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Short communication

Validation of a generic analytical procedure for determination of residual solvents in drug substances

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Abstract

A generic analytical procedure for determination of residual solvents in drug substances is described and validated. The procedure is based on methods described in the European and United States parmacopeias, but is faster than the compendial procedures. It is applicable both during drug development and for quality control in commercial manufacture. The method is accurate, linear and shows a satisfactory level of precision. The solvents included in the validation comprise the five class 1 solvents, 17 out of 27 class 2 solvents, 17 out of 27 class 3 solvents and three unclassified solvents according to ICH guideline Q3C. The solvents can be detected and quantified at levels at or below the ppm limits given in the guideline. In most cases the quantification limit is in the lower ppm range. A strategy is proposed to choose between water or *N*,*N*-dimethyl formamide as a diluent. The need for re-validation of the method, mandatory for quantitative procedures according to the European Pharmacopeia, is minimised when using the generic procedure.

Keywords: Static head space gas chromatography; Validation; Generic analytical procedure; Residual solvents; Drug substances; Active pharmaceutical ingredients

1. Introduction

Organic solvents are used in the manufacturing processes for drug substances, drug products and exipients. The solvents are often not totally removed by practical manufacturing techniques, and consequently low levels are present in most pharmaceuticals. Acceptable levels of many residual solvents are included in regulatory guidance documents, in particular in guideline Q3C issued by the International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use (ICH) [1]. Limits given in this guideline are mainly based on toxicity. The analysis of residual solvents is an essential part in the quality control of drug substances used in preclinical or clinical trials as well as for use in commercial drug products.

Capillary gas chromatography with static headspace sampling (HS-GC) is widely used in fields such as forensic, clinical, food and aroma analysis [2]. The technique is robust, convenient and readily automated and validated and is the most common method for the control of residual solvents in pharmaceuticals [3]. It has been adopted, as a recommended method, by the pharmacopeias in the European Union (Ph.Eur.) and the United States (USP) [4,5,6].

In this report a generic analytical procedure for determination of residual solvents in drug substances is described and validated. The procedure is based on the method for identification and control of residual solvents according to Ph.Eur., system A, and USP, method IV, but is faster than the compendial procedures due to a faster heating rate and a shorter equilibration time. The European Pharmacopeia states that the test for quantifying residual solvents has to be validated. The aim in this study was to validate a single procedure for identification and quantification of common residual solvents at or below the levels given in ICH guideline Q3C. To be useful during drug development phases the procedure must be

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applicable to a wide variety of drug substances with a minimum need for re-validation.

The method validated is a gas chromatographic method with headspace injection using a flame ionisation detector. A standard addition procedure is normally used for quantification, but quantification by external standards may also be applied. The selectivity was evaluated for a large number of residual solvents using a standard column. Twenty-seven solvents were chosen for a validation including linearity, precision and quantification limit (QL). These solvents include ICH class 1 solvents except for 1,1-dichloroethene, and the most common class 2 and 3 solvents. For an additional set of 15 less frequently used solvents a precision experiment was performed to verify that these solvents can be reliably quantified at the ICH ppm limit or at least 100 ppm.

2. Experimental

2.1. Materials

Chemicals of a high purity level, analytical grade in most cases, were used for the validation experiments. As diluents, either water purified by filtrating through a water purification unit, or *N*,*N*-dimethyl formamide (DMF) of HPLC grade were used.

2.2. Generic procedure

2.2.1. Chromatography

The experiments were performed on an Agilent 6890 gas chromatograph (GC) equipped with an Agilent 7694 headspace sampler and a flame-ionisation detector. GC settings: inlet heater 150 °C, detector 290 °C, oven initial temperature 40 °C maintained for 4 min, then raised at a rate of 10 °C/min to 160 °C, maintained for 10 min. Column: DB-624 (6% cyanopropylphenyl/94% dimethyl polysiloxane) fused silica capillary column, film thickness 1.8 μm, length 30 m, 0.32 mm i.d. Helium was used as a carrier gas at 65 kPa (constant flow, approximately 33 cm/s corresponding to approximately 2 mL/min) and a split flow of 6 mL/min. Headspace sampler settings: equilibration temperature 75 °C, transfer line temperature 120 °C, equilibration time 30 min, agitation (shaking) low. An exact amount of the headspace volume corresponding to approximately 1 mL is injected.

