New Fast Approach for Achieving USP <467> compliance
APPLICATION NOTE - AN138

Introduction

The USP (United States Pharmacopeia) General Chapter <467> applies to existing drug substances, excipients, and products. The norm describes how to obtain a quantification of residual solvents and MDL. Residual Solvents (RS), formerly called Organic Volatile Impurities (OVIs), are defined as organic volatile chemicals that are used or produced in the manufacture of active substances or excipients, or in the preparation of drug products. These products may also be contaminated by such solvents from packaging, storage in warehouse, or from shipping and transporation. Because residual solvents do not provide any therapeutic benefit, but may be a potential toxic risk to human health and the environment, it must be ensured that they are either not present in products or are present only below recommended acceptable levels.

As claimed by the norm, solvents that are known to cause unacceptable toxicities should be avoided in the production of drug substances, excipients, or drug products unless their use can be strongly justified in a risk-benefit assessment. These types of solvents are grouped in "Class 1 Residual Solvents" that includes solvents to be avoided as known human carcinogens, strongly suspected human carcinogens, environmental hazards.

The "Class 2 Residual Solvents" includes solvents associated with less severe toxicity that need to be limited in order to protect patients from potential adverse effects. These are: nongenotoxic animal carcinogens or possible causative agents of other irreversible toxicity, such as neurotoxicity or teratogenicity, and solvents suspected of other significant but reversible toxicities.

Pharmaceutical manufacturers may face various challenges when attempting to meet the USP requirements.

The norm requires the use of a static headspace sampler coupled with a GC-FID system in order to recognize and quantify organic volatile impurities. Particularly, the "Valve&Loop" sampling system ensures the best results in terms of repeatability and, for this reason, it is the technique of choice for this application.

In the present work, the data obtained using the innovative DANI Master SHS Static Headspace Sampler coupled with the DANI Master GC Fast Gas Chromatograph are presented. The methodology was optimized to reduce total analysis and cycle times. Maximum laboratory productivity is thus guaranteed, thanks also to the widest sample capacity of the vial tray.

Moreover, the advanced capability of controlling both the pressure of the vial, and the pressure of the loop provided by the DANI Master SHS were exploited producing unmatched performances. DANI Master SHS, in fact, improved repeatability and precision for residual solvents analysis compared also to other market leaders.

Furthermore, as it's well known, regulated pharmaceutical arenas are currently striving to meet compliance with 21 CFR part 11, the FDA's rule governing electronic records and electronic signatures. Matching Part 11 compliance remains challenging. The technical controls for 21 CFR Part 11 compliance are built into the Empower™ (trademark of Waters[R] Corp.)software. This control enables the use of the best-in-class USP <467> Solution, which features the world's highest performance in terms of repeatability, sensibility, and precision, in a Waters [R] Empower™ environment.

Experimental Conditions

DANI Master SHS Static Headspace Sampler, equipped with DANI Master VH, was coupled to a DANI Master GC Fast Gas Chromatograph equipped with Split/Splitless injector and FID detector.

System Configuration and Control

Analytical conditions are summarized in the tables below.

Sample

USP <467> Residual Solvents standards, Class1, Class2A, and Class2B were prepared in purified water at their concentrations limits according to procedure "A" for water soluble articles of the method.

All standard solutions were certified by ULTRA SCIENTIFIC.

Master GC	
Inlet	SL/IN Large Volume
	deactivated liner, no glass wool
	230°C
Carrier Gas	Helium 0.8 mL/min
Split	1:10
Detector	FID, 250°C
Vial Pressurization Gas	Nitrogen
Oven Class 1	40°C (3 min) to 100°C@10°C/min
Column Class 1	HP Innowax 0.18 mm, 20 m, 0.18µm
Oven Class 2A	40°C (1 min) to 200°C at 15°C/min
Oven Class 2B	40°C (3 min) to 200°C @10°C/min
Column Class 2A 2B	DB 624 0.18mm, 20m, 1µm

Table 1: Master GC Analytical Conditions

Master SHS	
Oven Control	70° C
Manifold	90° C
Transfer Line	90° C
Vial Eq. Time	15 min
Shaking	High
Injection	Standard, 0.5 min

Table 2: Master SHS Analytical Conditions

RESULTS & DISCUSSION

The DANI Master SHS has different possibilities to control the vial pressurization and the loop fill step. In this work, the "Pressure" mode was used to pressurize the vial at a target pressure of 1 bar. The loop fill step was optimized using the following modes: loop "pressure" and "custom" modes.

In the loop "pressure" mode, the system controls the final pressure of loop before injection. The system was tested at two different target pressure of 0.25 bar and 0.5 bar.

In the "custom" mode, both the final loop pressure and the speed rate of depressurization are controlled.

