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Matrix media selection for the determination of residual solvents in pharmaceuticals by static headspace gas chromatography

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Abstract

The influence of the matrix medium used for the determination of residual solvents in pharmaceuticals by static headspace gas chromatography was investigated. The purpose of this paper is to propose a guide for the choice of a matrix medium suitable for the determination of residual solvents of interest. Dimethylsulfoxide (DMSO), *N*,*N*-dimethyformamide (DMF), *N*,*N*-dimethylacetamide (DMA), benzyl alcohol (BA), 1,3-dimethyl-2-imidazolidinone (DMI) and water were studied as matrix media, and seventeen solvents used for the synthesis and purification of drug substances were used as target analytes. The peak shape of each analyte was not affected by the matrix medium, whereas the peak intensities for all solvents were strongly affected by the matrix medium; for example, the peak intensity of methanol in a BA matrix was more than four times that in a DMSO matrix. With a few exceptions, the peak intensities are approximately doubled for every 20 °C rise in equilibrium temperature between 80 and 140 °C, and there is no difference in this behavior among the matrix media. In addition, the formation of artifacts from the matrix media, upon heating in a headspace sampling apparatus, was investigated. Artifacts were also formed following ultrasonication of sample solutions used to increase dissolution of the sample into the matrix medium selected. These artifacts included benzene and toluene which were restricted as Class 1 and 2 toxic solvents in the ICH guideline.

Keywords: Matrix medium; Residual solvents; Pharmaceuticals; Static headspace gas chromatography

1. Introduction

The determination of residual solvents in pharmaceuticals is very important because of the potential risk to human health from the toxicity [1]; the amounts of such solvents are therefore restricted by the Internal Conference on Harmonization (ICH) guideline Q3C (Impurities: Guideline for Residual Solvents) [2]. From another point of view, residual solvents may also affect the physicochemical properties and stability of not only drug substances but also drug products. For the determination of residual solvents, gas chromatography (GC), as described in standards, such as United States Pharmacopoeia (USP) 26 and European Pharmacopoeia (EP) 3, has been widely used as the most appropriate methodology. In the ICH guideline, although limits for residual solvents in pharmaceuticals are described in detail, the determination method is not described. Furthermore, the Japanese Pharmacopoeia (JP) 14, revised to include a residual solvent test, includes no definitive determination method.

Sampling techniques in GC include direct injection (DI) and headspace (HS) sampling. DI is simple and convenient, and requires only standard GC equipment, however, less volatile sample compounds or dissolution media would remain on the column, which could reduce the lifetime of the column and interfere with the subsequent analyses [1]. In addition, interactions between dissolution media and other sample compounds in the injection port would cause a variety of problems [3]. On the other hand, HS sampling minimizes these problems because only the volatile portion

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of the sample solution is subjected to analysis. Two types of HS sampling techniques are generally available: static and dynamic procedures [4–6]. Although the dynamic HS technique is more sensitive than static HS, it cannot be readily automated and is restricted to aqueous solutions.

The static HS sampling technique is based on thermostatic partitioning of volatile compounds in a closed vial between the sample dissolution medium and the surrounding gas phase, followed by the transfer of an aliquot of the vial headspace gas containing the volatile analytes to the GC equipment. For water-soluble samples, water is the matrix medium of choice. For water-insoluble samples, dimethylsulfoxide (DMSO), *N*,*N*-dimethyformamide (DMF), *N*,*N*-dimethylacetamide (DMA), benzyl alcohol (BA) and 1,3-dimethyl-2-imidazolidinone (DMI) are recommended as matrix media by many authors [1,7,8], and some of these media are described in USP 26 and EP 3. Among these solvents, how should analysts choose the most suitable one for individual determinations of residual solvents? Will any solvent do, as long as it can dissolve the objective sample? In this paper, we describe the influence of the matrix medium on the determination of residual solvents in pharmaceuticals by static HS–GC. The purpose is to propose a guide for the choice of a suitable matrix medium. Fourteen solvents often used for the synthesis and purification of drug substances were employed as target analytes. We also give some information about the formation of artifacts arising from the matrix medium on heating the sample solution in a HS sampling apparatus or from ultrasonication of the sample solution used to increase sample dissolution.

