8-Minute GC Analysis of Residual Solvents

Using an Rtx®-624 (G43) / Rtx®-WAX (G16) Column Pair

By Rick Lake, Pharmaceutical Innovations Chemist

- Dual-column detection/confirmation in 8 minutes.
- Columns produce desired selectivity and stable retention.
- Excellent peak shape and sensitivity, for reliable information.

The International Conference on Harmonization (ICH) publishes a guideline (Q3C) listing amounts of solvent residues that are acceptable in drug products and drug substances. The complete ICH list of regulated solvents, 61 compounds of differing chemical properties, is a challenge for separation on any single GC phase, as critical coelutions exist. Typically, residual solvents are identified by assaying samples and matching retention times with reference standards. If a response greater than the regulatory limit is obtained in a retention time window, a second sample is analyzed to confirm the compound's identity, using a column that has alternate selectivity. In some cases, GC/MS is employed for analyte verification. Assays for verification can be laborious and time intensive, and add unnecessary cost.

In the ICH guideline, residual solvents are grouped according to their toxicity. Class 1 compounds are carcinogens that pose a risk to both consumers and the environment. The use of these solvents is to be avoided but, if they are used, their use must be tightly controlled to ensure only trace level impurities in the final product. Class 2 compounds are non-genotoxic animal carcinogens, and concentrations of these compounds should be limited in pharmaceutical actives and products. Class 3 compounds have low toxic potential, and concentrations up to 0.5% are acceptable. Therefore, Class 3 compounds can be assayed by non-specific techniques, such as weight loss on drying. Because Class 2 compounds are the most likely prospects for GC analysis, we selected Residual Standards Class 2 Mix A and Residual Standards Class 2 Mix B (cat.#s 36271 and 36272, respectively) as the analytes for this work.

Because of advances in headspace technology – mainly dynamic sampling techniques – greater sensitivity now is achievable with this approach[1], and this makes a comprehensive dual-column assay feasible. By simultaneously using two columns with differing selectivities, e.g., a G43 column (Rtx®-1301 or Rtx®-624) and a G16 column (Rtx®-Wax or Stabilwax®), a single injection can be used both to detect residual solvents and to confirm their identities. Even with two columns, however, the complexity of the sample list makes it impossible for a single temperature program to provide the flexibility needed to resolve all compounds on each column. To overcome this barrier, we used a Tekmar HT3 dynamic headspace sampler and an Agilent 6890 GC equipped with a Gerstel Modular Accelerated Column Heater (MACH) System. One of the latest advances in fast GC technology, the MACH System incorporates columns encased individually in thermally controlled bundles and heated externally from the main GC oven (Figure 1).[2] This independent, low thermal mass configuration allows independent, very rapid temperature ramps, upward or downward.

Collected analytes were directed to the injection port, then were split onto the two columns via a "Y" Press-Tight® connector. Independent temperature programs for each column separated the analytes for detection on dual FIDs. Using our two columns in this novel and simple-to-use setup, we resolved all compounds in the combined reference mixes in less than 8 minutes (Figure 2) – a result not possible with a conventional GC system. There was one critical co-elution on each column, but these did not involve the same compounds, and thus posed no practical problem. Also, with the low thermal mass of the

Figure 1 Two column modules in a Gerstel MACH column heating system.

The MACH system allows independent temperature programming of up to four columns, simultaneously.

tech **tip**

Dual column assays also can be performed in conventional GC ovens, by connecting a deactivated guard column to two analytical columns via a "Y" Press-Tight® connector.

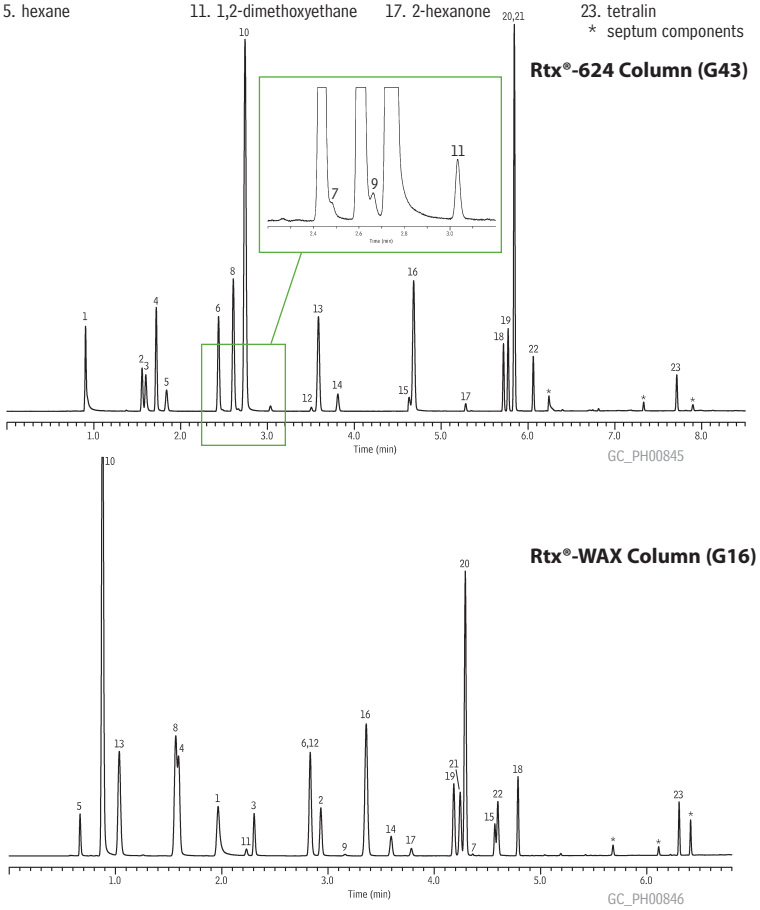
Universal "Y" Press-Tight® Connectors

Description	cat. #	price
Universal "Y" Press-Tight® Connector	20405	$61

Figure 2 Detect and confirm residual solvents with one injection, using Restek columns in a Gerstel MACH System.

