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Residual solvents determination in pharmaceutical products by GC-HS and GC-MS–SPME

Costin C. Camarasu *, Mária Mezei-Szűts, Gábor Bertók Varga

Gedeon Richter Ltd., Central Analytical Laboratory, Gyömrői út 19-21, Budapest H-1103, Hungary

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Abstract

Solid-phase microextraction (SPME) has been applied to the residual solvents determination in pharmaceutical products and was compared with the static headspace. Three fibers with different polymer films were compared and the polydimethylsiloxane/divinylbenzene coated fiber was found to be the most sensitive for the analyzed analytes. Between the investigated sample preparation techniques, gastight-SPME proved to be the most sensitive, with DL values ranging from 5 pg ml^{-1} to 2 ng ml^{-1}. Headspace SPME is more precise, with RSD of peak areas values ranging from 2 to 3%. The headspace SPME method was successfully validated. The validation data are reported in the text. The most important difference between the two techniques is that the gastight SPME showed better behavior towards very volatile solvents. Compared with the static headspace technique, both SPME methods showed superior results, being compatible with the pharmaceutical samples. © 1998 Elsevier Science B.V. All rights reserved.

Keywords: Extraction methods; Solid phase microextraction; Residual solvent analysis; Headspace analysis

1. Introduction

The residual solvents determination in drug substances, excipients or drug products is known to be one of the most difficult and demanding analytical task in the pharmaceutical industry.

The practice shows that it is not a rare case when an on-going selectivity is quite hard to keep as unknown volatile components does appear in the chromatogram of the investigated pharmaceutical products. The identification of these unknown components requires the selectivity and mass spectral capabilities of GC–MS. In order to reach the quantitation limits required by regulatory agencies [1], sample preparation methods should be used. The sample preparation method should be precise, simple, cheap and it should allow easy automation. The common extraction techniques for volatile organic compounds are compared in Table 1 from previous points of view.

In Table 1, we highlighted the headspace and SPME sample preparation methods as being the most suitable from all points of view for the determination of residual solvents in pharmaceutical products.

* Corresponding author. Fax: +36-1-2605888; e-mail: costin@orthodox.com.

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In SPME, the analytes are extracted into a stationary phase which is attached to a length of fused silica fiber [2]. The fiber is contained in a microsyringe for protection and ease of sampling. In SPME, an exhaustive extraction does not occur but an equilibrium is established as analytes partition between the stationary phase and the aqueous phase or its headspace phase. By sampling from the headspace above the sample matrix, SPME can extract a wide range of organic compounds from various matrices [3–12]. At equilibrium, in headspace SPME [3] the number of moles n_f of an analyte extracted by the fiber coating is given by the expression:

$$n_f = \frac{K_1 K_2 V_f C_o V_s}{K_1 K_2 V_f + K_2 V_h + V_s} \quad (1)$$

where V_f, V_h and V_s are the volumes of the fiber coating, the headspace and the sample, respectively; C_o is the initial concentration of the analyte in the sample and K_1 and K_2 are coating-headspace and headspace-sample partition coefficients.

For very volatile compounds, static headspace can provide excellent sensitivity. However, for less volatile target analytes, sensitivity deteriorates. For static headspace sampling with a gastight syringe, the number of moles of an analyte extracted, n_g is:

$$n_g = \frac{K_2 V_g C_o V_s}{K_2 V_h + V_s} \quad (2)$$

where V_g is the volume sampled by the gastight syringe from the headspace, V_h and V_s are the volume of the headspace and sample, respectively, C_o is the initial concentration of the analyte in the sample and K_2 is the headspace sample partition coefficient.

Headspace SPME and the static headspace techniques are complementary, the former extracting higher boiling-point compounds better and the latter favoring compounds with lower boiling-points [13].

For the gastight SPME (the device which include both the gastight syringe with a volume V_g and SPME with a coating volume V_f), the amount of analytes extracted, n by this device equals:

$$n = n_f + n_g \quad (3)$$

For the experiments performed in the present work, the volume of the fiber was ~ 0.6 μl and the volume of the aqueous sample was 2 ml. For the compounds analyzed, the product $K_1 K_2$ is less than 1000. As a consequence, the product $K_1 K_2 V_f$ is negligible. From Eqs. (4) and (5), we have:

$$r_f = \frac{n_f}{n} = \frac{K_1 V_f}{V_g + K_1 V_f} \quad (4)$$

and

$$r_g = \frac{n_g}{n} = \frac{V_g}{V_g + K_1 V_f} \quad (5)$$

where r_f and r_g are the normalized sensitivities for headspace SPME and gastight syringe sampling, respectively (in this case and for all analytes n is normalized to 1).

Eqs. (4) and (5) show that although the sensitivity of each method depends on Henry's constant of an analyte, the normalized sensitivity of the headspace SPME and gastight syringe techniques compared with gastight SPME is determined only by the coating-headspace partition coefficient K_1, of the target analyte. Due to very volatile components usually having smaller K_1 values, the gastight syringe technique gives quite better sensitivities than SPME. As K_1 increases, the sensitivity of SPME improves, whereas that of the gastight syringe decreases.

Therefore, it can be stated that the gastight SPME does combine the complementary nature of gastight syringe and headspace SPME.

This paper describes the development of a fast headspace SPME sample preparation method followed by a GC–MS qualitative identification of the sample. We were also interested in comparing the headspace SPME, the static headspace and gastight SPME sample preparation methods from the point of view of suitability for the residual solvents determination method in pharmaceutical products [14].

2. Experimental

2.1. Samples and standards

An International USP 467 Mixture in methanol (Restek Corporation, 110 Benner Circle, Bellefonte PA 16823) was used for this study as a primary stock solution. Working standards were prepared by dilution of 100 μl (first dilution), respectively 10 μl (second dilution) primary stock solution in 10 ml methanol to give the concentrations presented in Table 2. The third dilution solution was prepared by adding 100 μl of first dilution solution in 10 ml methanol. Aqueous samples in 10 ml headspace amber vials were prepared by mixing 2 ml deionized water with 1 g sodium chloride. Aqueous samples were also prepared by mixing 2 ml deionized water with 1 g sodium chloride and with 100 mg proprietary drug substance. VOCs from the working standards were spiked into the vials to produce the concentration desired. When the sample concentration was calculated, the weight of sodium chloride was excluded because it was used as a matrix modifier to achieve a salting out effect.