2. Experimental

2.1. Reagents and materials

Table 1 lists the target analytes employed in the present study: these solvents are frequently used in the synthesis and purification of the drug substances at our company. All the solvents were of analytical reagent grade and obtained from Wako Pure Chemical Industries Ltd. (Osaka, Japan). Based on the ICH guideline Q3C [2], they are classified as Class 2 (solvents to be limited), Class 3 (solvents with low toxic potential) or other solvents for which no adequate toxicological data was found. The matrix media used were also of analytical reagent grade and obtained from Wako Pure Chemical Industries Ltd., which are listed together with their boiling points in Table 2.

2.2. Chromatographic systems and methods

A Shimadzu GC-2010 gas chromatograph equipped with flame ionization detector and a Perkin-Elmer HS-40 headspace injector were used. The principal column used was a 30 m × 0.53 mm I.D. fused silica capillary column coated with 3.0 μm film of 6% cyanopropylphenyl-94% dimethylpolysiloxane (OVI-G43, Supelco Co. Ltd., Bellefonte, PA, USA). A 30 m × 0.53 mm I.D. fused silica capillary column coated with 1.0 μm film of polyethyleneglycol (SUPELCOWAX-10, Supelco) was also used to allow for other conditions.

Table 1
List of analytes employed in the present study

Class[a]	Analyte
2	Methanol
	Acetonitorile
	Dichloromethane
	Toluene
	Hexane
	DMF
	DMA
	Pyridine
	1,4-Dioxane
3	Ethanol
	Acetone
	Ethyl acetate
	Tetrahydrofuran
	Isopropanol
	DMSO
Others	Isopropyl ether
	Heptane

[a] ICH guideline Q3C [2].

The GC and headspace parameters are as follows: the carrier gas was helium and the average column linear velocity was 35 cm s^{-1}. Nitrogen was used as the make-up gas at a flow rate of 50 ml min^{-1}. The injector was maintained at 160 °C with a split ratio of 5:1 and the detector at 250 °C. The column temperature was programmed at 40 °C for 20 min, then raised at a rate of 10 °C min^{-1} to 240 °C. The headspace injector parameters were 80–140 °C equilibration temperature, 60 min thermostating time, 3 min pressurization time, 0.04 min injection time and sample volume of 1.0 ml. The needle and transfer line temperatures were set at 10 and 20 °C higher than equilibration temperature, respectively. The headspace vial was 22-ml capacity and a polyperfluoroethylene coated butyl rubber septum and an aluminum crimp cap were used to seal the vial.

2.3. Standard preparation

Standard solutions containing three concentration levels of the analyte (250, 25, 0.5 μg ml^{-1}) were prepared by considering the different peak intensities. Approximately 0.1 g

Table 2
List of matrix media employed in the present study

Matrix medium	Boiling point (°C)
DMSO	189
DMF	153
DMA	166
BA	204
DMI	105
Water	100

of appropriate solvents with low detection limit (hexane, heptane and isopropyl ether: final concentration 0.5 μg ml^{-1}) were accurately weighed into a 100-ml volumetric flask, diluted to volume with a matrix medium, and mixed (Stock solution A). Separately, approximately 0.1 g of appropriate solvents with a medium detection limit (methanol, ethanol, acetone, isopropanol, acetonitrile, dichloromethane, ethyl acetate tetrahydrofuran, 1,4-dioxane, toluene and pyridine: final concentration 25 μg ml^{-1}) were accurately weighed into a 100-ml volumetric flask, diluted to volume with a matrix medium, and mixed (Stock solution B). One ml of Stock solution A and 50 ml of Stock solution B were pipetted into a 200-ml volumetric flask and then accurately weighed 0.5 g of appropriate solvents with high detection limit (DMSO, DMF and DMA: final concentration 250 μg ml^{-1}) were added, which were diluted to volume a with matrix medium and mixed (Standard solution). For the preparation of calibration curves, this standard solution was accurately diluted to obtain five different concentration levels (0.05, 0.1, 0.2, 0.3, 0.5 μg ml^{-1} for hexane, heptane and isopropyl ether; 2.5, 5,10,15, 25 μg ml^{-1} for methanol, ethanol, acetone, isopropanol, acetonitrile, dichloromethane, ethyl acetate tetrahydrofuran, 1,4-dioxane, toluene and pyridine; 25, 50, 100, 150, 250 μg ml^{-1} for DMSO, DMF and DMA).