Shaking of the vials at a low agitation speed is applied during the equilibration time of 30 min. In the compendial procedures, 60 min equilibration time is recommended. However, it has been shown for modern headspace samplers with continuous agitation of the sample that equilibrium is reached after less than 20 min [7,8].

2.2.2. Standard solutions

Standard solutions are prepared from standard stock solutions. Standard stock solutions are prepared in DMF. Standard solutions are prepared in water if the analysis of the sample is to be performed in water, or in DMF if DMF is used as a diluent.

2.2.3. Sample solution

In the generic procedure the sample size is 0.25 g. The sample size may be varied without any major impact on the analysis and the results. Detection limits and quantification limits are of course lower if a higher amount of weighed sample is used and vice versa. However, the entire sample should be dissolved in the diluent.

2.2.4. Procedure

The samples are weighed directly into 22 mL headspace vials. For standard addition procedures equal amounts of sample are used for sample and standard sample solution. To the sample 4 mL of the diluent is added. To the standard sample the standard solution and diluent are added so that the sum of standard solution and diluent is 4 mL. An external standard is prepared in the same way as the standard sample solution from standard solution and diluent but omitting the weighed sample. The vials are immediately sealed and mixed thoroughly until the sample is dissolved. A blank is prepared using 4 mL of the diluent, but without sample or standard solution. The vials with the blank solution, sample solution and standard solution are placed in the headspace sampler and the analysis is started.

If linearity is suspected to be an issue, the analysis may be carried out by using more than one standard sample solutions at different levels.

2.2.5. Evaluation

Using the peak area of the analytes in the sample solution and the standard sample solution or external standard, respectively, the amount of each solvent used to prepare the standard solution, and the weighed amount of sample the content of each residual solvent in the sample is calculated (standard addition or external standard principle).

If more than one standard is used linear regression may be used for evaluation.

3. Results and discussion

3.1. Selectivity

The DB-624 column (6% cyanopropylphenyl/94% dimethyl polysiloxane) is a standard stationary phase, which is adopted as a first choice by the Ph.Eur. and also recommended by the USP compendial method [4,5]. However, the temperature program used in the generic procedure was optimised and is faster than that exemplified by Ph.Eur. and USP. To evaluate selectivity, the aim was to cover most of the residual solvents included in ICH guideline Q3C. A number of solvents, although some of them commonly used in the synthesis of drug substances and also

included in the list of retention times in Table 1, were excluded from further validation experiments for the following reasons:

(1) Poor head-space properties (ethylene glycol, ethoxyethanol, methoxyethanol, *N*,*N*-dimethylacetamide, *N*,*N*-dimethylformamide, *N*-methylpyrrolidone, dimethyl sulfoxide, sulfolane, formamide).
(2) Poor chromatographic properties and/or effectively analysed by alternative methods (acetic acid, formic acid, pyridine, chlorobenzene (in DMF not separated from DMF peak).
(3) Presumed to be easily detected by the described procedure or by similar procedures but to our experience uncommon as solvents (xylene, anisole, cumene, ethyl formate, isobutyl acetate, methyl acetate, pentane, propyl acetate).

For the identification and control of solvents listed under (1) and (2) above, the described method must be modified or other techniques should be used. Three solvents not classified in ICH Q3C, i.e. isooctane, isopropyl ether and *tert*-butanol, are included in the validation. These solvents have to our experience occasionally been used for drug substance synthesis. Retention times are listed in Table 1.

The retention times listed in Table 1 indicate that some of the common solvents coelute. These are in particular 1-propanol and isopropyl ether, 1,2-dichloroethene and methylethyl ketone, tetrahydrofurane and chloroform, benzene and 1,2-dichloroethane, isopropyl acetate and isooctane, and some more solvents are not well separated. If a coeluting pair can be expected to be present the temperature program needs to be optimised or a column with a different stationary phase has to be used to control these solvents.