2.2. Sampling devices

2.2.1. SPME device

The solid phase microextraction (SPME) extractor and three fibers used in this study were purchased from Supelco (Bellefonte, PA).

The silica fibers were coated with a 100 μm film of polydimethylsiloxane (PDMS), 65 μm of poly-

Table 1
The comparison of common sample preparation techniques

Technique	Detection limit (MS)	Precision (%)	Expense	Time	Simplicity	Ease of automation
Purge and trap	pg ml^{-1}	1–30	High	30 min	No	No
CLS[a]	pg ml^{-1}	3–20	High	3 h	No	No
Headspace	ng ml^{-1}	2–20	Low	30 min–1 h	Yes	Yes
SPME[b]	pg ml^{-1}	0.6–12	Low	5–30 min	Yes	Yes
MIMS[c]	pg ml^{-1}	N/A	High	Real time	Yes	No
Membrane permeate ITMS[d]	ng ml^{-1}	4–13	High	1 h	No	No

[a] Closed loop stripping.
[b] Solid phase microextraction.
[c] Membrane introduction mass spectrometry.
[d] Ion trap mass spectrometry.

Table 2
The concentrations of standard solutions

Component	Stock solution (μg ml^{-1})	First dilution (μg ml^{-1})	Second dilution (ng ml^{-1})	Third dilution (ng ml^{-1})
Acetonitrile	50	0.5	50	5
Dichloromethane	500	5	500	50
Chloroform	50	0.5	50	5
Trichloroethylene	100	1	100	10
1,2-Dichloroethane	100	1	100	10
Benzene	100	1	100	10
1,4-Dioxane	100	1	100	10
Pyridine	100	1	100	10

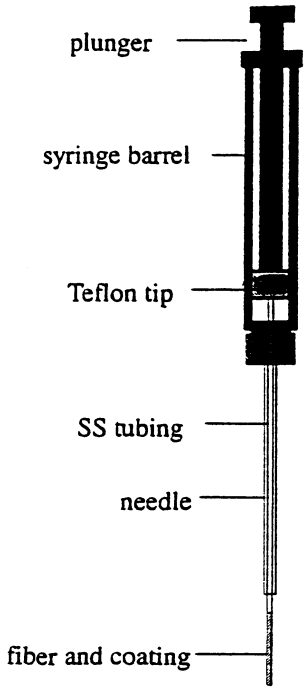

Fig. 1. The gastight SPME device.

dimethylsiloxane/divinylbenzene (PDMS/DVB), respectively, 65 μm of carbowax/divinylbenzene (CW/DVB). The volume of the polymer film was $\sim 5 \times 10^{-5}$ cm^3, and its surface was ~ 0.06 cm^2.

2.2.2. Gastight SPME device

The gastight SPME device is presented in Fig. 1. A fused silica fiber, 1 cm in length and coated with a 65 μm film of polydimethylsiloxane/divinylbenzene (PDMS/DVB) was connected to 30 gauge stainless steel (SS) tubing. The other end of this SS tubing-fiber assembly was then mounted on the plunger of a Hamilton 500 μl gastight syringe (Supelco, Mississauga, ON) [3]. When the tubing-fiber assembly was withdrawn into the syringe needle, a certain volume of gas could also be withdrawn into the gastight syringe through the needle opening. During sampling, the fiber was first withdrawn into the syringe needle which was then used to punch through the sample vial septum. The fiber was then exposed to the headspace by depressing the plunger for a predetermined period of time to establish equilibrium between headspace, the coating and the sample matrix. The plunger was then withdrawn to a predetermined mark, thereby effecting withdrawal of 200 μl of headspace gas into the gastight SPME device.

The extracted analytes (in the gaseous phase as well as those adsorbed on the coating) were immediately injected into the GC injector by depressing the plunger, the headspace gas being forced from the syringe as the plunger was depressed. The analytes adsorbed by the fiber coating were thermally desorbed in the hot injector. During desorbtion, the temperature of the column was maintained at a low value in order to achieve a focusing effect.

Each day, a column blank was followed by a fiber blank and a water blank to determine the extent of any laboratory contamination.

The fibers for headspace SPME and gastight SPME were conditioned at their corresponding maximum operation temperature overnight.

All sampling was conducted at room temperature while the aqueous phase was under constant magnetic stirring of 900 rot min^{-1}. The sampling time for both headspace SPME and gastight SPME was 30 min based on the optimization of SPME extraction.

The fiber coating was desorbed in the injector at 200°C for 1 min. The carry-over was found to be less than 1% for all VOCs and was determined by running consecutive fiber blanks to determine the fraction of the original mass desorbed remaining on the fiber.

3. GC-HS

The GC-Headspace instrument used in this study was a Fisons Instruments HRGC Mega 2 Series, MFC 800 (Model 8560) gas chromatograph equipped with a HS 800 automated headspace sampler and a FID detector. The headspace incubation temperature was 80°C, the incubation time was 1 h, the needle temperature was 90°C and the injected amount was 1 ml of headspace. The chromatograph was fitted with a 50 m × 0.32 mm i.d. CP-SIL 5CB column coated with 5 μm film of stationary phase (Chrompack,

Middleburg EA, The Netherlands). The injector temperature was 200°C, and the detector temperature was 260°C. The injector was operated in splitless/split mode with a splitless time of 1 min. The carrier gas used was hydrogen at a linear velocity of 30 cm s^{-1}.

The column temperature was maintained at 40°C for 1 min after the injection, then programmed at 3°C/min to 130°C/min to 180°C where it was held for 15 min.

All data were acquired with Chrom-Card for Windows Version 1.19-2B, 27 August, 1996 validated software (CE Instruments, Milan, Italy).

4. GC-MS

The GC-ion trap mass spectrometer (GC-MS) used in this study was a Finnigan MAT GCQ system (Finnigan MAT, Austin, TS). The GC was equipped with a TPI injector. The GC was fitted with a 50 m × 0.32 mm i.d. CP-SIL 5CB column coated with 5 μm film of stationary phase (Chrompack, Middleburg EA, The Netherlands). The injector temperature was 200°C and was operated in splitless/split mode with a splitless time of 1 min. The temperature program of the column was the same as for the GC-HS. Helium was used as a carrier gas at a constant linear velocity of 35 cm s^{-1}.

