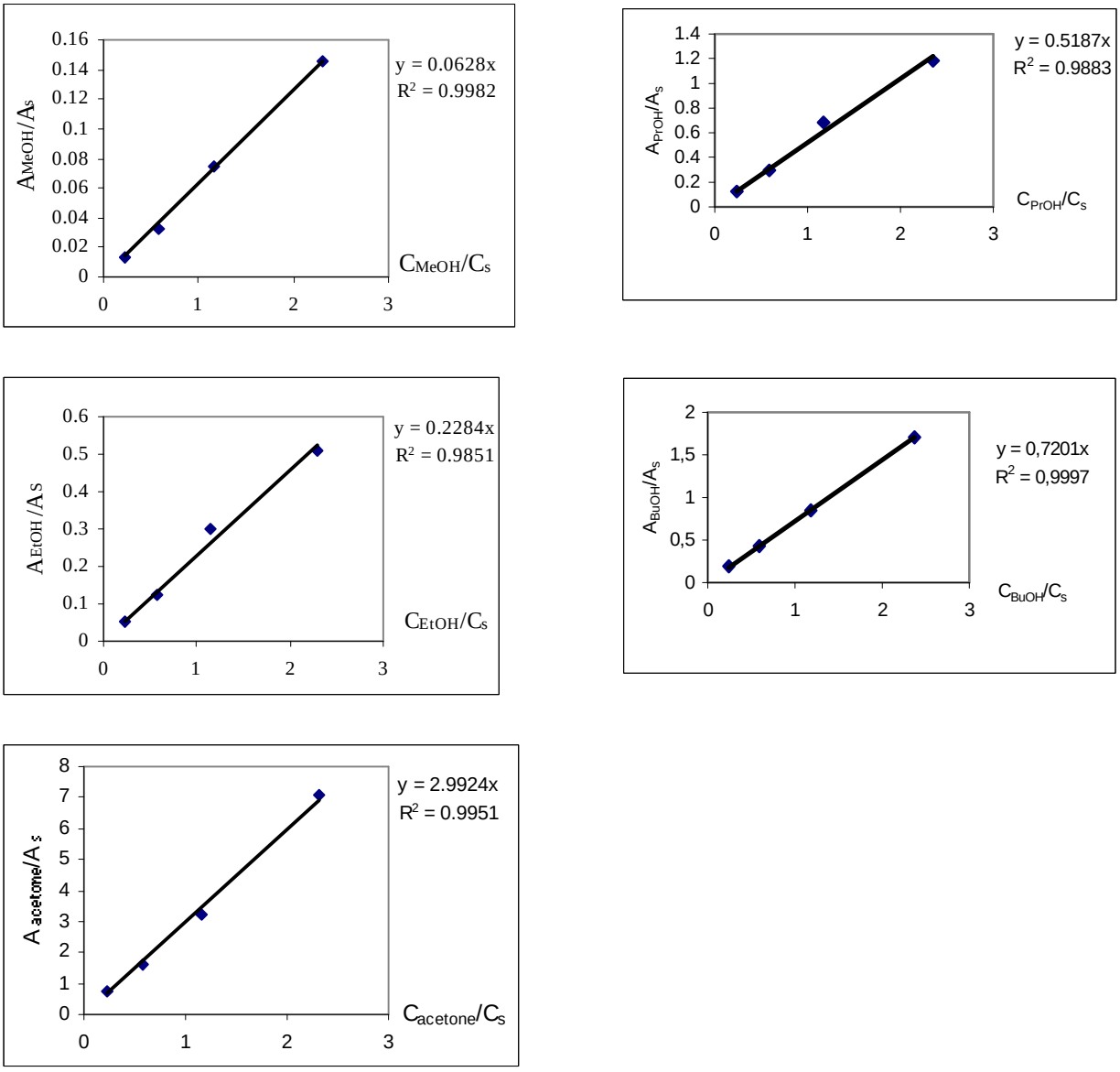


Fig. 2.

Linearity for the analysis of residual solvents in aqueous solution by PT-GC with ISTD calibration.

Table IV. Calibration data for determination of the relative sensitivity of residual solvents (benzene, toluene and o-xylene) in their standard aqueous solution by PT-GC with the ISTD calibration (internal standard decane) at room temperature (23°C).