The selectivity of the DB-624 column was also evaluated by the Working Party on Residual Solvents (Technical) of the European Pharmacopeia Commission [9]. Coelution of common solvents was reported but the coelutions were not always the same from one laboratory to another. The Ph.Eur. proposes a second column (DB-WAX) to verify identity. Fast separation of a limited number of residual solvents by static headspace GC has been reported by George and Wright [10] who separated 18 common solvents in 6 min. Chen et al. [11] separated most class 2 and 3 solvents in less than 5 min using a 10 m × 0.1 mm i.d. DB-624 column.

The described generic method separates most of the frequently used solvents in considerably shorter time than that recommended by the compendial methods. In practice, however, only a limited number of solvents is likely to be present in a drug substance and needs to be separated. In addition, during drug development, the identity of solvents is often verified by GC–MS. This is especially true in cases where unexpected solvent peaks appear in the chromatogram.

3.2. Linearity

The linearity of the method was investigated in water and DMF, respectively, at seven concentration levels in a range between 4 and 720 μg, corresponding to approximately 15 ppm to 3% (w/w), based on a 0.25 g sample. Four replicates were prepared at each level.

The linear regression plots for three solvents in water and DMF as diluent, respectively, are shown in Figs. 1–3. Results of the statistical evaluation of the linearity experiments are summarised in Tables 2 and 3.

The method is linear within a wide range for the solvents included in the validation. The correlation coefficients (R^2) were all above 0.97 in water and above 0.99 in DMF. The intercept included zero or was close to zero in all cases. Lower correlation coefficients were generally obtained in water than in DMF, which is further discussed in the Section 3.5 below.

Non-linearity in the determination of residual solvents has never been observed in our laboratory. It is merely a detector characteristic than a phenomenon likely to be observed in this type of analyses. Non-linearity observed for the described method would be an indication of degradation (i.e. generation or depletion of a solvent), non-equilibrium or leaks. It should initiate trouble-shooting. For a linear method standard addition quantification is generally presumed accurate. If the matrix effect is negligible accurate results can be expected even for quantification by an external standard.

3.3. Precision

For the set of 27 solvents, the repeatability was evaluated at a level corresponding to 15 ppm, or 5 ppm in some cases, based on a 0.25 g sample. The results are shown in Table 4. The repeatability at the levels represented in Table 4 is satisfactory, with a R.S.D. below 10% in all cases except for 1-butanol in DMF (R.S.D. 15%). In many cases the R.S.D. is 3% or even lower.

For the 15 less common solvents listed in Table 5 the repeatability ($n = 3$) was evaluated at a levels corresponding to 100 ppm and 200 ppm.

The repeatability at 100 ppm and 200 ppm is satisfactory for the solvents included in Table 5. In two cases, 3-methyl-1-butanol and 1-pentanol, no signals were obtained at 100 ppm or 200 ppm, and therefore the analysis was repeated at 500 ppm and 1000 ppm as indicated in the table.

Pyridin was initially included among the solvents in Table 5. It is detectable at the 100 ppm level in both diluents. However, pyridine heavily contaminated the system so that no repeatability could be determined.

All experiments according to the described generic procedure were performed without using an internal standard. Internal standards are not regarded necessary for headspace analyses [9] but may be used to improve precision, if needed. The precision of the analysis should be checked on a regular basis, either as an integrated part of the method (system

