

# The simplest solution for fast screening of organic impurities in pharmaceutical products

## Key Words

- USP 467
- Headspace Analysis
- Organic Impurities
- Pharmaceutical Products

## Introduction

The high toxicological impact of residual volatile solvents in pharmaceutical products demands for a stringent control of the intermediate bulks. The USP 467 is the method in use for the detection of organic volatile impurities. In this procedure, methods I, V and VI are based on direct aqueous injections, while methods II, III and IV for headspace sampling.

Since water damages most capillary columns and interferes with the elution of some compounds by distorting peak shape and upsetting the baseline, the headspace technique is preferred. In addition, the vapor phase above the sample is free of many of the interference present in these types of matrices and thus gives higher sensitivity, better performance with selective detectors, and prolonged column lifetime. Speed of analysis and accuracy of results are both improved, together with a reduction in the amount of manual sample handling.

The fast heating and cooling oven capability of the new TRACE GC 2000 combined with the simplicity and rapidity to start-up of the HS 2000 headspace autosampler, were tested for fast screening of volatile impurities in pharmaceutical products.

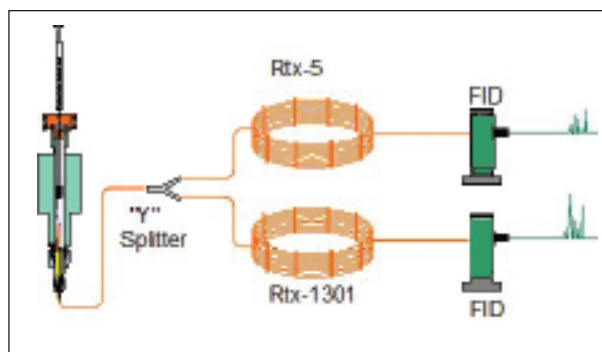


Figure 1: Dual column system

A dual column system, figure 1, was used to overcome any coelution problems and for confirmation of identity. The headspace autosampler uses a gas-tight syringe that is flushed between injections to prevent carryover. The proprietary high temperature syringe was tested for analysis with the higher boiling point solvent. The elimination of injection valves and heated transfer lines makes the autosampler very easy to use with little or no maintenance required.

## Selection of the Dissolution Solvent

Many of the solvents used in the production of pharmaceuticals are water-soluble, therefore their extraction from water is difficult. There are also a number of these products that are not water-soluble. However for comparison to the original method USP 467, five organic volatile impurities were run by headspace in water.

Figure 2 shows clearly a baseline disruption due to the water coeluting with 1,4-Dioxane. This effect, together with the needs to expand the list of the organic compounds monitored by this method, made the selection of a suitable non-aqueous dissolution solvent a key factor for the success of this procedure. Different dissolution solvents were tested.

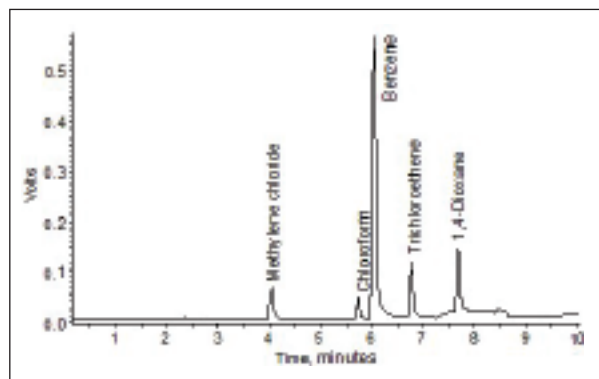


Figure 2: USP 467 organic impurities in water

Finally N,N-dimethylacetamide (DMA) was chosen. DMA has the advantage of a higher boiling point than the analytes of interest, eliminating interference from the solvent peak. It also has the benefit of dissolving many substrates of a hydrophobic nature.

## Results

In the original Method USP 467, five organic impurities were initially selected for their possible health effects. Since many solvents are used in the manufacturing process, the list has been modified several times. These were taken into account in the selection of the impurities tested, using a very comprehensive list of organic compounds. These were dissolved in DMA stock solution, which were then used in making the working standards. One ml of sample was placed into a 20ml vial.

A polar deactivated precolumn was used with a 5mm i.d. direct injection liner connected to a “Y” tee (figure 1). The flow was split between the two megabore columns connected to the flame ionization detectors. Electronic pressure control was used to control all gases for the instrument. Incubation temperature was set at 100°C, while the powerful sample shaking available through the HS 2000 permitted to achieve a gas-liquid equilibrium in the vial in 20 minutes. Injection volume was optimized at 0.5 ml with a syringe temperature of 110°C.

Figure 3a, 3b show the chromatograms obtained for a 10 ppm standard on the Rtx-1301 and the Rtx-5 columns. The automated overlapping mode used by the HS 2000 to condition the samples, the fast cooling performance of the TRACE GC oven, the single automated injection into two dissimilar megabore columns, all together permitted to perform the analyses of over 20 organic impurities in less than 22 minutes.