2.4. Ultrasonication of sample solutions

Five milliliters of the matrix medium, placed into the headspace vial and sealed, was irradiated with ultrasonic waves (SONO Cleaner 200Z, Kaijo Co. Ltd., Tokyo, Japan [38 kH, 200 W]), with shaking for 10 min.

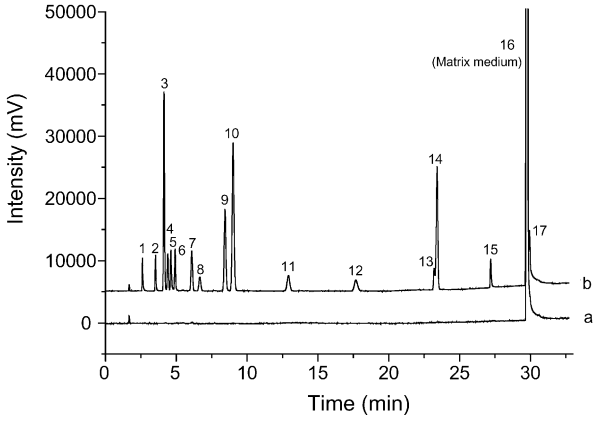

Fig. 1. Headspace gas chromatograms of each analyte dissolved in DMSO matrix on OVI-G43 column at the equilibrium temperature of 80 °C. (a) Blank solution, (b) standard solution. Peak identities and concentrations are: (1) methanol 25 μg ml^{-1}, (2) ethanol 25 μg ml^{-1}, (3) acetone 25 μg ml^{-1}, (4) isopropanol 25 μg ml^{-1}, (5) acetonitrile 25 μg ml^{-1}, (6) dichloromethane 25 μg ml^{-1}, (7) hexane 0.5 μg ml^{-1}, (8) isopropyl ether 0.5 μg ml^{-1}, (9) ethyl acetate 25 μg ml^{-1}, (10) tetrahydrofuran 25 μg ml^{-1}, (11) heptane 0.5 μg ml^{-1}, (12) 1,4-dioxane 25 μg ml^{-1}, (13) toluene 25 μg ml^{-1}, (14) pyrideine 25 μg ml^{-1}, (15) DMF 250 μg ml^{-1}, (16) DMSO 250 μg ml^{-1}, (17) DMA 250 μg ml^{-1}.

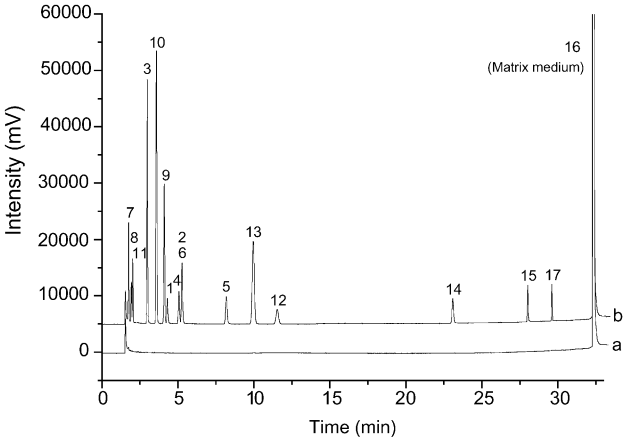

Fig. 2. Headspace gas chromatograms of each analyte dissolved in DMSO matrix on SUPELOCOWAX-10 column at the equilibrium temperature of 80°C. (a) Blank solution, (b) standard solution. Peak identities and concentrations are referred to the annotation in Fig. 1.