In this mode, a 0.5 bar final pressure was used at two different pressure rates of 100 and 200 mbar/s. These conditions were applied to the Class 2A standard mixture. Results are reported below in Table 3.

The best performance in terms of repeatability and sensitivity were obtained with the "pressure" mode at 0.5 bar and the "custom" mode at the same pressure. These results were confirmed also for the Class 2B and Class 1 standard mixtures as shown in Table 4 and Table 5. In addition, for the Class 1 standard mixture the "custom" mode was furtherly optimized by using a higher pressure rate of 200 mbar/s .

Class 2A Mix
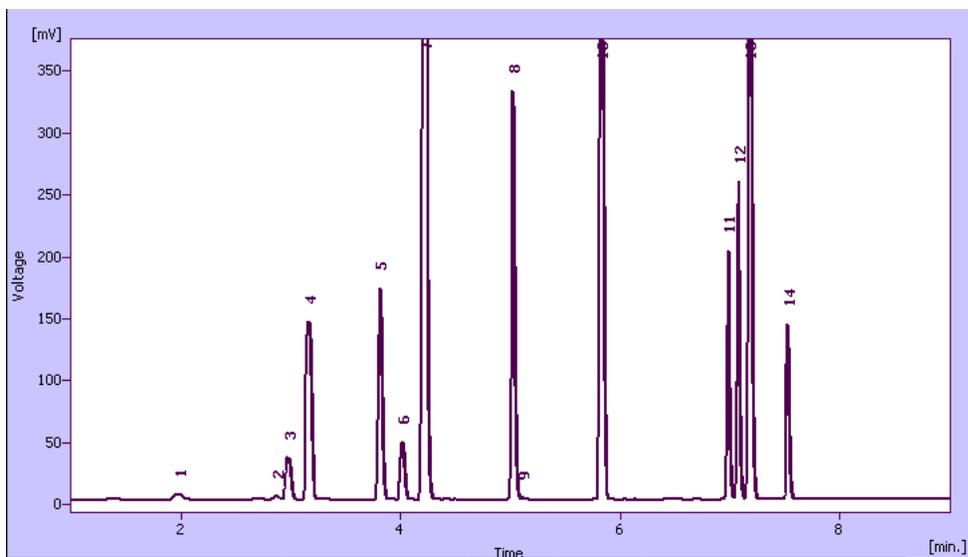
CLASS 2A MIX		Loop press 0.25 bar		Loop press 0.5 bar		Loop 0.5 bar 100mbar/S	
		RSD%	Area	RSD%	Area	RSD%	Area
1	Methanol	0.58	18.82	0.47	23.58	0.61	22.44
2	Acetonitrile	0.51	8.21	0.40	10.56	0.55	9.95
3	Dichloromethane	1.62	90.26	1.08	120.89	1.10	111.41
4	Trans-1, 2Dichloroethene	2.29	351.29	1.51	475.41	2.02	417.24
5	Cis-1,2-Dichloroethene	1.87	335.13	1.21	449.22	1.35	410.72
6	THF	0.84	87.63	0.56	116.36	0.45	108.97
7	Cyclohexane	2.46	1985.05	0.85	2581.35	1.58	2416.74
8	Methylcyclohexane	2.88	513.18	2.34	697.92	3.37	610.63
9	1,4-Dioxane	1.97	3.27	0.89	4.13	0.76	3.90
10	Toluene	2.05	1055.48	1.28	1413.70	1.51	1290.48
11	Chlorobenzene	1.93	264.37	1.24	354.35	1.33	321.76
12	Ethylbenzene	2.16	334.66	1.27	448.13	1.51	410.33
13	m,p-Xylene	2.16	1445.00	1.06	1900.54	1.40	1759.65
14	0-Xylene	2.01	181.41	1.19	242.27	1.30	223.71

*Table 3*: RSD% and Area obtained for Class 2A standard mixture with different loop pressurization modes.