	C_i / C_s	A_i / A_s	f_i
Benzene	0.003	0.005	1.65
	0.024	0.037	1.54
	0.060	0.088	1.47
	0.120	0.190	1.58
	0.301	0.507	1.69
Mean			1.59
SD			0.09
RSD%			5.53
Toluene	0.003	0.01	1.72
	0.024	0.04	1.64
	0.059	0.09	1.52
	0.119	0.19	1.63
	0.297	0.51	1.73
Mean			1.65
SD			0.08
RSD%			5.07
o-xylene	0.003	0.01	1.72
	0.024	0.04	1.62
	0.060	0.09	1.55
	0.121	0.20	1.64
	0.301	0.52	1.71
Mean			1.65
SD			0.07
RSD%			4.26

Table V. Calibration data for determination of the relative sensitivity of residual solvents (benzene, toluene and o-xylene) in their standard aqueous solution by PT–GC with the ISTD method (internal standard decane) at.40 °C.

	C_i / C_s	A_i / A_s	f_i
Benzene	0.003	0.007	2.45
	0.024	0.059	2.44
	0.060	0.137	2.28
	0.120	0.294	2.44
	0.301	0.643	2.14
Mean			2.35
SD			0.14
RSD%			5.93
Toluene	0.003	0.008	2.55

	0.024	0.058	2.46
	0.059	0.143	2.41
	0.119	0.295	2.48
	0.297	0.645	2.17
Mean			2.41
SD			0.14
RSD%			5.97
o-xylene	0.003	0.007	2.47
	0.024	0.059	2.45
	0.060	0.146	2.42
	0.121	0.296	2.46
	0.301	0.639	2.12
Mean			2.38
SD			0.15
RSD%			6.21

Table VI. Calibration data for determination of the relative sensitivity of residual solvents (benzene, toluene and o-xylene) in their standard aqueous solution by PT–GC with the ISTD method (internal standard decane). at 60 ^{o}C.

	C_i / C_s	A_i / A_s	f_i
Benzene	0.003	0.011	3.54
	0.024	0.087	3.60
	0.060	0.227	3.77
	0.120	0.408	3.39
	0.301	0.941	3.13
Mean			3.49
SD			0.24
RSD%			6.93
Toluene	0.003	0.012	3.90
	0.024	0.089	3.75
	0.059	0.236	3.98
	0.119	0.422	3.56
	0.297	0.969	3.26
Mean			3.69
SD			0.29
RSD%			7.78
o-xylene	0.003	0.012	3.95
	0.024	0.092	3.81
	0.060	0.224	3.72
	0.121	0.433	3.59
	0.301	0.977	3.24
Mean			3.66
SD			0.27
RSD%			7.33