The external EI ion source was operated at an electron energy of 70 eV, and the filament emission was set at 200 mA. The ionization waveform was set to On. The ion trap was operated at a target value of 50, a trap offset of 10 V and at a sampling rate of two scans per second. The multiplier was set at a multiplier gain of 3.9 E5. The system gave unit resolution. The ion trap manifold temperature was set at 180°C and the transfer line was set at a temperature of 200°C. The ion trap was calibrated automatically with FC-43 standard substance using the m/z 69, 131, 264, 414 and 502 by the autotune routine of the GCQ software.

All data were acquired with GCQ MS/MS Version 2.0, March 1996 (Finnigan MAT, Austin, TX) validated software.

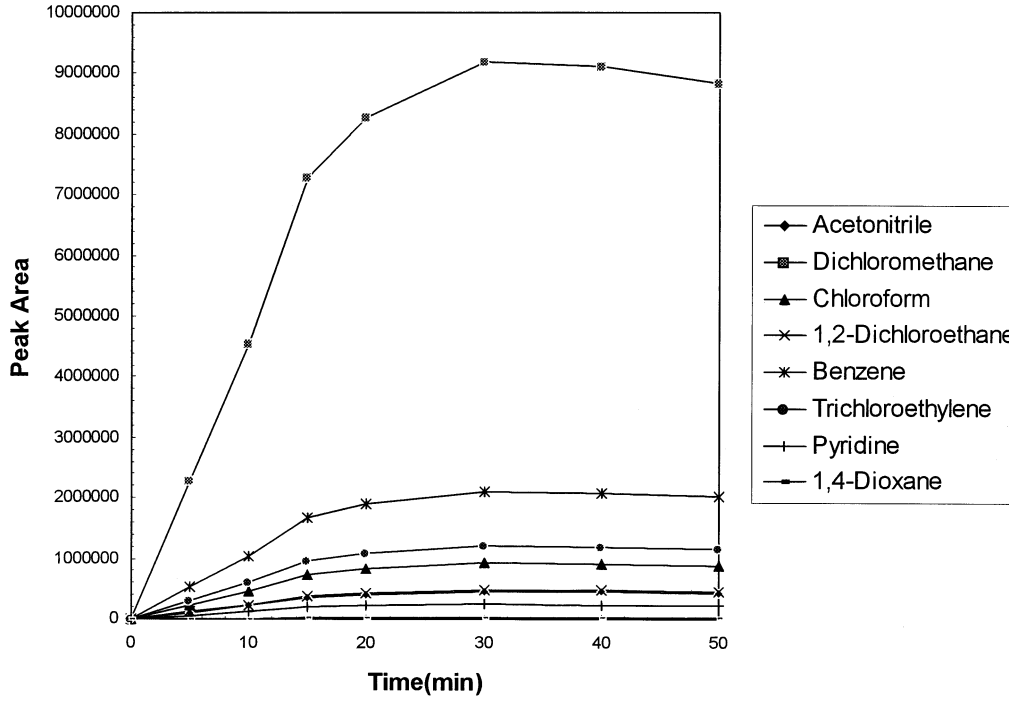

Fig. 2. Extraction time optimization for gastight SPME.

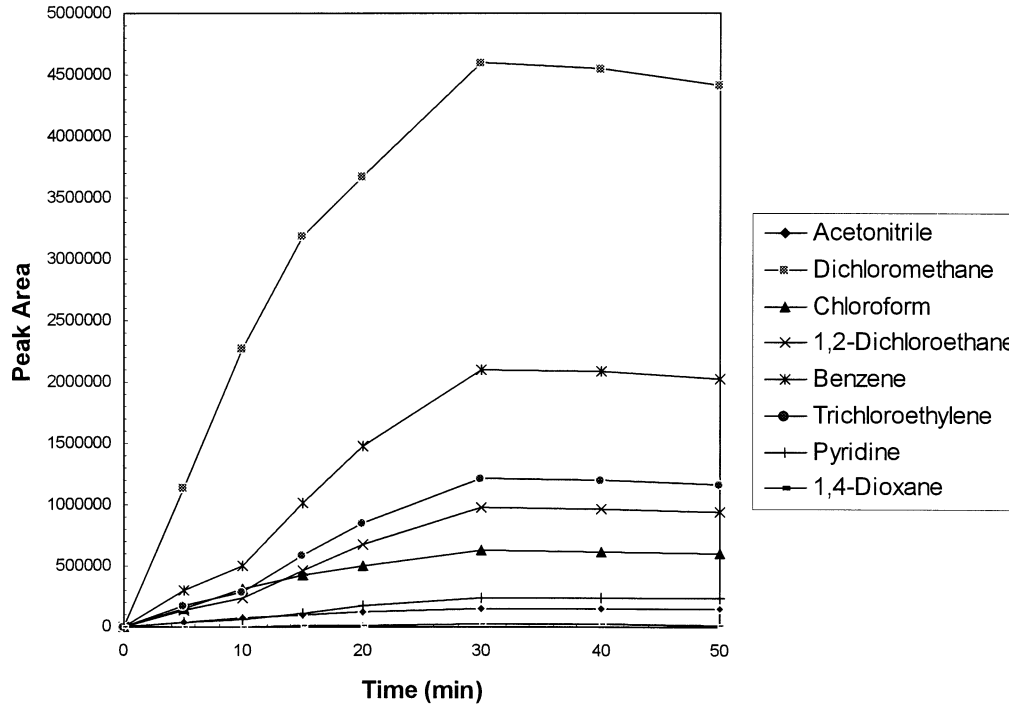

Fig. 3. Extraction time optimization for headspace SPME.

5. Results and discussion

In the present work, we used an International USP 467 Mixture as target analytes in the investigation of SPME-GC-MS as this mixture does contain Class 1 and Class 2 solvents in suitable concentrations.

We have found that saturation of the aqueous phase with sodium chloride increased the extraction efficiency of each analyte. The percentage increase ranged from ~ 20 to almost 300%.