Table 1
Retention times of residual solvents

Solvent name	ICH Q3C class	Ppm limit[a] according to ICH Q3C	Retention time (min)
Benzene	1	2	7.97
Carbon tetrachloride	1	4	7.70
1,2-Dichloroethane	1	5	7.97
1,1-Dichloroethene	1	8	4.19
1,1,1-Trichloroethane	1	1500	7.47
Acetonitrile	2	410	4.69
Chlorobenzene	2	360	12.47
Chloroform	2	60	7.22
Cyclohexane	2	3880	7.55
1,2-Dichloroethene	2	1870	6.77
Dichloromethane	2	600	4.92
1,2-Dimethoxyethane	2	100	7.94
N,*N*-Dimethylacetamide	2	1090	13.81
N,*N*-Dimethylformamide	2	880	12.14
1,4-Dioxane	2	380	9.33
2-Ethoxyethanol	2	160	9.85
Hexane	2	290	5.76
Methanol	2	3000	2.79
2-Methoxyethanol	2	50	8.20
Methylbutyl ketone	2	50	11.43
Methylcyclohexane	2	1180	9.11
Nitromethane	2	50	6.66
Pyridine	2	200	10.45
Tetrahydrofuran	2	720	7.17
Tetralin	2	100	18.82
Toluene	2	890	10.55
1,1,2-Trichloroethene	2	80	8.84
Xylene (*m*-xylene)	2	2170	12.77
Acetone	3	5000[b]	4.28
1-Butanol	3	5000[b]	8.77
2-Butanol	3	5000[b]	7.07
Butyl acetate	3	5000[b]	11.61
tert-Butylmethyl ether	3	5000[b]	5.36
Dimethyl sulfoxide	3	5000[b]	13.62
Ethanol	3	5000[b]	3.73
Ethyl acetate	3	5000[b]	6.90
Ethyl ether	3	5000[b]	3.86
Heptane	3	5000[b]	8.35
Isobutyl acetate	3	5000[b]	10.80
Isopropyl acetate	3	5000[b]	8.09
Methyl acetate	3	5000[b]	4.77
3-Methyl-1-butanol	3	5000[b]	10.41
Methylethyl ketone	3	5000[b]	6.80
Methylisobutyl ketone	3	5000[b]	10.31
2-Methyl-1-propanol	3	5000[b]	7.89
1-Pentanol	3	5000[b]	11.10
1-Propanol	3	5000[b]	6.08
2-Propanol	3	5000[b]	4.53
tert-Butanol	–	–	5.14
Isopropyl ether	–	–	6.08
Isooctane	–	–	8.09

[a] The ICH ppm limits are based on a daily dose of 10 g and on the permitted daily exposure (PDE, expressed in mg/day).

[b] 5000 ppm of class 3 solvents are acceptable without justification. Higher amounts may be acceptable provided they are realistic in relation to manufacturing capability and good manufacturing practise (ICH).

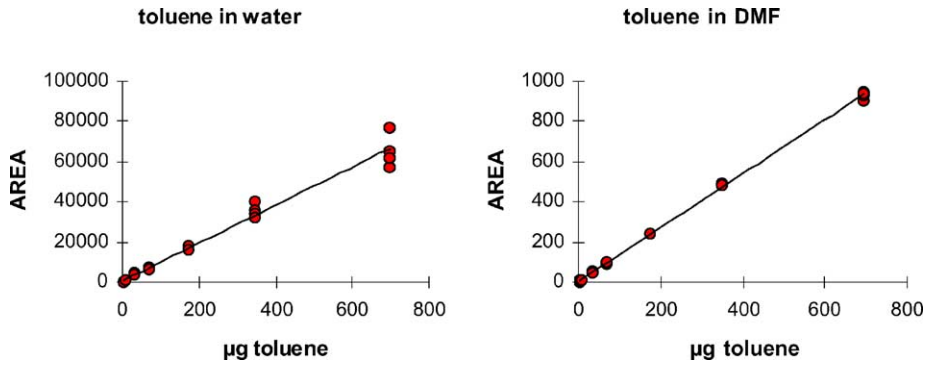

Fig. 1. Linear regression plot of toluene in water (left) and DMF (right).

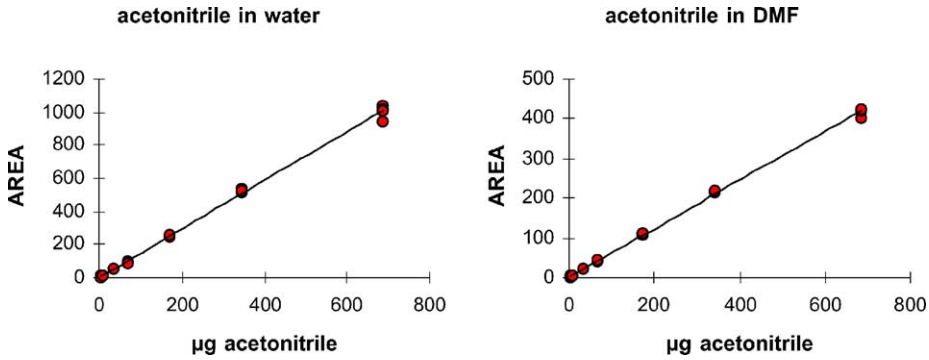

Fig. 2. Linear regression plot of acetonitrile in water (left) and DMF (right).

