Determining Organic Volatile Impurities (OVIs) in pharmaceutical products

Organic Volatile Impurities – 4 minute cycle time!

The production of pharmaceuticals is tightly regulated. US and European Pharmacopeia lay down the law: Pharmaceutical products must be analyzed for Organic Volatile Impurities (OVIs), the technique mainly used is Headspace GC.

The conventional GC method used for the determination of solvent residues or Organic Volatile Impurities (OVIs) according to the European pharmacopeia typically requires a 35 minute GC run. When the Pfizer R&D Dept. in Sandwich, U.K. started looking into whether the analysis could be accelerated, they turned to the Research Institute for Chromatography (RIC) of Professor Pat Sandra. The result of the cooperation has now been published (*J. Sep. Sci. 2006, 29, 695 – 698*) and it shows that the method can be accelerated significantly.

For the OVI determination, Pfizer was using a 6890 GC from Agilent Technologies equipped with a split/splitless inlet and a flame ionization detector (FID). The column used was a DB 624 type phase, 30 meters long, 320 µm i.d. with 1 µm film thickness. This column meets the requirements of the EU and US Pharmacopeia, enabling good separation of all listed polar and non-polar solvents. The separation takes around 35 minutes, not counting the cool down time which in turn adds between 5 and 10 minutes depending on the ambient temperature in the laboratory.

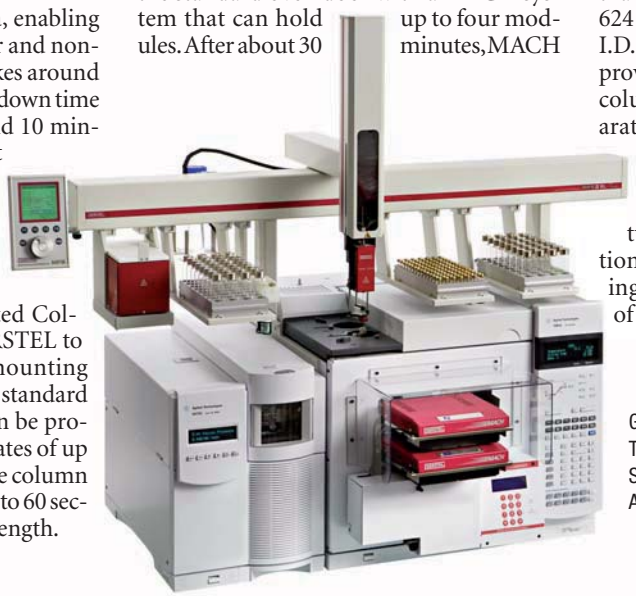
The aim was to shorten the GC cycle time, improving throughput and productivity, without changing the basic method. The RIC added a Modular Accelerated Column Heater (MACH) from GERSTEL to the 6890 GC. MACH enables mounting of up to 4 column modules with standard capillaries on the GC. MACH can be programmed to heat the column at rates of up to 1800 °C/min. Cool-down of the column from 240 to 40 °C is achieved in 30 to 60 seconds depending on the column length.

MACH is based on Low Thermal Mass (LTM) technology that only heats the GC column. Unlike standard GC ovens, MACH column modules do not use large amounts of insulation, metal chambers, and large volumes of air, all of which need to be heated and cooled over the course of a temperature programmed analysis cycle. Because MACH technology does not require the heating and cooling of these ancillary components, significantly shorter GC cycle times and higher sample throughput can be achieved. MACH is controlled from Agilent Technologies' ChemStation software or directly through the MAESTRO software.

Upgrade your GC in less than 30 minutes

The 6890 GC was upgraded by replacing the standard oven door with a MACH system that can hold up to four modules. After about 30 minutes, MACH had been installed and the GC reconfigured and ready to run. Column modules were mounted on the outside of the GC using an opening in the MACH GC oven door. During the run, the GC oven is kept isothermal at high temperature. This means that no special accessories or connectors are required to keep the column ends and connectors heated, minimizing system complexity. Not having to cycle the GC oven temperature provides energy savings. No heating energy is expended to repeatedly heat the oven to high temperatures. This in turn means that less heat is released to the lab environment and subsequently that less energy is required for air conditioning in the summer.