3. Results and discussion

3.1. Influence of matrix medium on peak shapes of analytes

Fig. 1 shows the chromatograms of a standard solution prepared with a DMSO matrix, as representative of all matrix media, and its blank on OVI-G43 column at the equilibrium temperature of 80 °C. The standard solution contains three concentration levels of the analytes for the adjustment of peak intensity (see the annotation in Fig. 1). Dichloromethane, hexane, isopropyl ether, heptane and toluene were not applied as analytes in the water matrix medium because of their low solubilities. No difference in not only the peak shapes but also the separation patterns was observed among the matrix media studied although the peak intensities depended on the matrix medium (details are described in Section 3.3). Suffi-

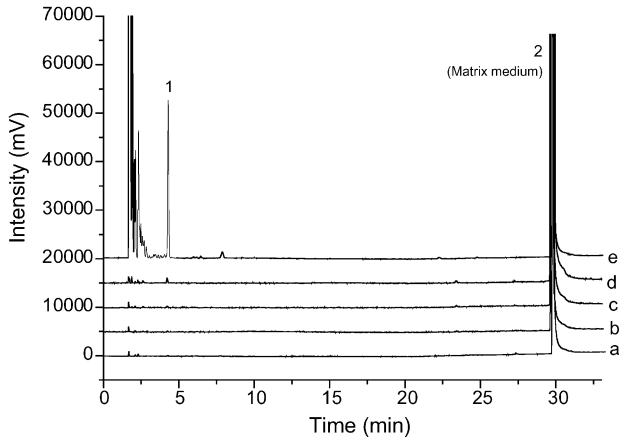

Fig. 3. Headspace gas chromatograms of DMSO matrix blanks on OVI-G43 at the equilibrium temperature of 80 °C (a and e), 100 °C (b), 120 °C (c), 140 °C (d). (e) Irradiated with ultrasonic wave (38 kHz, 200 W) for 10 min. Peak: (1) dimethylsulfide.

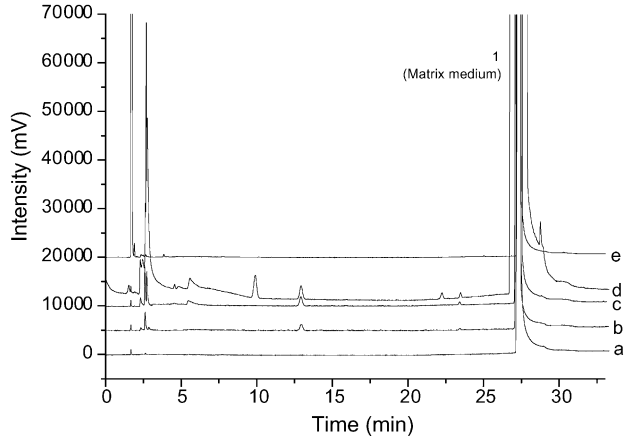

Fig. 4. Headspace gas chromatograms of DMF matrix blanks on OVI-G43 at the equilibrium temperature of 80 °C (a), 100 °C (b), 120 °C (c), 140 °C (d). (e) Irradiated with ultrasonic wave for 10 min.

cient separation between toluene and pyridine peaks were not observed, however, they were completely separated in an alternative procedure using SUPELCOWAX-10 as a capillary column (Fig. 2).

3.2. Impurities contained in the matrix media

In the measurements of DMSO matrix media, trace amounts of impurities (5.9 and 6.2 min) were detected at the equilibrium temperature of 80°C. Some authors [1,8] reported that DMSO contains dimethylsulfide and dimethyldisulfide as impurities, however, the retention times of the impurities detected in DMSO matrix blank were not in agreement with those of dimethylsulfide (4.3 min) and dimethyldisulfide standards (22.2 min). On the other hand, no impurity was detected in other matrix medium blanks (Figs. 3a–7a), whereas the existence of some impurities in BA such as methanol, toluene and other oxidation products was also reported [9,10].

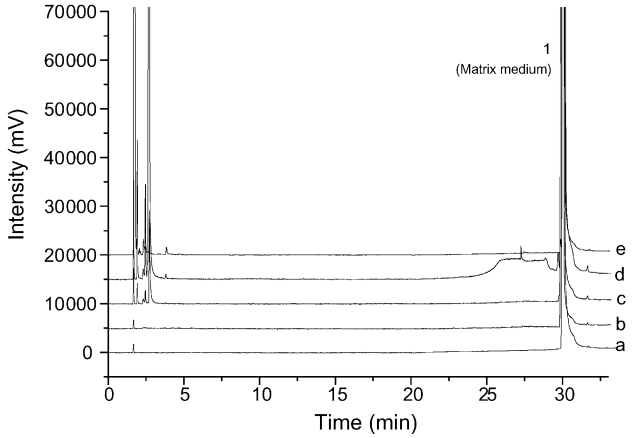

Fig. 5. Headspace gas chromatograms of DMA matrix blanks on OVI-G43 at the equilibrium temperature of 80 °C (a and e), 100 °C (b), 120 °C (c), 140 °C (d). (e) Irradiated with ultrasonic wave for 10 min.