suitability test) or by other regular controls of instrument performance.

3.4. Detector response and quantification limits

The signal obtained from a solvent analysed by headspace GC using a flame ionisation detector is a combination of the detector response of the solvent and its concentration in the gaseous phase in the headspace vial. As a measure of the signal obtained from each solvent in the two different diluents signal to noise (S/N) ratios are included in Table 4. As a general rule, the detector response and consequently the S/N-ratio is higher in water than in DMF. The only exception is methanol, which has a slightly higher response in DMF than in water. The reason for these differences between water and DMF is the fact that the partition coefficient for most organic solvents is higher to DMF than to water. As a consequence the concentration of the analytes in the gaseous (headspace) phase is higher for water than for DMF as diluent.

A S/N-ratio of 10 is generally regarded as a quantification limit. For most of the 27 common solvents included in Table 4 the S/N-ratio is considerably higher, indicating a QL well below the 15 ppm level or 5 ppm level, respectively. For chloroform and 1-butanol in DMF the S/N-ratio at 15 ppm is slightly below 10, indicating a QL corresponding to 20–25 ppm.

In addition to the data in Table 4 and to verify that benzene at the low ICH limit of 2 ppm is covered by the method, benzene was evaluated in the presence of sample matrix

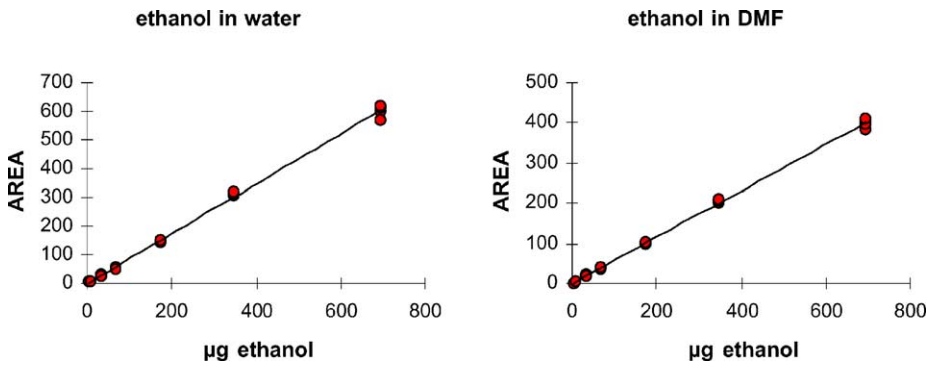

Fig. 3. Linear regression plot of ethanol in water (left) and DMF (right).