1. methanol
2. acetonitrile
3. dichloromethane
4. *trans*-1,2-dichloroethylene
5. hexane
6. *cis*-1,2-dichloroethylene
7. nitromethane
8. tetrahydrofuran
9. chloroform
10. cyclohexane
11. 1,2-dimethoxyethane
12. trichloroethylene
13. methylcyclohexane
14. 1,4-dioxane
15. pyridine
16. toluene
17. 2-hexanone
18. chlorobenzene
19. ethyl benzene
20. *m*-xylene
21. *p*-xylene
22. *o*-xylene
23. tetralin

* septum components



Headspace Conditions - see our web page: www.restek.com/buzz

Instrument Conditions

Instrument:	Agilent 6890 with Gerstel Modular Accelerated Column Heater (MACH)
Column:	Column 1: Rtx®-624 (G43) 20m, 0.18mm ID, 1.00µm (cat.# 40924) Column 2: Rtx®-WAX (G16) 20m, 0.18mm ID, 0.4µm (custom)
Sample:	cat.# 36271 and cat.# 36272 diluted in 0.5mL DI water/~0.2g sodium sulfate in 20mL headspace vial; components at 0.10 - 6.00µg - see our web page.
Inj.:	headspace trap injection, split ratio 20:1, flow split after injector to two columns, using a 0.32mm ID intermediate polarity deactivated guard column (cat.# 10044) and a "Y" Press-Tight® connector (cat.# 20405)
Inj. temp.:	220°C
Carrier:	helium, constant flow
Flow rate:	Column 1: 0.85mL/min.; Column 2: 0.99mL/min.
Oven temp.:	250°C
Gerstel temps.:	Column 1: 50°C (2 min.) to 80°C at 20°C/min. (1 min.), to 200°C at 40°C/min. (2 min.) Column 2: 35°C (2 min.) to 60°C at 100°C/min. (1 min.), to 200°C at 40°C/min. (2 min.)
Det.:	FID at 250°C, hydrogen: 40mL/min., air: 450mL/min., makeup gas: 45mL/min.

1. Restek Advantage 2006 vol. 1, pp.14-15 (2006); request: lit. cat.# 580035.
2. Direct inquiries about the Gerstel MACH System to Gerstel Inc. Phone: 410-247 5885; e-mail: sales@gerstelus.com

MACH System modules, the cooldown and equilibration time between samples is considerably shorter than with a conventional GC oven.

Dynamic headspace sampling coupled with a Gerstel MACH column heating system makes possible rapid, comprehensive assays of residual solvents. By using other column combinations and other independent temperature programs, this system can be adapted to quickly resolve other complex mixes.

Residual Solvents Class 2 - Mix A (15 components)
In dimethyl sulfoxide, 1mL/ampul
cat. # 36271 (ea.) $39

Residual Solvents Class 2 - Mix B (8 components)
In dimethyl sulfoxide, 1mL/ampul
cat. # 36272 (ea.) $35

Residual Solvents Class 2 - Mix C (8 components)
In dimethyl sulfoxide, 1mL/ampul
cat. # 36273 (ea.) $35

European Pharmacopoeia/ICH Q3C(M) Class 2 Mix C (14 components)
In dimethyl sulfoxide, 1mL/ampul
cat. # 36274 (ea.) $37

European Pharmacopoeia/ICH Q3C(M) Class 2 Mix A (6 components)
In dimethyl sulfoxide, 1mL/ampul
cat. # 36275 (ea.) $35

Fused Silica Guard Columns/Transfer Lines

Nominal ID	Nominal OD	length	cat. #	price
0.32mm	0.45 ± 0.04mm	5-Meter	10044	$45
0.32mm	0.45 ± 0.04mm	5-Meter	10044-600	$225

gc column **ordering** info

To order Gerstel MACH GC Columns, call:
800-413-8160
410-247-5885
e-mail: sales@gerstelus.com

Rtx®-624 (G43) (fused silica)
(Crossbond® 6% cyanopropylphenyl/94% dimethyl polysiloxane)

ID	df (µm)	temp. limits	length	Module	Gerstel cat. #
0.18mm	1.00	-20 to 240°C	20-Meter	5"	015200-019-GI
0.18mm	1.00	-20 to 240°C	20-Meter	3"	015200-020-GI

Rtx®-WAX (G16) (fused silica)

ID	df (µm)	temp. limits	length	Module	Gerstel cat. #
0.18mm	0.4	-20 to 250°C	20-Meter	5"	015200-021-GI
0.18mm	0.4	-20 to 250°C	20-Meter	3"	015200-022-GI