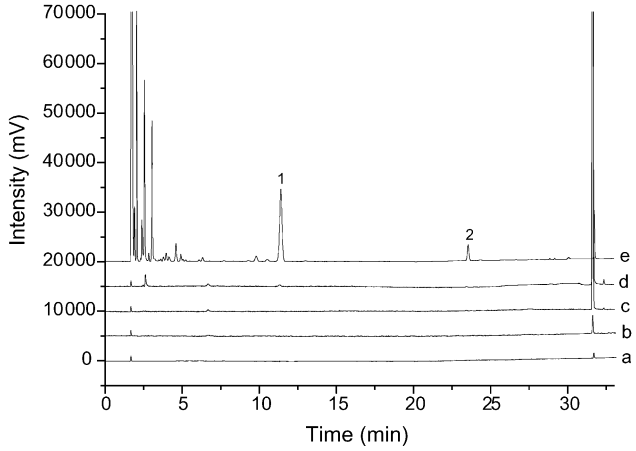

Fig. 6. Headspace gas chromatograms of BA matrix blanks on OVI-G43 at the equilibrium temperature of 80 °C (a and e), 100 °C (b), 120 °C (c), 140 °C (d). (e) Irradiated with ultrasonic wave for 10 min. Peak: (1) toluene; (2) benzene.

3.3. Influence of the nature of the matrix medium on peak intensity

The GC peak response (PR) of an analyte in the gas phase is described by the following equation [11–13]:

$$\mathrm{PR} = fC_0\left(K + \frac{V_\mathrm{G}}{V_\mathrm{S}}\right)^{-1}$$

where f is the analyte-specific response factor, C_0 the initial concentration of the analyte in the solution, K the partition coefficient of the volatile analyte between the liquid and gas phases and $V_\mathrm{G}/V_\mathrm{S}$ the ratio of the volume of the gas (V_G) to the volume of the liquid (V_L). That is to say, the peak response is inversely proportional to the sum of the partition coefficient of the analyte and the volume ratio. In general, the partition coefficient makes a much greater contribution to the analyte peak response than dose the volume ratio [8,11].

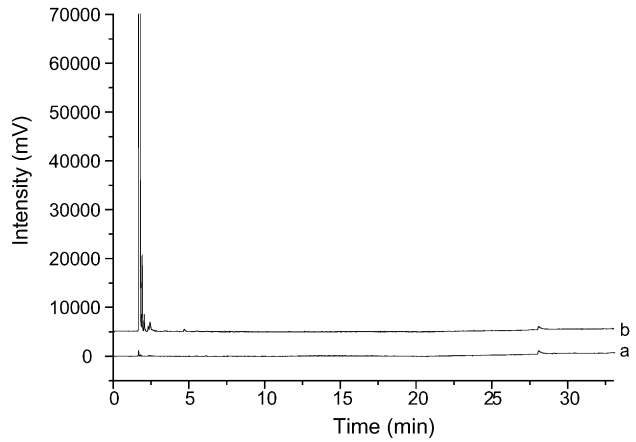

Fig. 7. Headspace gas chromatograms of DMI matrix blanks on OVI-G43 at the equilibrium temperature of 80 °C. (b) Irradiated with ultrasonic wave for 10 min.

Table 3
Peak intensity ratio of each analyte on OVI-G43 (upper) and SUPELCOWAX-10 (lower) at the equilibrium temperature of 80 °C