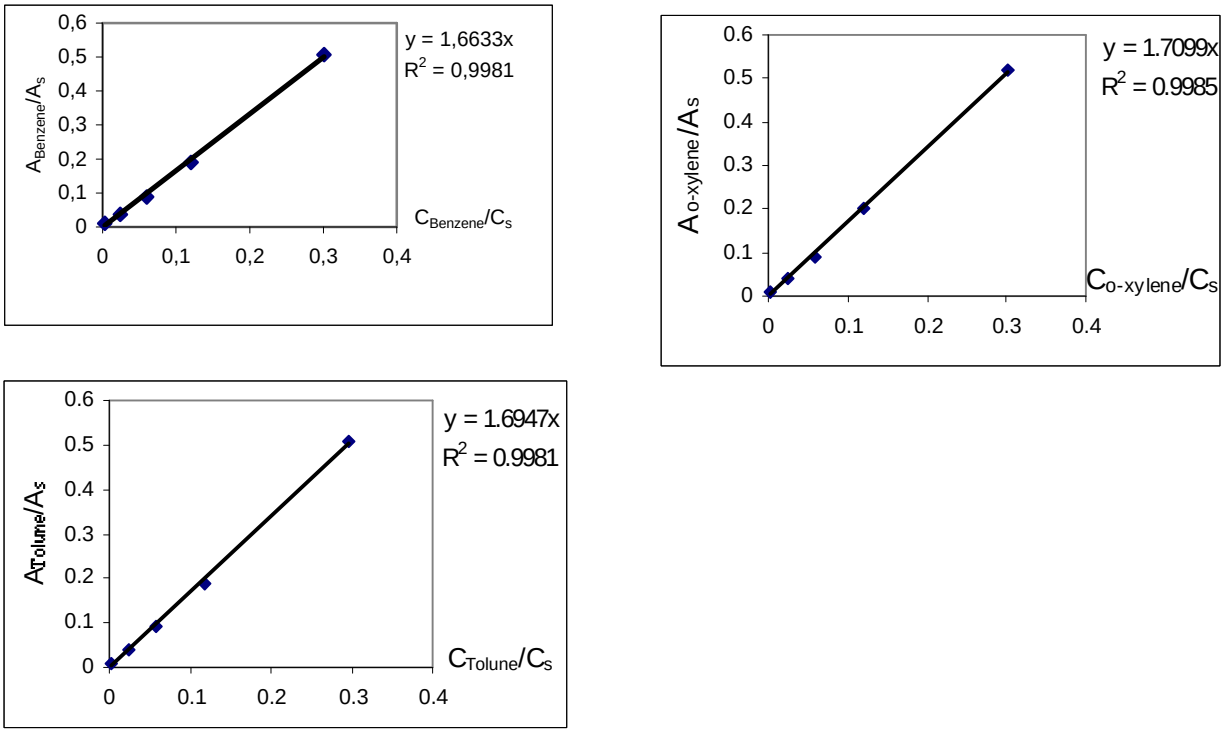


Figure 3

Linearity for analysis of residual solvents in aqueous solution by PT-GC with ISTD calibration.

Table VII Results from determination of residual solvents in pharmaceutical base material (A) by PT-GC with ISTD.

		23 oC		40 oC		60 oC	
		A^*_i/A^*_s	$C_{i,x}$ µg/g	A^*_i/A^*_s	$C_{i,x}$ µg/g	A^*_i/A^*_s	$C_{i,x}$ µg/g
	Mean		197.50		193.40		187.60
MeOH	SD		6.14		10.97		13.11
	RSD%		3.11		5.67		6.99
	Mean		179.30		188.50		203.40
EtOH	SD		6.23		9.54		12.36
	RSD%		3.47		5.06		6.08
	Mean		142.20		205.40		2.33
Acetone	SD		3.06		8.40		9.52
	RSD%		2.15		4.09		4.07
	Mean		49.00		94.50		98.70
PrOH	SD		1.72		5.21		6.49
	RSD%		3.51		5.51		6.58
	Mean		77.40		127.90		132.70
BuOH	SD		2.99		6.77		6.05
	RSD%		3.87		5.29		4.56

Table VIII Results from determination of residual solvents in pharmaceutical base material (B) by PT-GC with ISTD at different temperature.

		23 oC		40 oC		60 oC	
		A^*_i/A^*_s	$C_{i,x}$ µg/g	A^*_i/A^*_s	$C_{i,x}$ µg/g	A^*_i/A^*_s	$C_{i,x}$ µg/g
	Mean		30.37		28.79		29.02
Benzene	SD		1.44		1.77		1.86
	RSD%		4.74		6.13		6.42
	Mean		31.60		28.99		28.03
Toluene	SD		1.44		1.80		1.81
	RSD%		4.56		6.22		6.47
	Mean		31.56		29.71		28.40
o-xylen	SD		1.34		1.84		1.85
	RSD%		4.25		6.18		6.52

Table IX Results from measurement of the recovery of residual solvents from aqueous solutions by PT-GC with ISTD calibration at different temperature.

T ^{o}C		MeOH	EtOH	Acetone	PrOH	BuOH
	Recovery %	92.00	93.00	91.00	95.00	96.00
23	SD	4.19	3.92	4.20	3.82	3.79
	RSD%	4.55	4.21	4.61	4.02	3.95
	Recovery %	94.50	95.60	93.70	96.2	97.50
40	SD	8.41	8.13	9.84	7.87	7.90
	RSD%	8.90	8.50	10.50	8.20	8.10
	Recovery %	95.60	96.40	94.80	97.30	98.10
60	SD	10.90	10.80	12.03	8.54	9.38
	RSD%	11.40	11.20	12.80	9.80	9.56

Table X. Results from measurement of the recovery of residual solvents from aqueous solutions by PT-GC with ISTD calibration at different temperature.