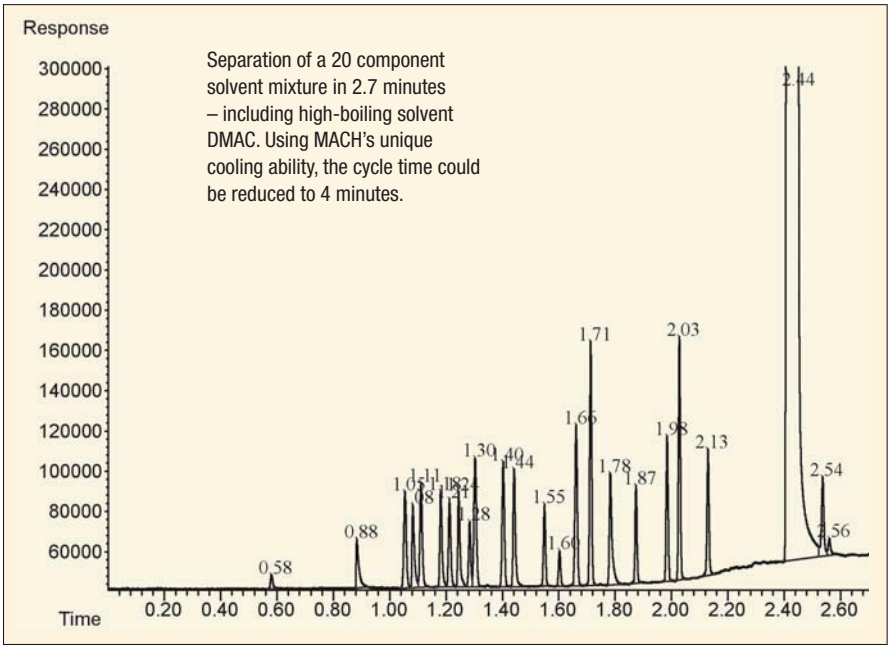
For the task at hand, the RIC chose a MACH module with a column that was shorter and with smaller internal diameter than the one originally used by Pfizer: DB 624 stationary phase, 25 meters long, 180 µm I.D. and 1 µm film thickness. This column provides more efficiency per unit length of column as well as enhanced speed of separation. The improvement was significant: Separation of a 20 solvent mixture was achieved in approximately 2.7 minutes – with good sensitivity, reproducibility, and linearity over a wide concentration range. Thanks to ultra-efficient cooling, the cycle time was reduced to a total of only 4 minutes.