Table 2
Linearity of 27 residual solvents using water as a diluent

Solvent name	Linear regression data (range 4–720 μg)		
	R^2	Slope (95% CI)	Intercept (95% CI)
Benzene	0.9814	87.367–97.633	−984.64 to 2160.2
Carbon tetrachloride	0.9982	3.9590–4.1108	−9.2386 to 0.3788
1,2-Dichloroethane	0.9989	14.905–15.344	−11.279 to 8.8806
1,1,1-Trichloroethane	0.9983	22.940–23.793	−39.632 to 2.3591
Acetonitrile	0.9977	1.4429–1.4995	−7.6032 to 9.3085
Chloroform	0.9843	6.5901–7.2983	−71.846 to 147.05
Cyclohexane	0.9978	103.69–107.73	−483.24 to 708.86
Dichloromethane	0.9969	8.9306–9.3414	−16.059 to 116.05
1,4-Dioxane	0.9969	0.6230–0.6514	−3.7593 to 5.4159
Hexane	0.9712	96.131–110.46	−1713.2 to 2566.2
Methanol	0.9978	0.4553–0.4730	−3.1592 to 2.1848
Toluene	0.9810	89.107–99.712	−1035.1 to 2176.3
1,1,2-Trichloroethene	0.9792	20.751–23.339	−274.94 to 514.31
Acetone	0.9951	3.0193–3.1950	−16.457 to 36.687
1-Butanol	0.9942	1.8139–1.9292	−10.300 to 25.466
tert-Butylmethyl ether	0.9867	40.391–44.352	−357.28 to 867.07
Ethanol	0.9981	0.8561–0.8866	−6.1805 to 3.0555
Ethyl acetate	0.9889	8.0994–8.8206	−56.714 to 169.24
Ethyl ether	0.9973	33.714–35.146	−38.658 to 386.10
Heptane	0.9702	98.523–113.52	−1875.9 to 2737.1
Isopropyl acetate	0.9897	14.171–15.385	−135.99 to 231.83
Methylethyl ketone	0.9963	5.1935–5.4535	2.2180 to 81.867
1-Propanol	0.9945	1.3301–1.4122	−7.5375 to 17.614
2-Propanol	0.9947	1.4386–1.5255	−4.1487 to 21.807
tert-Butanol	0.9956	3.5939–3.7918	0.0576 to 63.6961
Isopropyl ether	0.9864	74.134–81.503	−621.73 to 1225.1
Isooctane	0.9991	11.390–11.673	−0.5759 to 89.180

Table 3
Linearity of residual solvents using *N*,*N*-dimethylformamide (DMF) as a diluent

Solvent name	Linear regression data (range 4–720 μg)		
	R^2	Slope (95% CI)	Intercept (95% CI)
Benzene	0.9993	2.6482–2.7066	0.1996 to 18.089
Carbon tetrachloride	0.9996	0.3064–0.3121	−0.3880 to -0.0556
1,2-Dichloroethane	0.9998	0.5764–0.5836	−0.1866 to 0.1428
1,1,1-Trichloroethane	0.9996	1.4804–1.5084	−1.3350 to 0.0424
Acetonitrile	0.9990	0.6020–0.6178	−0.8779 to 3.8287
Chloroform	0.9990	0.1066–0.1093	−0.1042 to 7.261
Cyclohexane	0.9991	11.138–11.415	−0.8440 to 80.937
Dichloromethane	0.9992	0.4437–0.4539	0.0284 to 3.3288
1,4-Dioxane	0.9991	0.3899–0.3995	−0.2528 to 2.8361
Hexane	0.9990	19.553–20.047	−7.0901 to 140.47
Methanol	0.9993	0.5745–0.5867	−0.3853 to 3.3152
Toluene	0.9992	1.3257–1.3572	−1.2574 to 8.2675
1,1,2-Trichloroethene	0.9993	0.4211–0.4304	−0.0406 to 2.7964
Acetone	0.9992	1.8207–1.8625	−0.3299 to 12.298
1-Butanol	0.9967	0.2037–0.2133	−1.8127 to 1.1875
tert-Butylmethyl ether	0.9991	6.6760–6.8376	−0.2975 to 49.650
Ethanol	0.9988	0.5679–0.5840	−2.2569 to 2.6185
Ethyl acetate	0.9993	1.1619–1.1877	−0.1942 to 7.9065
Ethyl ether	0.9991	9.5191–9.7568	−1.5315 to 68.961
Heptane	0.9991	10.798–11.059	1.2199 to 81.436
Isopropyl acetate	0.9992	1.0362–1.0596	0.1163 to 7.2177
Methylethyl ketone	0.9993	1.2581–1.2859	−0.4257 to 8.0829
1-Propanol	0.9988	0.3630–0.3731	−1.5952 to 1.5179
2-Propanol	0.9992	0.5963–0.6098	−0.8267 to 3.2013
tert-Butanol	0.9992	0.8988–0.9195	−0.8559 to 5.8206
Isopropyl ether	0.9991	8.8419–9.0566	−0.8160 to 52.997
Isooctane	0.9979	102.25–106.14	−449.61 to 782.78