The first step in our headspace SPME method development was to establish the time required for all target analytes to reach a equilibrium. In order to maximize the sensitivity of this technique, the thickest available polidimethylsiloxane coated fiber (100 μm) that could be accommodated into the syringe needle was used. Figs. 2 and 3 shows that all analytes attained equilibrium after 30 min for both headspace SPME and gastight SPME. For dichloromethane, the gastight SPME was shown to be almost twice as sensitive as headspace SPME. The difference between headspace SPME and gastight SPME is clearly illustrated by the relative behavior of chloroform (boiling point, 62°C) and 1,2-dichloroethane (boiling point, 84°C). Chloroform is better extracted by gastight SPME as it is more volatile and 1,2-dichloroethane is better extracted by headspace SPME, thus supporting the expected behavior. The more polar compounds, like acetonitrile, pyridine and 1,2-dioxane, have longer equilibration times and worse sensitivities, mainly due to their stronger affinity to the aqueous phase.

In the following experiments, a 30-min extraction time was chosen.

After establishing the equilibration time, the detection limits were investigated by extracting spiked aqueous solutions as described in the Section 2. The detection limit was performed by comparing measured signals from the selected ion chromatogram of samples with a known low concentration of analyte with those of blank samples. The acceptance criteria was a signal/noise ratio of a minimum 3:1.

Three different fibers with different coatings, i.e. polydimethylsiloxane/divinylbenzene (PDMS/DVB), polydimethylsiloxane (PDMS) and carbowax/divinylbenzene (CW/DVB) were compared in order to find the most sensitive coating for all analytes under study. Table 3 shows the method detection limits. Between the investigated fibers, the PDMS/DVB coated fiber showed the best sensitivity toward all analytes, being almost ten times more sensitive than the PDMS coated fiber and almost four times more sensitive than CW/DVB. For acetonitrile, chloroform and 1,2-dichloroethane, it was demonstrated that the PDMS/DVB coated fiber was only two times more sensitive than the CW/DVB coated fiber. For dichloromethane, chloroform, dioxane and pyridine, the PDMS/DVB coated fiber was five times more sensitive than the PDMS coated fiber. The PDMS coated fiber showed better behavior than the CW/DVB coated fiber only in the case of pyridine when it was two time more sensitive. For dichloromethane and dioxane the CW/DVB and PDMS fibers showed similar sensitivities.

Table 3
The detection limits of employed methods

Component	Detection limits for employed methods (ng ml^{-1})				
	Headspace SPME			Gastight SPME	Static headspace
	PDMS/DVB[a]	CW/DVB[b]	PDMS[c]		
Acetonitrile	0.1	0.2	1	0.05	2
Dichloromethane	0.01	0.04	0.06	0.005	0.5
Chloroform	0.01	0.02	0.05	0.007	7
Trichloroethylene	0.01	0.03	0.1	0.01	7
1,2-Dichloroethane	0.01	0.02	0.1	0.02	7
Benzene	0.01	0.04	0.1	0.01	0.1
1,4-Dioxane	2	10	10	2	20
Pyridine	0.5	5	3	0.7	30

[a] Polydimethylsiloxane/Divinylbenzene fiber.
[b] Carbowax/Divinylbenzene fiber.
[c] Polydimethylsiloxane fiber.

Table 4
The repeatability of analytical data

Component	Concentration (ng ml^{-1})	Quantification mass (m/z)	Repeatability of peak areas RSD (%) of five replicates		
			G-SP[a]	H-SP[b]	HS[c]
Acetonitrile	50	41	2	3	3
Dichloromethane	500	49	2	3	5
Chloroform	50	83	3	2	5
Trichloroethylene	100	130	5	2	5
1,2-Dichloroethane	100	63	3	2	5
Benzene	100	78	4	2	3
1,4-Dioxane	100	88	5	2	10
Pyridine	100	79	7	2	10

[a] Gastight SPME.
[b] Headspace SPME.
[c] Static headspace.

Table 5
The validation data for Headspace SPME method

	Acetonitrile	DCM[a]	Chloroform	TCE[b]	1,2-DCE[c]	Benzene	Dioxane	Pyridine
Linearity data								
Correlation coefficient	0.9992	0.9998	0.9994	0.9999	0.9994	0.9999	0.9990	0.9995
Slope	1168	2149	12251	21779	3567	21975	35	2097
Standard error	14	9	103	71	30	62	0.6	19
Intercept	1521	1767	5400	15639	2508	12624	53	3081
Standard error	935	5481	6118	8730	3720	7613	84	2922
Confidence interval	−538,	−9916	−7640	−3086	−5470	−3704	−140	−3528
(95%)	3580	13449	18441	34365	10488	28953	247	9692
Concentration range (ng ml^{-1})	0.4–200	0.04–2000	0.04–200	0.04–400	0.04–400	0.04–400	8–400	2–400
Number of standards	11	18	16	16	16	16	10	10
Accuracy data								
Mean recovery (%)	93	95	97	99	96	99	92	93
Concentration range (ng ml^{-1})	0.5–200	5–2000	0.5–200	1–400	1–400	1–400	1–400	1–400
Number of standards	7	7	7	7	7	7	7	7
Precision								
Repeatability								
Concentration (ng ml^{-1})	50	1000	50	100	100	100	100	100
Number of replicates	7	7	7	7	7	7	7	7
RSD of peak areas (%)	3	3	2	2	2	2	2	2

Table 5 (Continued)

	Acetonitrile	DCM[a]	Chloroform	TCE[b]	1,2-DCE[c]	Benzene	Dioxane	Pyridine
Intermediate precision[d]								
Concentration (ng ml^{-1})	50	1000	50	100	100	100	100	100
Number of replicates	3	3	3	3	3	3	3	3
RSD of peak areas (%)	4.1	3.1	3.9	3.3	2.9	2.7	2.9	1.62
Variance between groups	0.7778	1103.4	1.3333	0.7778	1.4444	1.3333	1.0000	0.6411
Variance within groups	1.0000	784.9	1.2222	2.6667	0.6667	0.5556	1.0000	7.2455
F_{calc} ($F_{crit} = 5.143$)	0.778	1.406	1.091	0.292	2.167	2.400	1.000	0.088
Quantitation limit (ng ml^{-1})	0.4	0.04	0.04	0.04	0.04	0.04	8	2

[a] Dichloromethane.
[b] Trichloroethylene.
[c] 1,2-Dichloroethane.
[d] During three consecutive days, by one analyst on the same instrument.