Class 2B Mix
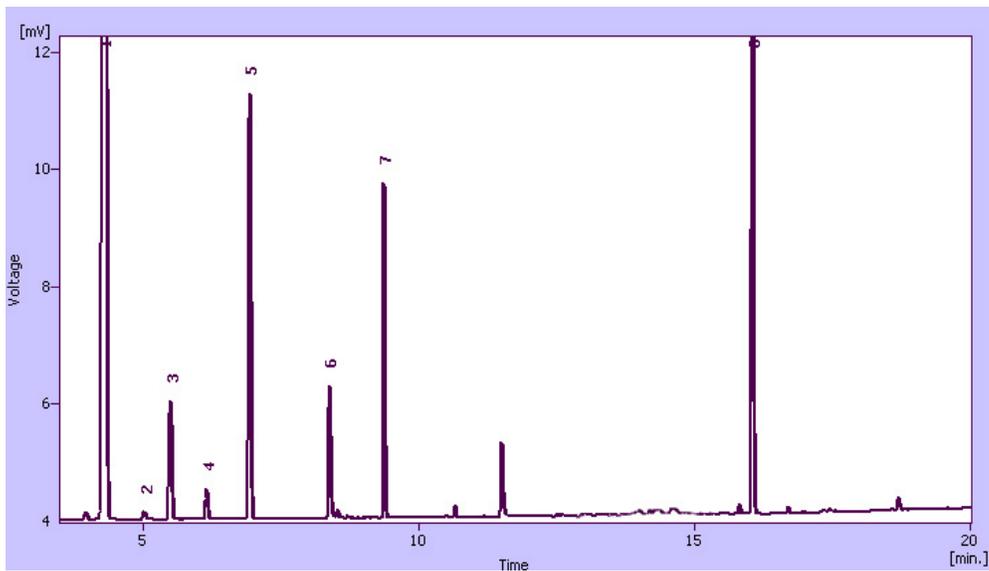
CLASS 2B MIX		Loop press 0.5 bar		Loop 0.5 bar 100mbar/s	
		RSD%	Area	RSD%	Area
1	Hexane	1.91	136.55	4.51	117.50
2	Nitromethane	1.03	0.50	1.72	0.45
3	Chloroform	0.33	6.67	1.02	5.93
4	1,2-Dimethoxyethane	0.73	1.54	2.32	1.36
5	Trichloroethene	0.75	18.80	1.59	16.53
6	Pyridine	0.91	5.69	0.77	5.68
7	2-Hexanone	0.32	12.05	0.75	10.71
8	Tetralin	0.50	118.72	1.19	105.67

Table 4: RSD% and Area obtained for Class 2B standard mixture with different loop pressurization modes.

Class 1 Mix
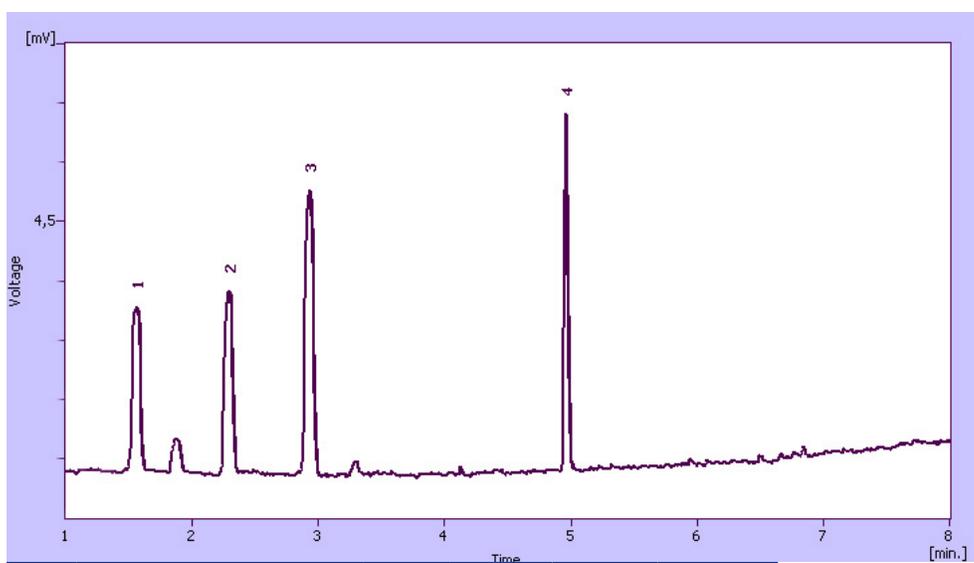
	CLASS 1 MIX	Loop press 0.5 bar		Loop 0.5 bar 200mbar/s	
		RSD%	Area	RSD%	Area
1	1,1-Dichloroethene	0.57	1.13	0.82	2.25
2	1.1.1.-Trichloethane/Carbon tetrachloride	1.89	1.28	0.87	2.02
3	Benzene	1.42	2.02	0.92	2.17
4	1,2-Dichloroethane	1.13	1.24	0.87	1.12

Table 5: RSD% and Area obtained for Class 1 standard mixture with different loop pressurization modes.

CONCLUSION

The advanced capability of the Master SHS Static Headspace Sampler to control the pressurization and loop fill steps together with an accurate and precise temperature control provides outstanding results in terms of area repeatability for all the class of residual solvents described in USP <467>. RSD% lower than 1% were obtained in most of the cases. Moreover, the digital control of the loop pressure allowed to obtain a significant increase in sensitivity. Analytical conditions were optimized to produce these results in the shortest analysis time for the maximum productivity.
The Master SHS confirms the reliability of the "Valeve&Loop" technique and introduces advanced features for improved performances.

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