The Analysis of Residual Solvents by Headspace Sampling and GC According to USP 467: Procedure A

Application Note

INTRODUCTION

In the pharmaceutical industry, residual solvents are defined as organic volatile chemicals that are produced during the manufacturing of active pharmaceutical ingredients or derived directly from the packaging of the pharmaceuticals. Residual solvents do not provide any therapeutic benefits and should be removed where possible.

Quality assurance laboratories routinely test products for the presence of residual solvents. The United States Pharmacopeia (USP) method 467 is the harmonised test method for the identification and quantification of the organic volatile impurities by gas chromatography. USP 467 details three classes of solvents, in accordance to their health hazards. Additionally, the analytical method is split into two procedures; procedure A is for the identification of the residual solvents at the limit of detection whereas procedure B is for the confirmation of the analyte identity.

This application note details procedure A of USP 467; the identification of residual solvents at the limit of detection using a SCION 456 GC with FID coupled to the Teledyne Tekmar HT3 headspace autosampler (HS).

EXPERIMENTAL

Standards containing the residual solvents at the USP limit were prepared in accordance to method USP 467 (ppm=mg/kg). Stock solutions were prepared in DMSO with the actual samples prepared in water. The total sample volume was constant at 6mL in 20mL headspace vials, with the final residual solvent concentrations corresponding to the USP concentration limits, as detailed in Table 1. The three classes of solvents were prepared and analysed separately, each with six replicates prepared and analysed.

Procedure A of USP 467 was performed on a SCION 456 with FID coupled to the Teledyne Tekmar HT3 headspace autosampler. The HS mode was static. The analytical parameters of the instrumentation can be found in Table 2.

Table 1. Identity of residual solvents, classes and USP limit (ppm)

Peak Number	Identity	USP Limit (ppm)
Class 1		
1	1,1-dichloroethene	8
2	1,1,1-trichloroethane	1500
3	Carbon Tetrachloride	4
4	Benzene	2
5	1,2-dichloroethane	5
Class 2A		
1	Methanol	3000
2	Acetonitrile	410
3	Dichloromethane	600
4	t-1,2-dichloroethene	1870
5	c-1,2-dichloroethene	1870
6	Tetrahydrofuran	720
7	Cyclohexane	3880
8	Methylcyclohexane	1180
9	1,4-dioxane	380
10	Toluene	890
11	Chlorobenzene	360
12	Ethylbenzene	2170
13,14	m-xylene, p-xylene*	2170
15	o-xylene	2170
Class 2B		
1	Hexane	290
2	Nitromethane	50
3	Chloroform	60
4	1,2-dimethoxyethane	100
5	Trichloroethene	80
6	Pyridine	200
7	2-hexanone	50
8	Tetralin	100

*m-xylene and p-xylene co-elute

Table 2. Analytical instrumentation conditions

Conditions	
S/SL	260°C, 50:1
Column	SCION 624 30m x 0.25mm x 1.4μm
Oven Programme	40°C (hold 10 min), 10°C/min to 240°C (3 min)
Carrier Gas	Helium 2.2mL/min
FID	250°C
Incubation	80°C for 45 minutes
Transfer Line	105°C