Table 4
Repeatability (n = 4) of the determination of residual solvent at a level corresponding to approximately 15 ppm (5 ppm in some cases)

Solvent	Solvent added		Water		DMF	
	μg	ppm	R.S.D. (%)	S/N	R.S.D. (%)	S/N
Benzene	3.5	14	2.0	6019	1.6	214
Carbon tetrachloride	1.3	5.1	1.4	44	4.3	52
1,2-Dichloroethane	1.0	4.0	1.3	206	6.9	13
1,1,1-Trichloroethane	1.1	4.3	9.1	262	2.4	24
Acetonitrile	3.4	14	1.7	68	5.7	27
Chloroform	3.6	14	2.0	435	2.2	8
Cyclohexane	3.4	14	2.1	5727	0.13	529
Dichloromethane	3.7	15	2.1	586	2.8	20
1,4-Dioxane	3.7	15	2.0	39	3.3	36
Hexane	3.4	14	1.9	5129	0.83	1198
Methanol	3.5	14	4.0	19	9.2	32
Toluene	3.5	14	1.9	7152	3.5	112
1,1,2-Trichloroethene	3.5	14	1.9	1526	1.7	37
Acetone	3.5	14	0.5	146	1.7	89
1-Butanol	3.6	14	1.0	91	15	6
tert-Butylmethyl ether	3.6	14	1.5	2035	0.95	367
Ethanol	3.5	14	4.2	36	6.3	18
Ethyl acetate	3.6	14	1.2	590	1.1	86
Ethyl ether	3.4	14	2.3	1850	0.70	324
Heptane	3.5	14	2.2	7149	0.98	961
Isopropyl acetate	3.5	14	1.4	1087	2.5	84
Methylethyl ketone	3.5	14	1.6	379	0.78	60
1-Propanol	3.5	14	3.8	50	8.5	10
2-Propanol	3.4	14	1.4	69	5.6	16
tert-Butanol	3.7	15	1.3	50	3.8	30
Isopropyl ether	2.9	12	1.6	3169	0.96	437
Isooctane	3.6	14	2.3	91	0.35	554

(esomeprazole sodium) at three low levels, using DMF as a diluent. The data are summarised in Table 6 and demonstrate that benzene can be quantified at the 2 ppm level. The correlation coefficient for linearity was 0.9983.

For most of the less common solvents 100 ppm was a level well above the QL except for two ICH class 3 solvents, 3-methyl-1-butanol and 1-pentanol. For these solvents the QL is slightly below 500 ppm. The S/N-ratios for methylbutyl ketone and nitromethane were evaluated and included in Table 5, since for these ICH class 2 solvents the ppm limit is 50 ppm (cf. Table 1). The S/N ratios indicate a QL below 50 ppm for methylbutyl ketone and nitromethane in DMF.

3.5. Choice of diluent

Comparing the two diluents water and DMF, there are some striking differences worth considering when choosing a suitable diluent. The precision is generally better in DMF

Table 5
Repeatability (n = 3) of the determination of residual solvent at levels corresponding to 100 ppm and 200 ppm

Solvent	R.S.D. (%) in water		R.S.D. (%) in DMF	
	100 ppm	200 ppm	100 ppm	200 ppm
1,1-Dichloroethene	2.6 (10 ppm)	4.4 (24 ppm)	0.96 (10 ppm)	0.62 (24 ppm)
Chlorobenzene	5.1	5.4	–	–
1,2-Dichloroethene	0.74	6.9	0.24	0.41
Dimethoxyethane	2.6	3.0	0.33	1.0
Methylbutyl ketone	5.3 (50 ppm)	5.1 (100 ppm)	1.7 (50 ppm)	1.5 (100 ppm)
Methylcyclohexane	5.1	7.0	1.8	1.4
Nitromethane	2.6 (50 ppm)	3.8 (100 ppm)	2.5 (50 ppm)	3.4 (100 ppm)
Tetrahydrofurane	4.3	3.8	1.5	0.95
Tetralin	1.0	8.0	7.3	2.8
2-Butanol	5.4	2.7	3.1	3.1
Butyl acetate	2.3	4.8	2.7	1.9
3-Methyl-1-butanol	4.0	4.5	16 (500 ppm)	11 (1000 ppm)
Methylisobutyl ketone	5.3	5.4	1.3	0.78
2-Methyl-1-propanol	6.8	2.8	4.7	3.7
1-Pentanol	8.4	5.1	15 (500 ppm)	8.1 (1000 ppm)

