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Application News

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Gas Chromatography Mass Spectrometry

Simultaneous determination of residual solvents in pharmaceutical packaging materials using headspace-GC/MS

Abstract

A highly sensitive and precise method utilizing Headspace-GCMS-QP2010 Ultra has been developed for the analysis of residual solvents in pharmaceutical packaging materials. The established method is rapid and easy to perform and is the preferred method for residual solvent analysis in quality control laboratories.

Introduction

Common pharmaceutical packaging consists of plastics and thin metal foils such as blister packs and bottles. Manufacturing of these packaging materials produces residual solvents. Furthermore, inks and adhesives (in the form of prescription labels) printed on the pharmaceutical packaging may migrate and transfer to these residual solvents. These organic volatile solvents are in direct contact with the pharmaceutical drugs, thereby increasing the risk of contamination, and the possible harm to human safety. Therefore, a careful assessment of residual solvents, and quality control of the pharmaceutical product is crucial.

In 2012, US FDA announced for pharmaceutical manufacturers to avoid the use of dibutyl phthalates (DBP) and di(2-ethylhexyl) phthalates (DEHP) in pharmaceutical drugs and biologic products. In the meanwhile, due to PAEs are also commonly used as plasticizers for packaging materials, and their presence in pharmaceutical packaging may result in leaching and the eventual contamination of PAEs in drugs. Consequently, according to the latest 2015 edition of the Chinese Pharmacopoeia, guideline issued that prohibited the use of diethyl phthalate (DEP) as pharmaceutical excipients in Chinese Pharmacopoeia regulated products. This application note established a rapid, simple and highly-sensitive method for the detection of these phthalates in pharmaceutical products.

Experimental

Instrumentation and Analytical Conditions Headspace Sampler: HS-20
GC-MS: GCMS-QP2010 Ultra
The analytical conditions used are shown in Table 1.

Table 1 Analytical Conditions of HS-20 and GCMS-QP2010 Ultra

Headspace conditions		
Vial equilibration	:	80 °C
Sample line temperature	:	160 °C
Transfer line temperature	:	170 °C
Vial warming time	:	30 min
Injection time	:	0.5 min
Injection volume	:	1 mL
GC-MS conditions		
Column	:	Rtx-624 60 mx0.32 mmx1.8 µm
Column temp. Program	:	35 °C (2min) → 20 °C/min → 200 °C
Injection mode	:	Split
Split ratio	:	10:1
Control mode	:	Constant linear velocity
Linear velocity	:	36.0 cm/sec
Ion source temp	:	230 °C
Interface temp	:	230 °C
Acquisition mode	:	SIM Mode

Sample preparation

Each packaging sample, of appropriate dimensions, was shredded and placed into a 20 mL headspace vial. Septum was placed and capped immediately.

Results and Discussion

Standard chromatograms

The 16 volatile organic solvents (residual solvents) investigated in this study are listed in Table 2. The mixed stock solution of the volatile organic solvents at 10 000 µg/ml was prepared and further diluted to 500 µg/ml. 10 µl of the 500 µg/ml mixed stock solution (5 µg) was added to the headspace vial, capped and analyzed immediately. The total ion current chromatogram (TIC) for the residual solvents (5 µg) were detected as shown in Figure 1. The retention time and MS parameters of the residual solvents are tabulated in Table 2.

Linearity and repeatability

Mixed stock solution of the residual solvents at 10 000 µg/ml was diluted with water to prepare calibration solutions of concentrations 1, 2, 5, 10, 20, 50, 100, 200 and 500 µg/ml. 10 µl of these standard calibration

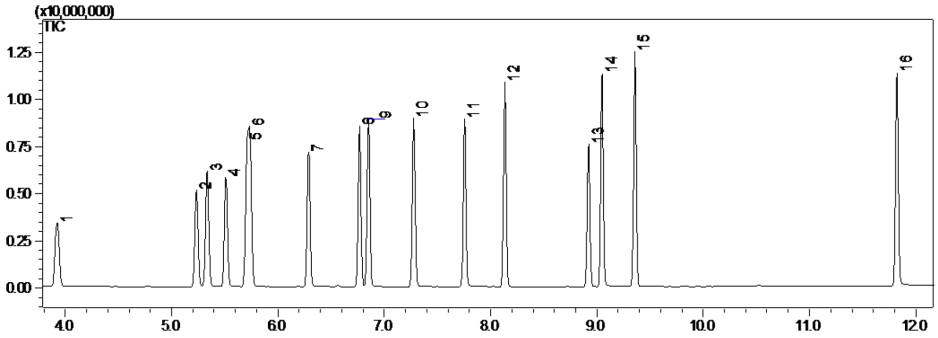

Fig. 1 Total ion current chromatogram (TIC) for 5 µg of stock solution

Table 2. Mass spectrometry parameters for the GC-MS determination of target compounds