RESULTS

Identification of all sample components can be found by referring to the specific class sections of Table 1. Figures 1-3 detail the overlay chromatogram obtained for Class 1, Class 2A and Class 2B residual solvents whilst Tables 3-5 show the repeatability of the instrumentation when six replicates of each residual solvent class were analysed.
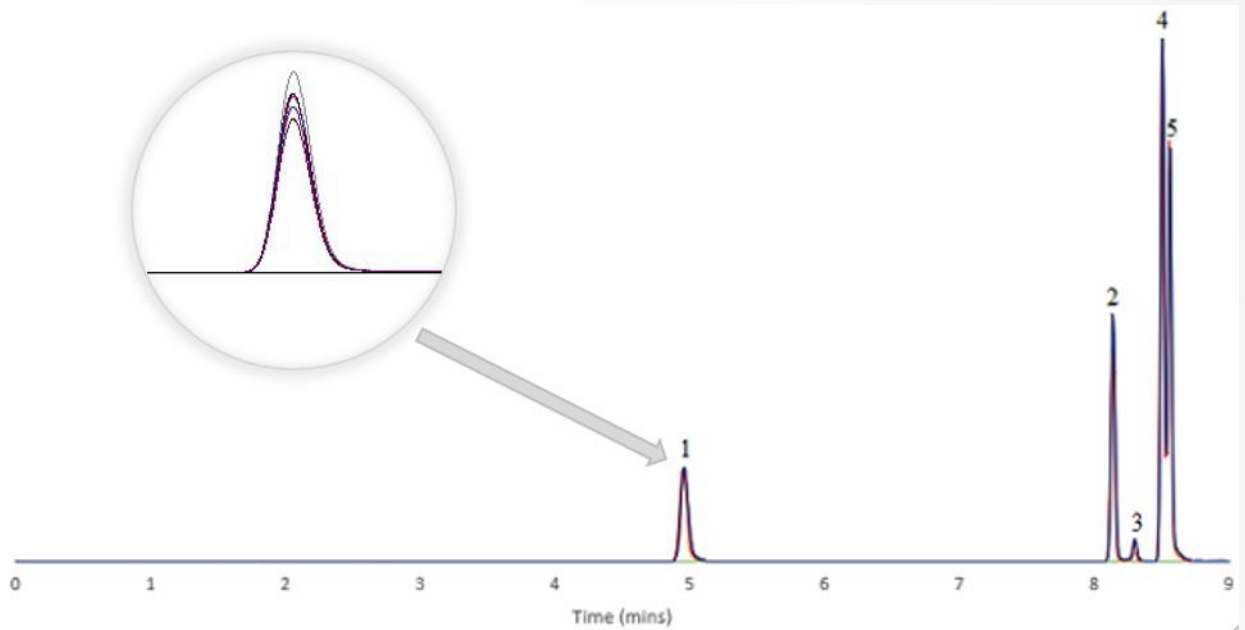
Fig 1. Overlay of six chromatograms of Class 1 residual solvents with a magnified insert of 1,1-dichloroethene
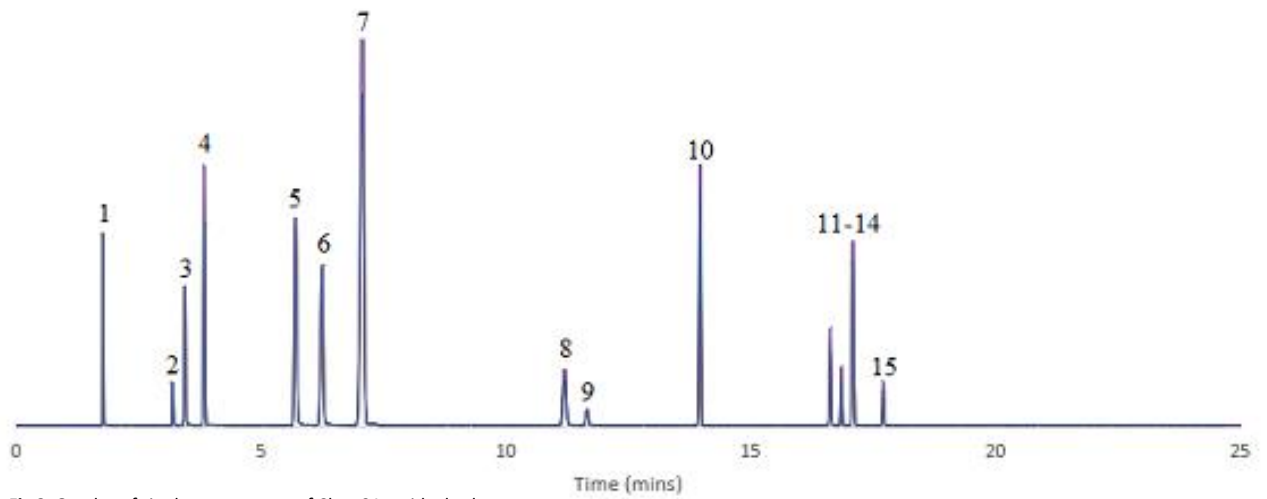

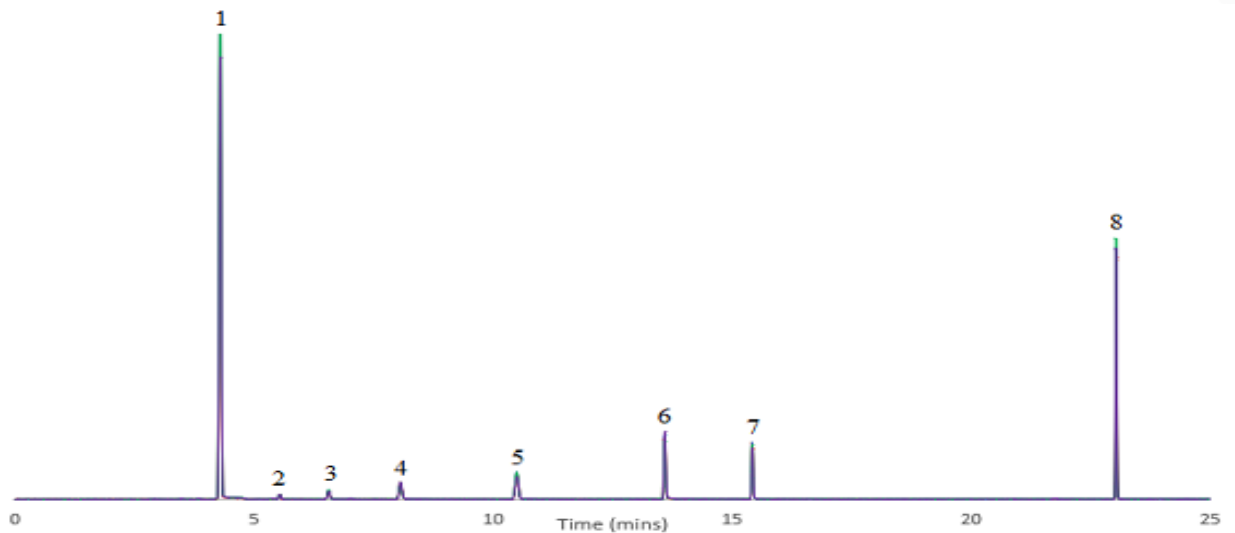**Fig 2**. Overlay of six chromatograms of Class 2A residual solvents