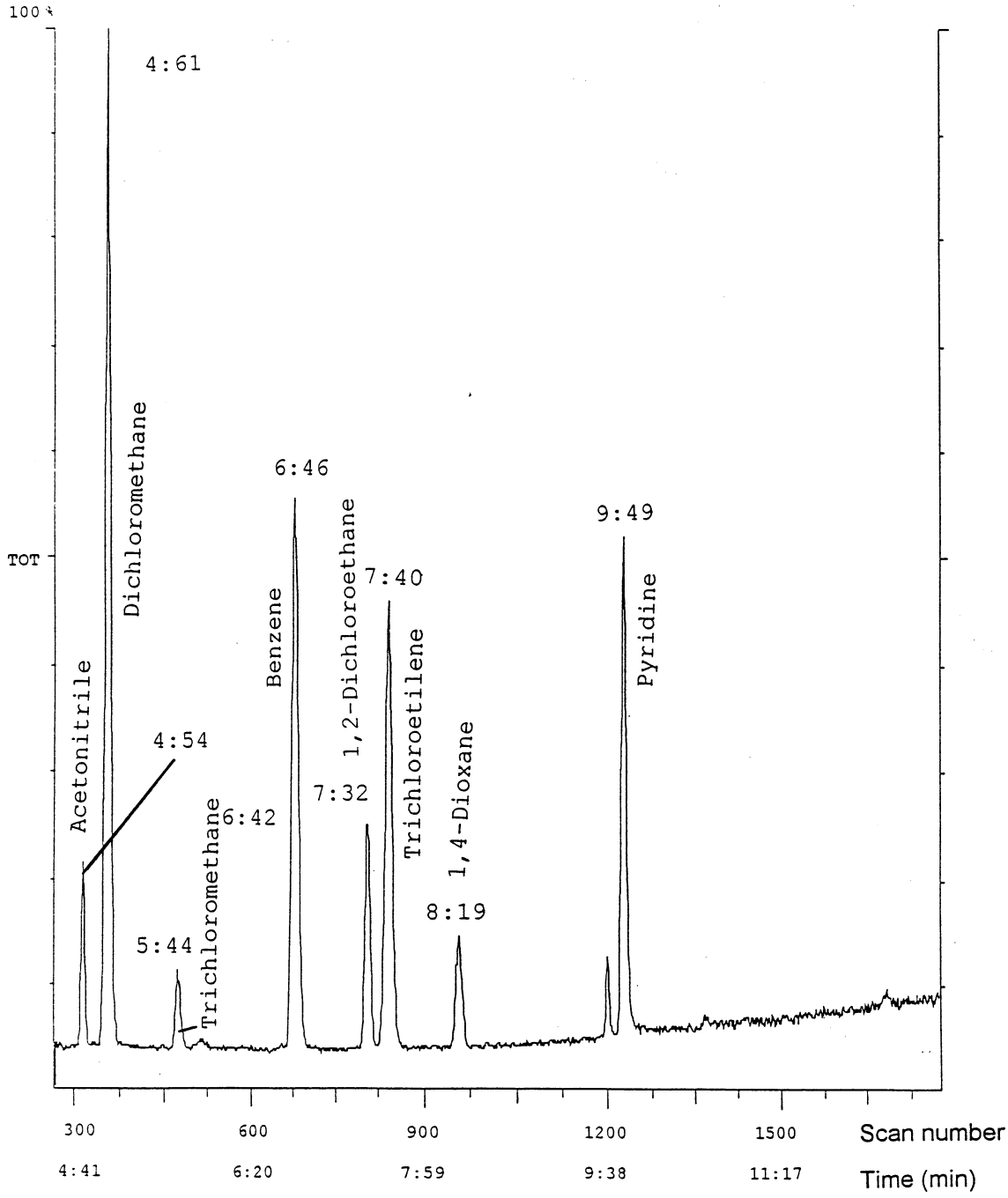

Fig. 4. The headspace SPME chromatogram of a 100 ng ml^{-1} standard solution.

Between the investigated sample preparation techniques, the gastight SPME was shown to be the most sensitive, mainly due to its inherent selectivity. For volatile components (i.e. dichloromethane and acetonitrile), the gastight SPME was almost twice more sensitive than

headspace SPME and almost one hundred times more sensitive than static headspace. For less volatile compounds, headspace SPME and gastight SPME showed similar sensitivities, both of them being almost ten times more sensitive than static headspace. For polar compounds (like