No.	Compound name	Retention time (min)	CAS	Quantifier Ion	Qualifier Ion 1	Qualifier Ion 2
1	Methanol	3.915	67-56-1	31	32	29
2	Acetone	5.228	67-64-1	43	58	42
3	Isopropanol	5.329	67-63-0	45	43	29
4	Acetonitrile	5.504	75-05-8	41	40	39
5	Dichloromethane	5.702	75-09-2	49	84	86
6	2-Methyl-2-propanol	5.732	75-65-0	59	31	41
7	1-Propanol	6.281	71-23-8	31	29	42
8	Ethyl acetate	6.761	79-20-9	43	29	45
9	2-Butanol	6.846	78-92-2	45	59	31
10	2-Methyl-1-propanol	7.27	78-83-1	43	41	42
11	1-Butanol	7.751	71-36-3	56	31	41
12	Ethyl propionate	8.128	109-60-4	43	61	73
13	Toluene	8.917	108-88-3	91	92	65
14	1-Pentol	9.04	71-41-0	42	55	41
15	Butyl acetate	9.351	123-86-4	43	56	41
16	2-Ethyl-hexanol	11.815	104-76-7	57	41	43

solutions were added to the respective GC headspace vials to give 0.01, 0.02, 0.05, 0.1, 0.2, 0.5, 1, 2 and 5 µg. The 9 calibration solutions were analyzed, quantified and plotted to give the calibration curves. Calibration curves of some residual solvents are shown in Figure 2. The Instrument Detection Limit (IDL), at S/N ratio of 3, of each compound was determined by injecting 0.2 µg standard mixture. The method calibration performance for the 16 residual solvents such as R and RSD of the retention time and area were also determined and shown in Table 3.

Sample analysis

A pharmaceutical packaging sample (Sample 1, capsule packaging material of dimensions 1.6cm × 2.7cm) were prepared and pretreated as described in the procedure 1.3 above. The sample was analyzed thrice, quantified and the amount of residual solvents are tabulated in Table 4.

Another pharmaceutical packaging sample (Sample 2, granule packaging material of dimensions 4.5cm × 5cm) was selected and prepared as indicated in procedure 1.3 described above. The prepared sample 2 was analyzed twice and the results are shown in Table 5.

Conclusion

This article introduces the analysis of 16 residual solvents utilizing Shimadzu GCMS-QP2010 Ultra with HS-20 headspace sampler. These volatile organic compounds demonstrated good linearity over the range 0.1~5µg. In summary, this study has proven a simple, rapid and sensitive GC-MS method for the routine analysis of residual solvents in pharmaceutical packaging materials.