Fig 3. Overlay of six chromatograms of Class 2B residual solvents

Table 3. Repeatability values of Class 1 residual solvents

	Peak 1	Peak 2	Peak 3	Peak 4	Peak 5
1	78925	104198	8999	190192	154104
2	76167	103124	9310	195009	153474
3	78046	106987	9221	194101	158034
4	76923	104729	9110	196531	159432
5	75453	105827	9331	196019	153829
6	78892	103004	8997	190945	152325
Ave	77401	104644	9161	193800	155199
Std. Dev.	1450	1555	148	2649	2837
RSD %	1.9	1.5	1.6	1.4	1.8

Table 4. Repeatability values of Class 2a residual solvents

	Peak 1	Peak 2	Peak 3	Peak 4	Peak 5	Peak 6	Peak 7
1	377412	132388	547744	980389	1378369	1030152	4149925
2	373438	132937	550042	970050	1345472	1040246	4097583
3	375231	133942	553201	964102	1383294	1024021	4001241
4	372941	133847	549982	978201	1353198	1056524	4059120
5	379255	132897	550021	961028	1370582	1043352	4135642
6	378987	133487	549953	972013	1374912	1034884	4138582
Ave	376210	133250	550157	970963	1367637	1038196	4097015
Std. Dev.	2747	609	1743	7601	14977	11343	57668
RSD %	0.7	0.5	0.3	0.8	1.1	1.1	1.4

	Peak 8	Peak 9	Peak 10	Peak 11	Peak 12	Peaks 13-14	Peak 15
1	567412	102388	1189237	349181	216299	972278	150725
2	560298	101154	1146633	347889	219626	982785	149070
3	575342	103425	1187911	348314	219827	948291	147284
4	574421	104551	1159321	345726	219428	992819	143717
5	568762	104092	1169327	349121	219627	989721	148402
6	555833	103241	1185320	349172	219444	948293	151952
Ave	567011	103141	1172958	348233	219041	972364	148525
Std. Dev.	7714	1224	17513	1340	1351	19935	2882
RSD %	1.4	1.2	1.5	0.4	0.6	2.1	1.9

Table 5. Repeatability values of Class 2b residual solvents

	Peak 1	Peak 2	Peak 3	Peak 4	Peak 5	Peak 6	Peak 7	Peak 8
1	1354879	15336	35370	75596	127646	164834	129982	439150
2	1457373	14936	34033	74957	123911	166594	126719	439764
3	1415244	15831	35277	74743	122417	168506	127210	455035
4	1417009	15494	35370	76975	124680	168853	126378	441902
5	1374230	14171	34749	73749	127582	163790	126582	447421
6	1419385	14872	34873	75312	128374	167652	129625	439939
Ave	1406363	15106	34945	75222	125768	166704	127749	443868
Std. Dev.	36460	580	519	1066	2427	2038	1619	6256
RSD %	2.6	3.9	1.5	1.4	1.9	1.2	1.3	1.4

The analysis of residual solvents following USP 467 procedure A was replicated six times. The overall RSD% average was 1.4% which is excellent for static headspace at the ppm concentrations.

The excellent repeatability demonstrates the robustness of the SCION 456 GC coupled to the Teledyne Tekmar HT3 headspace system. The varied concentrations and detector responses detailed throughout this application note required reliable integration and no detector saturation, which the SCION 456 and CompassCDS software offers with ease.

There is a concern regarding Class 1 solvents due to their toxicity. Therefore, USP 467 specifies that 1,1,1-trichloroethane must have a S/N greater than five with all remaining Class 1 solvents having a S/N greater than three. All S/N requirements passed these requirements and were calculated through the CompassCDS software, from a selected region of noise close to the analyte of interest. In addition, system suitability for the method requires a resolution of greater than 1 between acetonitrile and methylene chloride; using the SCION-624 column. A resolution of 8 was achieved, clearly exceeding the specification of USP 467.

CONCLUSION

The SCION 456 GC with Teledyne Tekmar HT3 headspace autosampler exceeds the requirements for procedure A of USP 467 method, for the identification of residual solvents. Processing of the data and determining specific requirements of the method is made easy using CompassCDS software. The excellent sensitivity satisfies the S/N requirements of USP 467. Identifying residual solvents at the varying ppm concentrations specified in the method, is easily achievable without saturating the detector or loss of resolution.