Analyte	Peak intensity ratio					
	DMSO	DMF	DMA	BA	DMI	Water
Methanol	(1)	1.80	1.51	4.44	1.79	1.54
	(1)	1.79	1.41	4.29	1.71	1.85
Ethanol	(1)	1.41	1.17	2.98	1.47	4.02
	(1)	1.15	1.13	2.95	1.42	3.71
Acetone	(1)	0.76	0.84	0.77	1.01	2.12
	(1)	0.75	0.80	0.76	0.98	1.86
Isopropanol	(1)	1.11	0.92	2.16	1.20	4.55
	(1)	1.09	0.88	2.15	1.17	4.31
Acetonitorile	(1)	0.94	1.00	2.28	1.25	1.62
	(1)	0.95	0.97	2.11	1.20	0.85
Dichloromethane	(1)	0.77	0.67	2.52	0.81	n.a.
	(1)	0.93	0.64	2.48	0.79	n.a.
Hexane	(1)	0.56	0.49	0.65	0.58	n.a.
	(1)	0.58	0.55	0.64	0.27	n.a.
Isopropyl ether	(1)	0.46	0.43	0.31	0.52	n.a.
	(1)	0.50	0.39	0.31	0.47	n.a.
Ethyl acetate	(1)	0.65	0.67	0.62	0.86	1.49
	(1)	0.64	0.64	0.62	0.84	3.45
Tetrahydrofuran	(1)	0.72	0.72	0.33	0.83	3.62
	(1)	0.72	0.69	0.33	0.81	3.54
Heptane	(1)	0.42	0.34	0.49	0.42	n.a.
	(1)	0.43	0.35	0.46	0.39	n.a.
1,4-Dioxane	(1)	0.80	0.86	0.48	1.05	1.42
	(1)	0.80	0.84	0.50	1.02	1.42
Toluene	(1)	0.54	0.50	1.02	0.59	n.a.
	(1)	0.53	0.47	0.96	0.53	n.a.
Pyridine	(1)	0.67	0.68	0.17	0.60	4.19
	(1)	0.70	0.69	0.18	0.81	4.53
DMF	(1)	n.a.	0.92	–	1.19	–
	(1)	n.a.	0.92	–	1.03	–
DMSO	n.a.	–	–	–	–	–
	n.a.	–	–	–	–	–
DMA	(1)	0.56	n.a.	–	1.62	–
	(1)	0.46	n.a.	–	1.20	–

n.a.: not applicable, –: data were not obtained because of no calibration curves.

Consequently, since the partition coefficient will mainly be governed by the nature of the matrix medium at the same equilibration temperature, the choice of the matrix medium is of great importance in attempts to increase the peak intensities of analytes of interest.

The peak intensity ratios when using different matrix media were estimated by the magnitude of the slopes of calibration curves (Table 3). The calibration curves prepared with analyte solutions at five concentration levels (see Section 2), prepared by diluting the standard solution, gave straight lines; the correlation coefficients were greater than 0.990 for non-volatile analytes, DMSO, DMF and DMA, and than 0.999 for the other volatile analytes. It is clear that the peak intensity for each analyte was greatly dependent on the matrix medium. Almost the same values were obtained by different two columns used in this study.

The detection limits (DL) at the equilibrium temperature of 80 °C were estimated (Table 4) using the following equation based on ICH guideline Q2B (Validation of Analytical Procedures: Methodology) [14].

$$\mathrm{DL} = \frac{3.3\sigma}{S}$$

where σ is the standard deviation of peak response and S the slope of the calibration curve. This result also indicated that the peak intensities for each analyte were influenced by the matrix medium.

Table 4
Detection limit of each analyte on OVI-G43 (upper) and SUPELCOWAX-10 (lower) at the equilibrium temperature of 80 °C