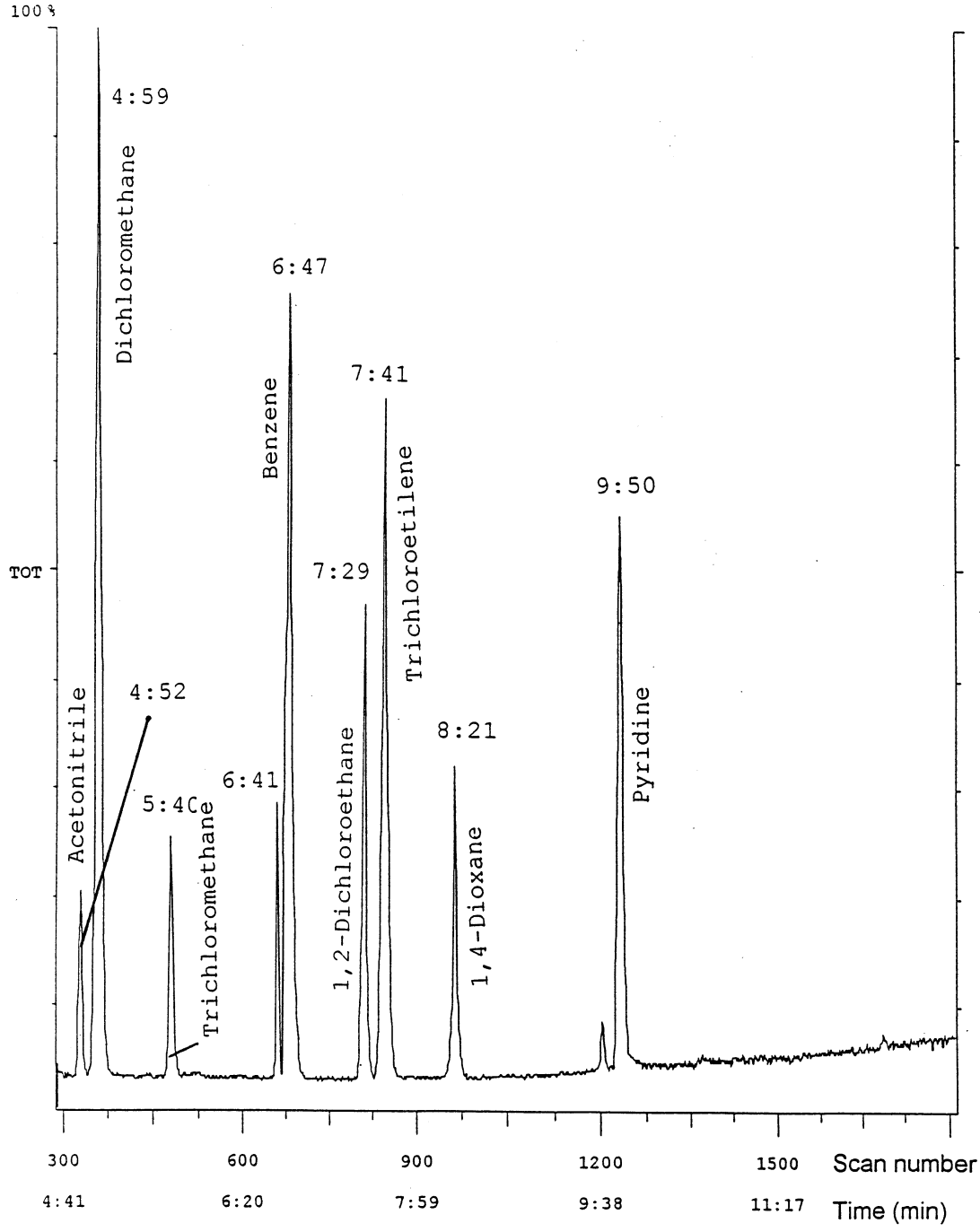

Fig. 5. The gastight SPME chromatogram of a 100 ng ml^{-1} standard solution.

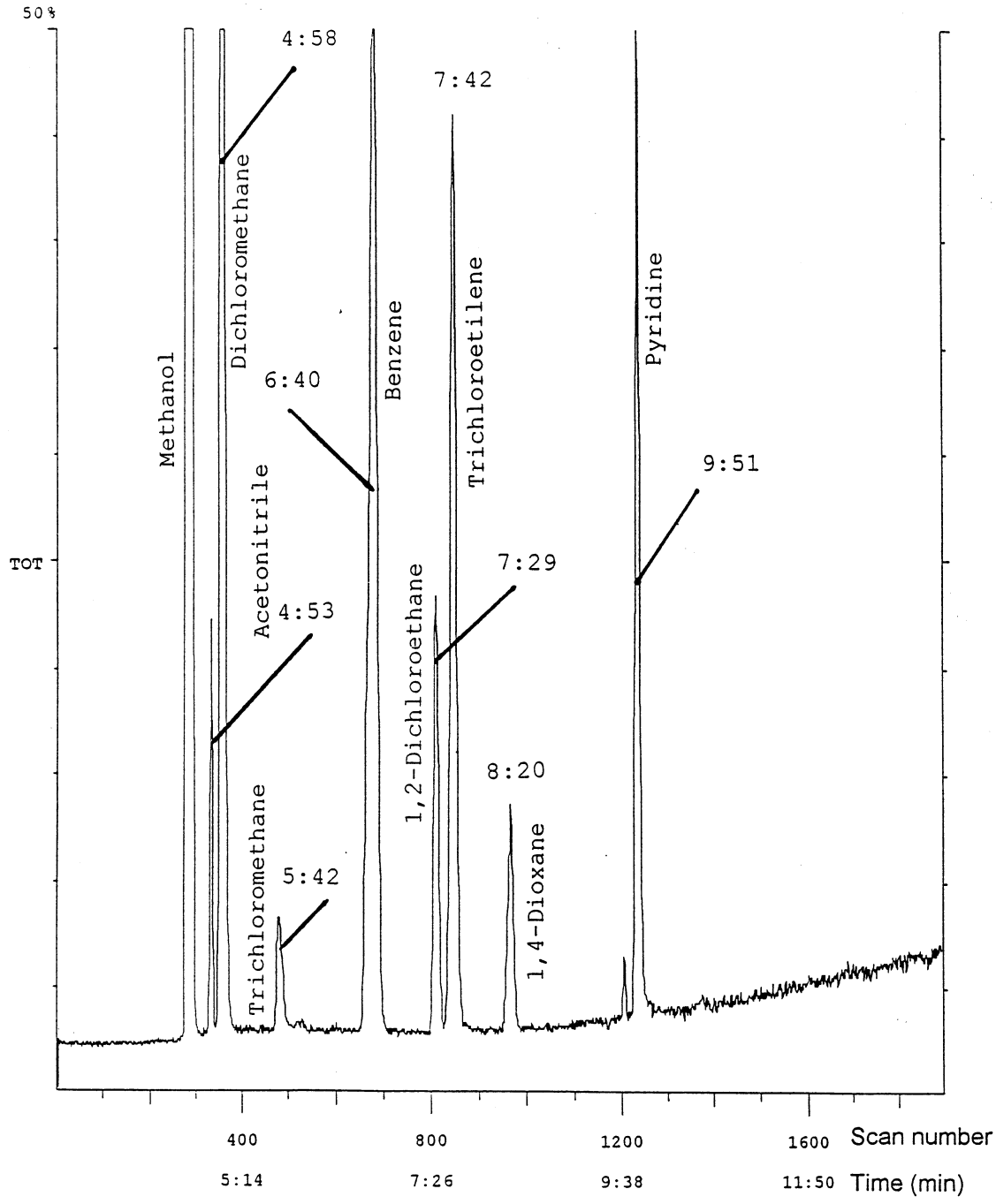

Fig. 6. Gastight SPME chromatogram of proprietary drug substance 1 spiked with 100 ng ml^{-1} standard solution.

1,2-dioxane), the headspace SPME was more sensitive than static headspace and gastight SPME.

Both headspace SPME and gastight SPME showed excellent sensitivities for all investigated compounds. As expected, the gastight SPME was

slightly more sensitive than Headspace SPME towards more volatile compounds.