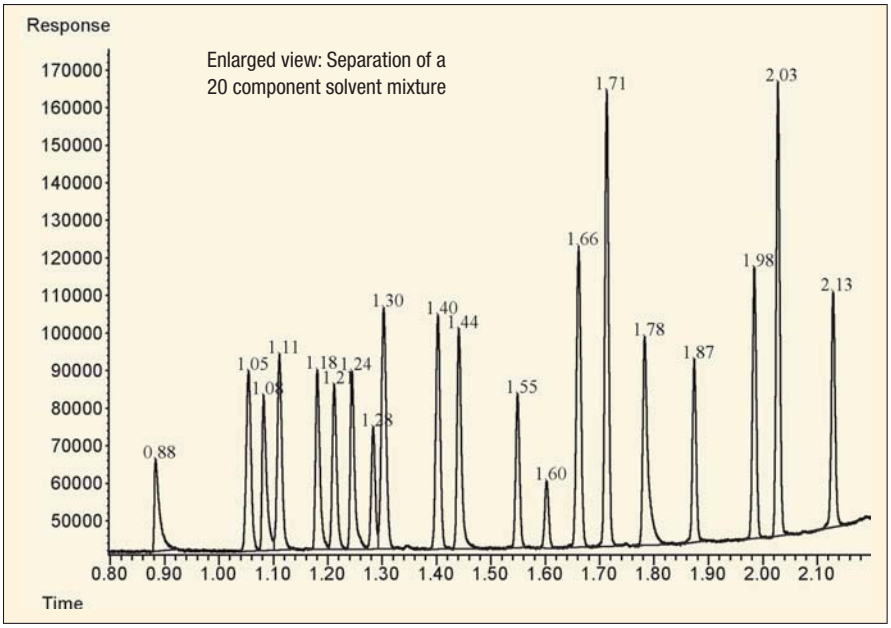


GC/MS-System from Agilent Technologies with the GERSTEL MultiPurpose Sampler (MPS XL) and GERSTEL Modular Accelerated Column Heater (MACH).

	Retention time (min)			Area	LOD	Correlation
	Mean	SD	RSD (%)	RSD (%)	% ($w/_w$)	r^2
Methanol	0.888	0.0005	0.055	2.85	0.0060	0.9960
Pentane	1.054	0.0005	0.051	0.77	0.0001	0.9993
Ethanol	1.085	0.0000	0.000	3.90	0.0041	0.9976
Diethyl-Ether	1.110	0.0000	0.000	1.25	0.0002	0.9998
Acetone	1.180	0.0004	0.032	2.28	0.0005	0.9948
2-Propanol	1.213	0.0004	0.031	4.93	0.0036	0.9991
Acetonitrile	1.246	0.0004	0.030	3.30	0.0028	0.9994
Dichloromethane	1.284	0.0005	0.038	3.50	0.0022	0.9984
t-Butanol	1.303	0.0000	0.000	5.18	0.0028	0.9980
Hexane	1.402	0.0005	0.038	1.47	0.0002	0.9999
n-Propanol	1.444	0.0004	0.026	4.68	0.0082	0.9990
Ethylacetate	1.549	0.0000	0.000	2.93	0.0016	0.9995
Chloroform	1.603	0.0004	0.024	3.81	0.0110	0.9997
Cyclohexane	1.661	0.0005	0.029	1.71	0.0003	0.9993
Benzene	1.713	0.0000	0.000	2.73	0.0007	0.9998
n-Butanol	1.785	0.0007	0.039	5.41	0.0237	0.9972
1,4-Dioxane	1.874	0.0005	0.026	7.70	0.0033	0.9904
4-Methyl-2-Pentanone	1.985	0.0004	0.019	8.21	0.0031	0.9985
Toluene	2.028	0.0000	0.000	3.10	0.0014	0.9995
n-Butylacetate	2.130	0.0004	0.018	7.03	0.0044	0.9974

◀ List of solvents with retention times (min), standard deviations and relative standard deviations (%) of the retention times. Additionally, relative standard deviations are listed for the peak areas obtained using a System Suitability Test mix (6 µg/mL test mix in DMAC, n=6, RSD% for the raw peak areas). Limits of Detection (% w/w) are listed based on S/N=3 in addition to the linearity achieved (r^2) for a three point calibration curve spanning concentrations 6, 25 and 100 µg/mL.





GERSTEL MultiPurpose Sampler (MPS) with integrated weighing option

Standard autosampler vials are placed in the balance by the MPS. Liquid samples, standards, reagents or diluents that are added are weighed and the weights registered separately. For each sample, multiple liquid additions can be defined by mouse-click in the MAESTRO software. Results are automatically transferred to pre-defined Microsoft Excel tables for convenient processing. Each sample is reported in a separate line, each addition in a separate column.

When the sample preparation steps have been finalized, the MPS can introduce the prepared sample to the GC or LC system.

Every step from sample preparation to sample introduction is conveniently and efficiently set up in the MAESTRO software. When combined with the Agilent ChemStation software, one integrated method and one integrated sequence table controls everything from sample prep to sample introduction and GC/MS or LC/MS analysis. The MPS weighing option simplifies the laboratory work flow as well as the data handling process, reducing the risk of operator error for improved convenience, productivity and certainty.