T ^{o}C		Benzene	Toluene	o-xylene
	Recovery %	94.5	95.8	96.20
23	SD	4.30	7.56	7.57
	RSD%	4.55	7.85	7.81
	Recovery %	95.9	96.3	96.90
40	SD	7.58	7.56	7.57
	RSD%	7.90	7.85	7.81
	Recovery %	96.15	96.75	97.01
60	SD	10.96	10.84	12.42
	RSD%	11.40	11.20	12.80

Table XI. Results from measurement of the limit of detection (LOD) of residual solvents from aqueous solution by PT-GC with ISTD calibration at different temperature.

T ^{o}C	Purged of component	$C_{i,x}$ □g/l
23 room temp	MeOH	15.0
	EtOH	15.0
	Acetone	8.0
	PrOH	8.0
	BuOH	8.0
	Benzene	4.0
	Toluene	4.0
	o-xylene	4.0
40	MeOH	15.0
	EtOH	15.0
	Acetone	8.0
	PrOH	8.0
	BuOH	8.0
	Benzene	4.0
	Toluene	4.0
	o-xylene	4.0
60	MeOH	15.0
	EtOH	15.0
	Acetone	8.0
	PrOH	8.0
	BuOH	8.0
	Benzene	4.0
	Toluene	4.0
	o-xylene	4.0

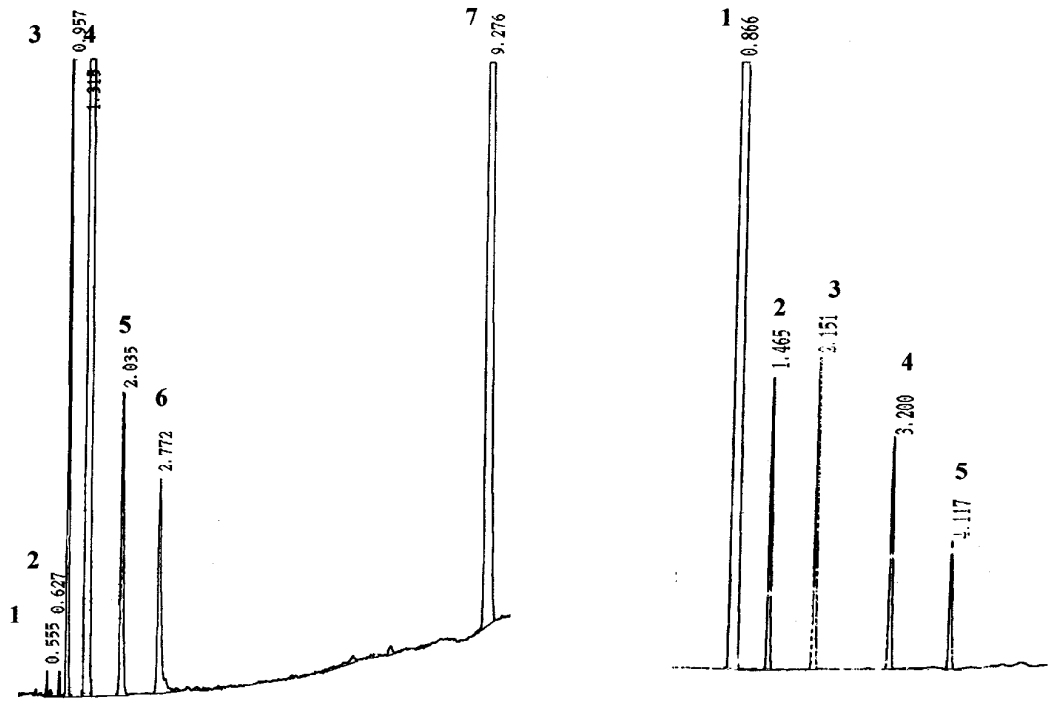


Figure 4
Chromatograms obtained from analysis of residual solvents in pharmaceutical base material (A).
1 = methanol, 2 = ethanol, 3 = acetone, 4 = CS_2, 5 = propanol, 6 = butanol, 7 = heptanol (internal standard)

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