Table 4 shows the repeatability of the developed method for static headspace, headspace SPME and gastight SPME techniques. The repeatability of the method was investigated by

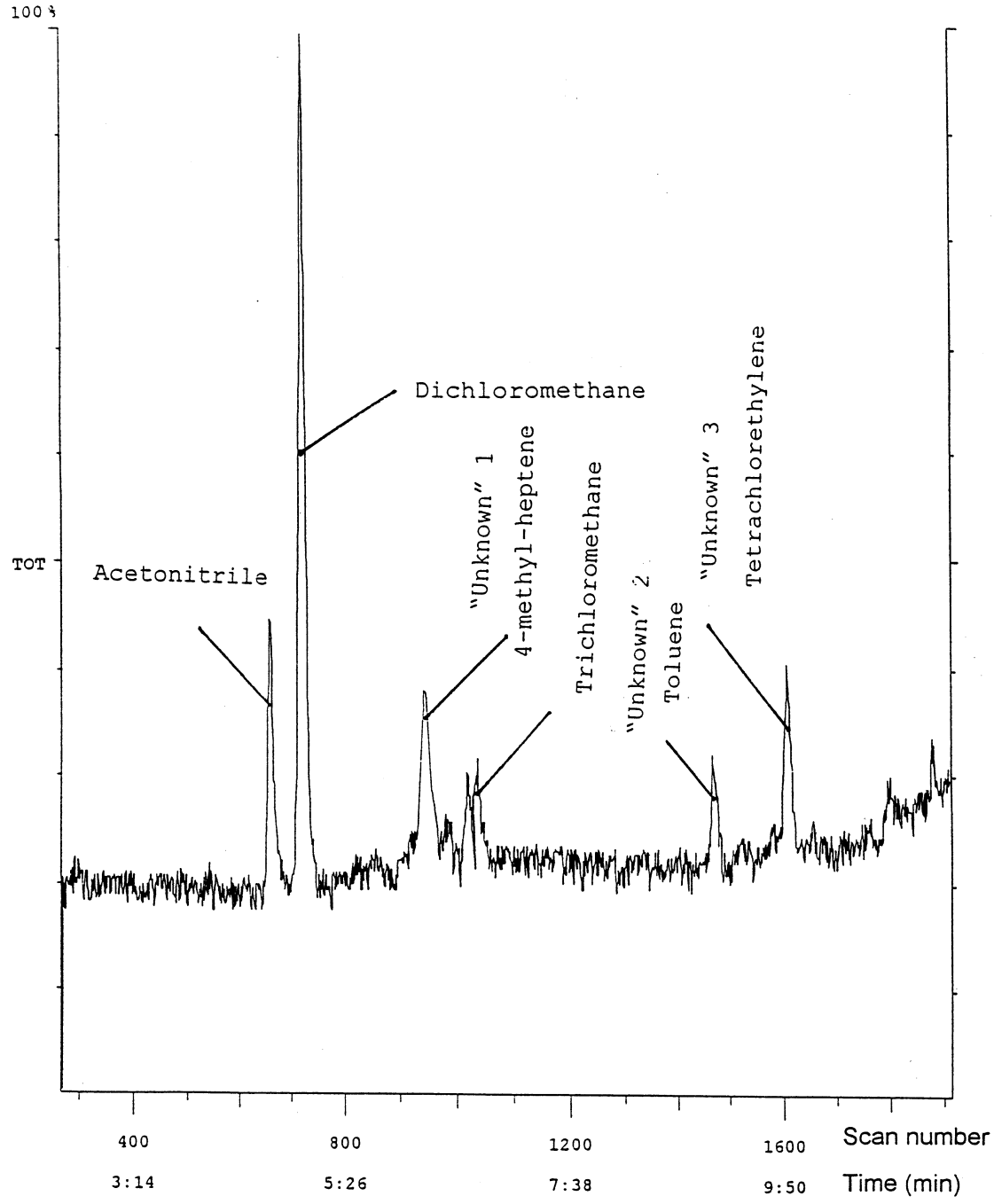

Fig. 7. Gastight SPME chromatogram of proprietary drug substance 2.