Analyte	Detection limit (μg ml^{-1})					
	DMSO	DMF	DMA	BA	DMI	Water
Methanol	0.919	0.981	0.828	0.307	0.632	0.316
	0.760	0.704	0.766	0.315	0.472	0.218
Ethanol	1.269	0.338	0.741	0.628	0.678	0.710
	0.636	0.493	0.395	0.298	0.524	0.360
Acetone	0.137	0.108	0.181	0.202	0.187	0.196
	0.148	0.328	0.168	0.102	0.204	0.217
Isopropanol	0.403	0.213	0.370	0.249	0.418	0.356
	0.389	0.411	0.491	0.167	0.665	0.089
Acetonitorile	1.021	0.964	0.946	0.559	0.917	0.955
	0.302	0.770	0.457	0.348	0.733	0.571
Dichloromethane	0.846	0.782	1.416	0.535	0.711	n.a.
	0.359	0.249	0.400	0.310	0.534	n.a.
Hexane	0.032	0.035	0.029	0.017	0.025	n.a.
	0.021	0.024	0.050	0.020	0.041	n.a.
Isopropyl ether	0.020	0.027	0.032	0.068	0.026	n.a.
	0.039	0.068	0.058	0.064	0.053	n.a.
Ethyl acetate	0.468	0.282	0.439	0.410	0.556	0.407
	0.107	0.244	0.229	0.188	0.374	0.133
Tetrahydrofuran	0.169	0.124	0.139	0.140	0.199	0.076
	0.137	0.175	0.078	0.261	0.215	0.078
Heptane	0.024	0.044	0.046	0.070	0.017	n.a.
	0.021	0.024	0.050	0.020	0.041	n.a.
1,4-Dioxane	0.955	0.952	1.215	3.154	1.482	0.816
	0.830	0.763	0.591	1.520	0.753	0.914
Toluene	0.208	0.765	0.538	0.273	0.443	n.a.
	0.085	0.208	0.189	0.140	0.560	n.a.
Pyridine	0.312	2.368	0.607	3.225	0.438	0.484
	0.433	1.100	1.045	3.948	0.578	0.329
DMF	7.905	n.a.	10.175	150[a]	23.314	>250[a]
	6.333	n.a.	7.474	100[a]	9.297	>250[a]
DMSO	n.a.	>250[a]	150[a]	>250[a]	100[a]	>250[a]
	n.a.	>250[a]	100[a]	>250[a]	50[a]	>250[a]
DMA	22.884	13.588	n.a.	>250[a]	11.633	>250[a]
	4.985	3.361	n.a.	>250[a]	6.970	>250[a]

n.a.: not applicable.
[a] Estimated by signal to noise ratio (s/n = 3) because of no calibration curves.

3.4. Influence of the matrix medium on the temperature coefficient

For the matrix media of DMSO, DMF, DMA and BA, the equilibrium temperature dependencies of peak intensities were examined (water and DMI were not applied because of low boiling points). When the equilibration temperature was raised to 100, 120 and 140 °C, plots of the natural logarithm of peak area versus absolute temperature showed good linearity (correlation coefficients were greater than 0.99). Their slopes, the temperature coefficients, were dependent on the analytes, however, they were almost independent of the matrix medium (Table 5); recall that peak area is approximately doubled for every 20 °C rise in temperature with a value of the temperature coefficient of 3.0.

3.5. Artifact formation

In order to improve the sensitivity of the determination, i.e., increase the peak intensity, there are generally two approaches, except for the selection of matrix medium. One is to raise the equilibration temperature in the HS sampling apparatus to increase the partition coefficient between the liquid and gas phases, described in the previous section, the other is to raise the concentration of sample solution.

Table 5
Influence of the matrix medium on the temperature coefficient

Analyte	Temperature coefficient			
	DMSO	DMF	DMA	BA
Methanol	0.032	0.032	0.035	0.028
Ethanol	0.033	0.032	0.034	0.031
Acetone	0.023	0.025	0.025	0.024
Isopropanol	0.032	0.036	0.034	0.031
Acetonitorile	0.028	0.030	0.030	0.025
Dichloromethane	0.025	0.027	0.027	0.018
Hexane	0.011	0.019	0.016	0.014
Isopropyl ether	0.015	0.022	0.020	0.024
Ethyl acetate	0.024	0.027	0.027	0.025
Tetrahydrofuran	0.021	0.024	0.025	0.028
Heptane	0.014	0.019	0.022	0.017
1,4-Dioxane	0.029	0.029	0.030	0.031
Toluene	0.027	0.032	0.030	0.024
Pyridine	0.029	0.029	0.028	0.042
DMF	0.035	n.a.	0.026	0.029
DMSO	n.a.	–	0.031	–
DMA	0.033	0.035	n.a.	–

n.a.: not applicable, –: data were not obtained because of no calibration curves.