Table 6
Precision and S/N data of benzene at low levels in the presence of sample matrix

Level added to sample (ppm)	R.S.D. of response (n = 3) (%)	S/N
0.88	3.0	27
1.76	2.2	47
2.64	1.0	70

than in water. This fact is not obvious from the data presented in the precision section since these data were chosen to evaluate the precision at low concentrations or close to the QL for some of the analytes. However, in the linearity study some of the solvents analysed in water showed correlation coefficients of 0.97–0.98, which is somewhat low, while the correlation coefficients in DMF are all above 0.99. When the data measured in water were analysed in detail it became obvious that this difference is due to variation rather than non-linearity. This is also illustrated by the plots in Figs. 1–3. In some cases for the water analyses a trend could be observed in the replicate samples, with the lowest response obtained from the last sample analysed. This is also in line with the observation that standard stock solutions prepared in water are not stable while stock solutions in DMF can be used for months without any significant changes observed. As already mentioned in the section above the explanation is probably a higher partition coefficient of the solvents to DMF than to water, leading to a higher headspace concentration in the water samples. These samples are therefore more sensitive to leaks during equilibration and injection.

The following strategy should be applied when choosing a diluent: The entire sample should be soluble in the diluent. If sensitivity is not an issue, DMF should be used because the analysis will probably be more precise. If sensitivity is an issue, and quantification is to be performed close to the QL of a solvent the use of water as a diluent will in most cases result in a higher response and thus a lower QL. However, as DMF is a better solvent for many organic compounds, including drug substances, the QL can also be improved by increasing the amount of sample.

None of the diluents are inert. Degradation and formation of artefacts have been reported for both aqueous solutions [9] and DMF [12] and have also been observed by us. This must also be considered when choosing a diluent.

4. Conclusion and need for re-validation

The method described has successively been used, with only minor modifications, for many drug substances during development. It is also used for quality control at commercial manufacturing sites. The method is accurate, linear and shows a satisfactory level of precision. The solvents included in the validation comprise the five ICH class 1 solvents, 17 out of 27 class 2 solvents, 17 out of 27 class 3 solvents and three unclassified solvents. All solvents can be detected and quantified at levels at or below the ppm limits given in the guideline. In most cases the quantification limit is in the lower ppm range.

Quantification limits can be adjusted, to some extent, by the amount of sample analysed and by choosing water or DMF as a diluent. Depending on the nature of the sample and the residual solvent the presence of sample matrix may effect the response of a solvent. However, when using a standard addition procedure for quantification, and provided linearity is not effected by the presence of sample matrix, the method is still universal. Introduction of non-linearity due to the sample matrix has not been observed for any development substance tested in our laboratory.

The method is not selective for all solvents tested. If all solvents likely to be present are well separated there is no need for re-validation. In some cases, a pair of poorly separated solvents may be resolved by optimising chromatographic parameters. On the other hand, if only well separated solvents are present the analysis time may be shortened by a faster temperature program.

In contrast to the European Pharmacopeia where validation of the test for quantification of residual solvents is prescribed, the results indicate only a minor need for re-validation when using the generic procedure described. Re-validation needs only be considered in cases of considerable deviations from the described procedure, especially when using a column with a different stationary phase or different dimensions. Selectivity, i.e. separation of closely eluting analytes, should be ensured by an appropriate system suitability test. If severe matrix effects are suspected re-validation of detection and quantification limits must be considered. An easy way to check for matrix effects is to compare the response of a standard solution containing sample matrix with an external standard.

In conclusion, the analytical procedure described is suitable and universal for the determination of a wide variety of residual solvents in pharmaceuticals with a minimum need for re-validation.

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