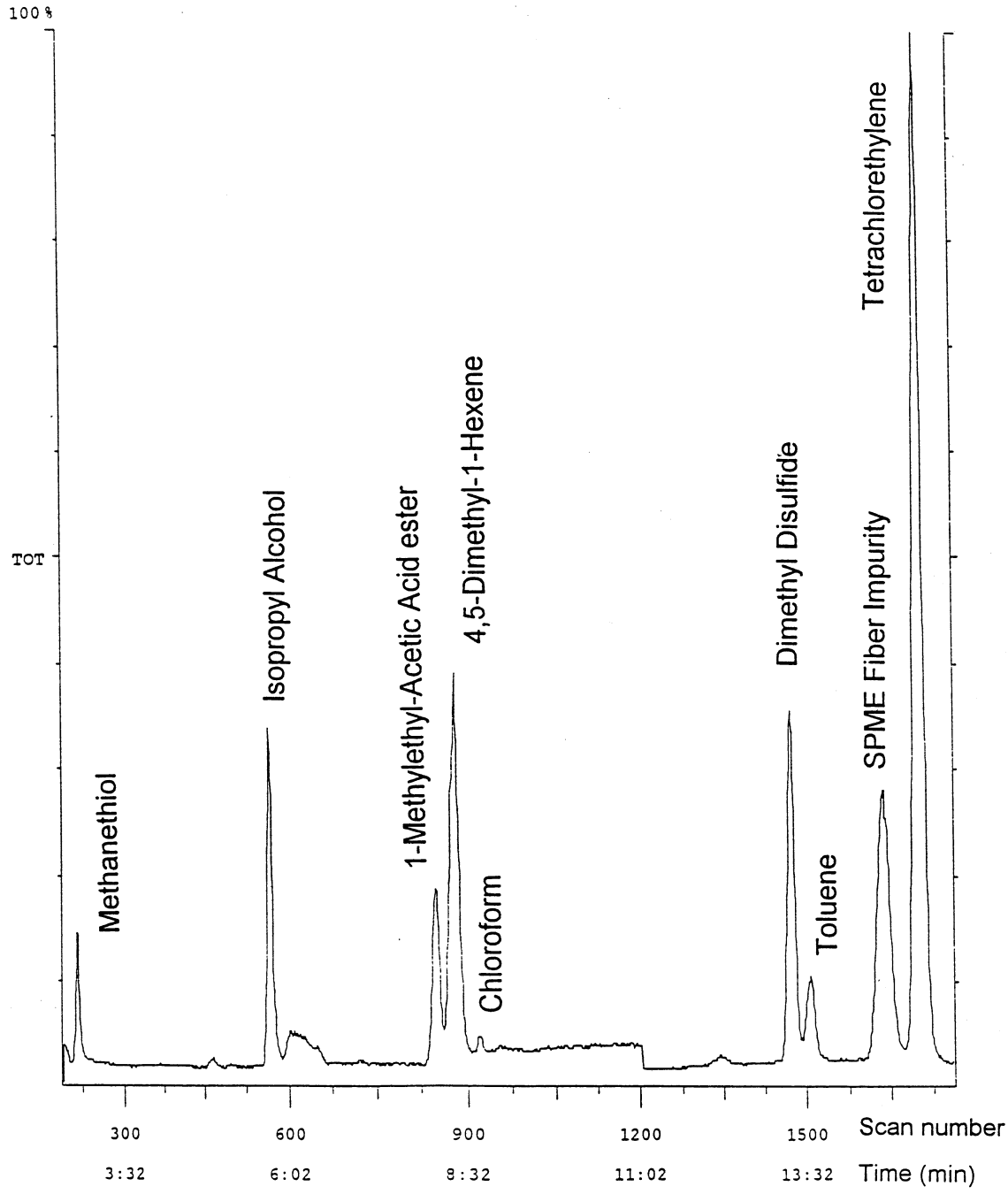

Fig. 8. Gastight SPME chromatogram of proprietary drug substance 3.

extracting spiked aqueous solutions with concentrations given in the Table 4. The repeatability data were calculated from the analyte peak areas of five replicates, within 1 day and by one analyst. Acceptable RSD's of peak areas were obtained for all sample preparation techniques used. For

volatile components, the gastight SPME showed better repeatability than for less volatile/more polar components. As expected, the pyridine gave the worst repeatability (RSD = 7%), taking into consideration its polarity and boiling point. The headspace SPME gave the best repeatability for all components. The static headspace showed worse repeatability which in the case of 1,2-dioxane and pyridine, the measured RSD's of peak areas were as high as 10%. We found that consistent stirring is one of the most important factors for repeatable SPME analysis.

The headspace SPME equipped with a polydimethylsiloxane/divinylbenzene coated fiber was chosen because of its better precision as sample preparation method for the determination of residual solvents in a proprietary drug product (peptide compound) of the Gedeon Richter LTD by GC-MS. The validation data of the selected method are presented in the Table 5. As can be seen, the method is linear for all investigated analytes with excellent correlation coefficients over the whole linear range. The intercept confidence interval for all analytes does contain the origin. The accuracy data were assessed on samples spiked with known concentrations of analytes. Accuracy was reported as percent recovery by the assay of known added amount of analyte in the sample. For all analytes the mean recovery was greater than 90%. Acetonitrile, dioxane and pyridine gave less recovery mainly because their polarity (affinity to the aqueous solution). The best recoveries were given by tricholoroethylene and benzene mainly because their high affinity to the polymer film.

The intermediate precision data were consistent and the assessed RSD of peak areas were similar to the repeatability ones.

The quantitation limits were investigated by extracting spiked aqueous solutions as described in Section 2. The quantitation limit was performed by comparing measured signals from the selected ion chromatogram of samples with known low concentration of analyte with those of blank samples. The acceptance criteria was a signal/noise ratio with a minimum value of 10:1.

From a chromatographic point of view, gastight SPME gave better peak shapes than headspace SPME. Fig. 4 shows the headspace SPME chromatogram of a 100 ng ml^{-1} standard solution in which the peak at 6.46 min is a co-elution of a water impurity with benzene. As seen in Fig. 5 (the gastight SPME chromatogram of a 100 ng ml^{-1} standard solution), the critical pair was quite well resolved. Fig. 6 shows the gastight SPME chromatogram of proprietary drug substance 1 spiked with 100 ng ml^{-1} standard solution. As can be seen from the chromatogram, even in a strong matrix (peptidic matrix, polar), the extraction could easily happen with recoveries (by assay of known added amount of analyte in the sample) greater than 90%. At the same time, the peak shape remained very good.

Fig. 7 shows the gastight SPME chromatogram of proprietary drug substance 2, in which three unknowns were extracted and identified by their mass spectrum. All mass spectra of unknowns were checked against NIST mass spectral library and the fit between measured and found spectra was $>94\%$. The identified compounds were found to be impurities of solvents used during synthesis which did concentrate into the products. Their concentrations were close to their detection limits.

Fig. 8 shows the gastight SPME chromatogram of proprietary drug substance 3. In this case, two unknown components did appear in the residual solvents chromatogram of this substance. The headspace SPME did not give a detectable signal for the first unknown. After analyzing the residual solvent profile of this substance by gastight SPME–GC-MS, we identified the two unknowns as being methanethiol and dimethyl disulfide. The mass spectral quality of methanethiol peak was surprisingly good allowing easy identification. All mass spectra of unknowns were checked against NIST mass spectral library and the fit between measured and find spectra was bigger than 94%. The unknown analytes were find to be thermal degradation products. In this case can be seen a certain loss of chromatographic resolution due to peak broadening caused by the slow thermal desorbtion of the components from the polymer film.

This slow mass transfer happens because the initial concentration of analytes in the aqueous phase was $\sim 100\ \mu g\ ml^{-1}$, which causes diffusion of the components deep into the polymer film and slow thermal desorbtion into the gas chromatographic injector.

6. Conclusions

Between the investigated polymeric films, the polydimethylsiloxane/divinylbenzene coated fiber showed by far the best sensitivities for all compounds. The fiber was able to extract compounds with different polarity and volatility.

Between the investigated sample preparation techniques, gastight SPME proved to be more sensitive and headspace SPME proved to be more precise. The most important difference between the two techniques is that the gastight SPME showed better behavior towards very volatile impurities, thus allowing lower detection/quantitation limits. At the same time, Gastight SPME gave better peak shapes than headspace SPME. Compared with the headspace technique, both SPME methods showed superior results, being from all point of view compatible with the pharmaceutical samples.

The SPME–GC-MS proved to be a powerful technique in the identification and determination of unknown solvent residues in pharmaceutical products. With this technique, we were able to identify residual solvents in our proprietary pharmaceutical products. Even if SPME techniques are not yet accepted as sample preparation methods by Pharmacopoeias, taking into consideration their precision, accuracy and speed of analysis, we can state that they are suitable for qualitative/quantitative residual solvent determination in pharmaceutical products.

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