3.5.1. High heating of sample solution in HS sampling apparatus

An easier way to increase the peak intensity is to raise the equilibrium temperature. However, heating the sample solution at higher temperatures may cause thermal degradation of the sample or/and matrix medium. If the degradation products include volatile compounds which can be detected by HS GC, this might cause interference in the analysis. In the chromatograms at an equilibrium temperature of more than 100 °C described in the previous section, some peaks were, in fact, detected from DMSO, DMF, DMA and BA matrix medium blanks (Figs. 3–6). In particular, a number of large peaks were detected from DMF and DMA matrix media, which interfere with the determination of analytes (Figs. 4 and 5). Since these peak areas were not doubled for every 20 °C rise in temperature (see Figs. 4b–d and 5b–d), they were considered not to be impurities originally contained in the matrix media themselves, but to be degradation products for at least DMF and DMA matrix media.

3.5.2. Ultrasonication of sample solution

Preparing a more concentrated sample solution also contributes to the improvement of sensitivity. To dissolve a greater quantity of a pharmaceutical sample into matrix media rapidly, they are usually irradiated with ultrasonic waves. In the chromatograms of the matrix media blank sonicated for 10 min (38 kH, 200 W), several unknown peaks were detected in the sonicated matrix media except for water (Figs. 3e–7). We have previously reported [15] that BA is degraded into benzene and toluene by irradiation of ultrasonic wave in preparing the sample solution for the determination of residual solvents by DI method. It was confirmed that the artifacts generated from BA, in this study, also included benzene and toluene by comparing their retention times with those of benzene and toluene standards using OVI-G43 (Fig. 6e) and SUPELCOWAX-10. Five replicate experiments revealed that benzene and toluene were generated 8.61 ± 2.41 and $4.77 \pm 1.29\ \mu g\ ml^{-1}$ (mean ± S.D., $n = 5$) for 10 min, which corresponds to 431 and 239 ppm when the sample concentration is 20 mg/ml. Furthermore, the retention time (4.4 min) of the major artifact generated from sonicated DMSO matrix media is in agreement with that of dimethylsulfide standard (Fig. 3e).

It is accepted that ultrasonic irradiation in liquid causes acoustic cavitation: the formation, growth, and implosive collapse of bubbles. When the cavity implodes, an enormous amount of local heat energy is generated, and peak temperatures of several thousands of degrees Celsius have been predicted [16–18]. Although there are only a few reports on the degradation of organic solvents themselves [19] using this energy, many synthetic or degradation studies of organic compounds in liquid medium have been reported [20–23]. Considering the results of these reports, it can be suggested that the enormous amount of local heat energy generated by the sonication may cause the cleavage of energetically weak bonds in solvent molecules to form the several radical compounds, which ultimately will generate stable molecules (radical rearrangements).

4. Conclusions

The effect of matrix medium on the determination of residual solvents in pharmaceuticals, by static headspace gas chromatography, was studied. In the pharmaceutical industries, the quantitative determination of residual solvents, at the concentration levels lower than the limits described in the ICH guideline, is indispensable in terms of quality control. For this purpose, the preparation of the sample solution requires a large amount of the sample to obtain a concentrated sample solution (e.g., 0.5 g of a sample is dissolved in matrix solvent to make 5 ml). It could be a serious problem for the determination of expensive products, products made for animal studies (i.e., toxicity testing for pre-clinical work) with small lot size and their intermediate products. We have demonstrated that the choice of matrix medium influences the peak intensities of all the solvents employed in this study. This knowledge should reduce the required sample amount by allowing selection of the most suitable matrix medium for individual pharmaceutical samples.

We have further given information about artifact formation caused by high heating or ultrasonic wave irradiation of the sample solution for the purpose of increasing the peak intensity. The heating of the sample solution is automatically performed in the same way as for the blank (matrix media only), in a headspace sampling apparatus, therefore, the formation of artifacts can be easily found by the comparison of a chromatograms obtained from the sample with

that from blank. On the other hand, ultrasonication is usually applied to the sample solution when dissolving a sample into a matrix medium, therefore, the formation of artifacts can be overlooked. Although BA is an excellent matrix medium for the more sensitive determination of many analytes (see Tables 3 and 4), the amounts of its artifacts, benzene and toluene, are restricted by the ICH guideline: concentration limit of benzene (Class 1 solvent: solvent to be avoided) is only 2 ppm and that of toluene (Class 2 solvent: solvent to be limited) is 890 ppm. Consequently, it is recommended that the use of sonication for sample preparation in the gas chromatographic determination of residual solvents in pharmaceuticals should be avoided.

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