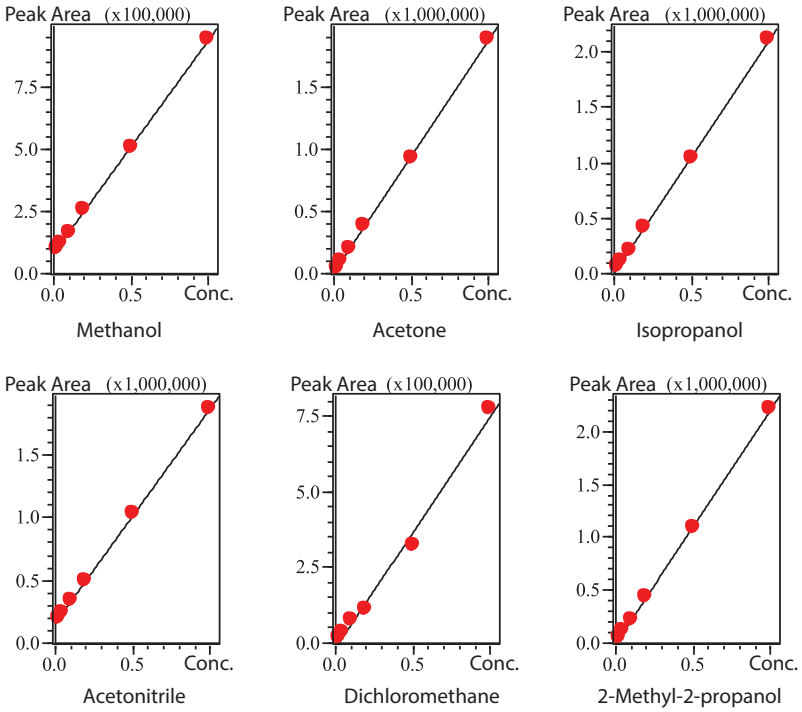

Figure 2. Calibration curves of some residual solvents

Table 3. Method validation data

No.	Compound name	R	RSD% (Area ratio)	RSD% (Retention time)	IDLs (µg)
1	Methanol	0.9999	1.04	0.01	0.0002
2	Acetone	0.9999	3.72	0.01	0.0007
3	Isopropanol	0.9999	1.81	0.00	0.0001
4	Acetonitrile	0.9999	3.30	0.01	0.0001
5	Dichloromethane	0.9953	8.20	0.00	0.0002
6	2-Methyl-2-propanol	0.9999	3.22	0.01	0.0002
7	1-Propanol	0.9998	3.04	0.00	0.0004
8	Ethyl acetate	0.9999	4.52	0.01	0.0028
9	2-Butanol	0.9998	3.39	0.00	0.0191
10	2-Methyl-1-propanol	0.9998	3.22	0.01	0.0211
11	1-Butanol	0.9999	6.77	0.00	0.0005
12	Ethyl propionate	0.9998	4.92	0.01	0.0002
13	Toluene	0.9876	11.69	0.01	0.0002
14	1-Pentol	0.9994	5.77	0.01	0.0005
15	Butyl acetate	0.9996	5.20	0.01	0.0004
16	2-Ethyl-hexanol	0.9995	8.89	0.01	0.0001

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Table 4. Sample results (capsule packaging materials)

No.	Compound name	Sample1-1	Sample 1-2	Sample 1-3	Average results	RSD%
1	Methanol	0.12	0.11	0.10	0.11	5.89
2	Acetone	0.03	0.03	0.03	0.03	11.73
3	Isopropanol	0.03	0.03	0.03	0.03	4.07
4	Acetonitrile	N.D	N.D	N.D	-	-
5	Dichloromethane	0.02	0.02	0.02	0.02	0.77
6	2-Methyl-2-propanol	N.D	N.D	N.D	-	-
7	1-Propanol	N.D	N.D	N.D	-	-
8	Ethyl acetate	0.13	0.14	0.11	0.12	10.25
9	2-Butanol	N.D	N.D	N.D	-	-
10	2-Methyl-1-propanol	0.21	0.20	0.23	0.21	7.53
11	1-Butanol	0.07	0.06	0.07	0.07	5.27
12	Ethyl propionate	N.D	N.D	N.D	-	-
13	Toluene	0.05	0.05	0.05	0.05	0.60
14	1-Pentol	0.02	0.02	0.02	0.02	1.21
15	Butyl acetate	N.D	N.D	N.D	-	-
16	2-Ethyl-hexanol	0.22	0.25	0.23	0.23	5.43

N.D.: Not detected

Table 5. Sample results (granule packaging materials)

No.	Compound name	Sample 2-1	Sample 2-2	Average results
1	Methanol	0.06	0.07	0.07
2	Acetone	N.D	N.D	N.D
3	Isopropanol	N.D	N.D	N.D
4	Acetonitrile	N.D	N.D	N.D
5	Dichloromethane	0.03	0.03	0.03
6	2-Methyl-2-propanol	N.D	N.D	N.D
7	1-Propanol	N.D	N.D	N.D
8	Ethyl acetate	N.D	N.D	N.D
9	2-Butanol	N.D	N.D	N.D
10	2-Methyl-1-propanol	N.D	N.D	N.D
11	1-Butanol	0.02	0.02	0.02
12	Ethyl propionate	N.D	N.D	N.D
13	Toluene	0.05	0.06	0.05
14	1-Pentol	0.02	0.02	0.02
15	Butyl acetate	N.D	N.D	N.D
16	2-Ethyl-hexanol	0.02	0.02	0.02

N.D.: Not detected