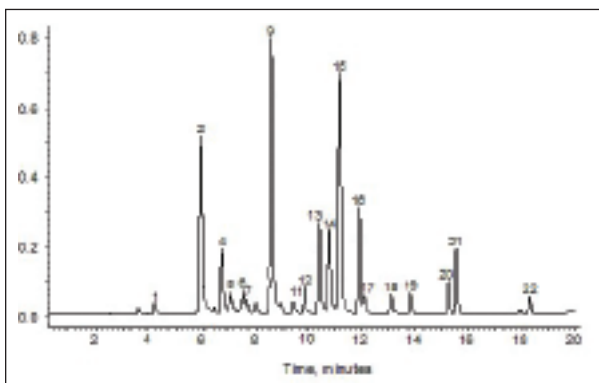


Figure 3a: Organic impurities in DMA on Rtx-1301

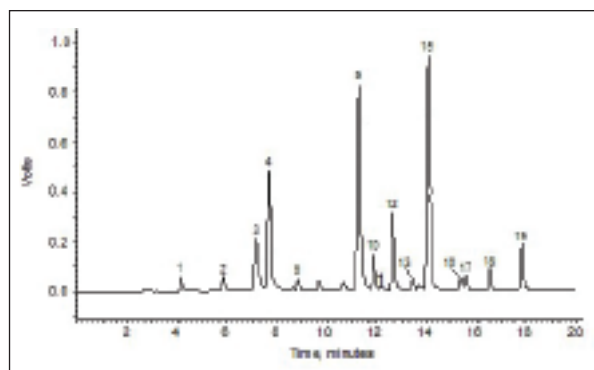


Figure 3b: Organic impurities in DMA on Rtx-5

Table 1 shows the repeatability of the method as well as the MDLs for both columns. The sensitivity achieved easily surpasses the required detection limits.

### Conclusions

TRACE GC 2000 and HS 2000 have been successfully used for a fast screening of organic impurities in pharmaceutical products. The use of non-aqueous solvents like DMA made detection of water-soluble compounds more sensitive. The instrument configuration adopted with two megabore columns connected to a dual FIDs provided confirmational analysis by a single injection.

	Rtx-1301 0.53 mm X 30 m, 3.0 µm				RTX-5 0.53 mm X 30 m, 5.0 µm				
	AVERAGE	STD DEV	RSD%	MLD PPM	AVERAGE	STD DEV	RSD%	MLD PPM	
1 Methanol	9.92	0.28	2.83	0.84	1 Methanol	10.355	0.474	4.577	1.517
2 Diethyl ether	8.88	0.25	2.81	0.74	2. Ethanol	9.872	0.279	2.830	0.894
3 Acetone	9.42	0.39	4.12	1.16	3 Acetone & Acetonitrile & Isopropanol	9.767	0.169	1.726	0.539
4 Isopropanol	9.28	0.88	9.49	2.62	4 Diethyl ether	8.997	0.134	1.490	0.429
5 Acetonitrile	9.50	0.64	6.70	1.90	5 Methylene chloride	9.966	0.144	1.443	0.460
6 Methylene chloride	9.68	0.61	6.31	1.82	6 Hexane & MEK	9.071	0.123	1.352	0.392
7 Hexane	8.93	0.13	1.41	0.38	7 Ethyl acetate	9.889	0.129	1.306	0.413
8 n-Propanol	9.46	0.69	7.33	2.07	8 Chloroform	9.102	0.394	4.333	1.262
9 Ethyl acetate	9.37	0.14	1.53	0.43	9 Tetrahydrofuran	9.661	0.095	0.983	0.304
10 MEK & Tetrahydrofuran	9.94	0.13	1.32	0.39	10 1,2 Dichloroethane	9.932	0.133	1.339	0.425
11 Chloroform	9.91	0.09	0.93	0.28	11 Benzene & Cyclohexane	9.547	0.114	1.195	0.365
12 Cyclohexane	9.50	0.09	0.91	0.26	12 Trichloroethene	9.761	0.220	2.256	0.705
13 Benzene	9.94	0.13	1.30	0.38	13 1,4-Dioxane	9.705	0.339	3.494	1.085
14 1,2-Dichloroethane	9.67	0.34	3.52	1.01	14 MIBK	9.721	0.442	4.549	1.415
15 Trichloroethene	9.37	0.74	7.93	2.21	15 Toluene	9.595	0.324	3.376	1.037
16 1,4-Dioxane	9.75	0.030	3.08	0.90					
17 n-Butanol	9.65	0.41	4.22	1.22					
18 Toluene	9.66	0.29	3.03	0.87					
19 Chlorobenzene	8.96	0.89	9.92	2.65					

Table 1. MDL and repeatability

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