

# Rapid Analysis of Residual Solvents in Pharmaceuticals

Restek  
Innovation!

## Using Static Headspace Sampling and Stop-Flow GC

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Kit is easily attached to Agilent 6890 GC!

- Resolve 35 residual solvents in 18 minutes.
- Simplify inventory—use one pair of chromatography columns and one set of conditions for all ICH Class I and Class II solvents.
- Complete, easy to install system.

The International Conference on Harmonization (ICH) makes recommendations concerning amounts of residual solvents considered safe in pharmaceutical finished goods. The ICH has published guidelines and daily exposure limits for 61 solvents, classified in three groups, according to their toxicity. Class I solvents are known carcinogens or environmental hazards, to be avoided if at all possible. Class II solvents are less toxic, but their use should be limited. Class III solvents have low toxicity or no health-related exposure limit.<sup>1</sup> All pharmaceutical products must be analyzed for residual solvents, regardless of the matrix, and an enormous number of methods potentially can be required to address the total list of solvents. The complexity and high cost of compliance are major hurdles in drug manufacture.

In February 2004, Teledyne Tekmar developed a universal analytical method for extracting and determining 32 ICH Class II and Class III residual solvents, using static headspace sampling.<sup>2</sup> Simultaneously, Restek chemists were developing an approach for resolving the Class I and Class II solvents, using a new technology known as Stop-Flow GC, but lacked a sample preparation method suitable for achieving the detection limits required by the ICH.<sup>3</sup> By using a Teledyne Tekmar 7000HT headspace autosampler unit in conjunction with Stop-Flow GC technology, it is possible to achieve resolution, sensitivity, and rapid sample turn-around times for the Class I and Class II residual solvents. In Stop-Flow GC the solvents are separated by passing the sample through a two-column ensemble consisting of a Stabilwax<sup>®</sup> column and an Rtx<sup>®</sup>-200 column coupled in series. Carrier gas flow through the

second (Rtx<sup>®</sup>-200) column is interrupted briefly (stop-flow pulses) to tune the separation at the outlet of the column ensemble.

In an analysis on two GC columns in series there are four possible outcomes for two sample components: 1) the two compounds are resolved at the column junction and remain resolved at the end of the ensemble; 2) the two compounds coelute at the junction, but are resolved on the second column; 3) the two compounds are resolved at the junction, but coelute at the end of the column ensemble; 4) the two compounds coelute at the column junction and at the end of the ensemble. For 1) and 2) no adjustment is necessary. For 4) other stationary phase combinations should be investigated to ensure separation on at least one of the two columns. For 3) Stop-Flow GC is appropriate. Carrier gas flow into the second column is interrupted briefly, immediately after one of the two compounds has crossed the junction, but while the other compound is still in the first column. The timing and duration of the stop-flow pulse are set to ensure that the two components remain separated when they reach the end of the column ensemble. The key to choosing a column ensemble for a specific application is to make separate analyses on each column, to ensure that no two compounds coelute on both stationary phases.

Figure 1 is the product of applying three stop-flow pulses at the junction point of the column ensemble, to pull apart three analytes: trichloroethene, acetonitrile, and chloroform. The other analytes are resolved by adjusting the carrier gas flow and temperature program, and

do not require pulses. The chromatogram includes all ICH Class I and Class II solvents, except ethylene glycol (which was not detected at 200ppm), at 200ppm each in 5mL of 1,3-dimethyl-2-imidazolidinone (DMI) solvent. By resolving closely eluting component pairs, Stop-Flow GC enables pharmaceutical laboratories to monitor all ICH Class I and Class II solvents with one pair of chromatography columns and a single set of conditions.

This analysis for 35 residual Class I and Class II solvents is rapid, sensitive, and reliable. If you are required to monitor solvents in pharmaceutical products, we welcome the opportunity to discuss Stop-Flow GC with you.

### References

1. ICH Guidance for Industry, Q3A Impurities: Residual Solvents US Dept. of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research (CBER). International Conference on Harmonization, Dec. 1997.
2. Wallace, B. and J. Kancler. *One Universal Method for Residual Solvents in Pharmaceuticals Using a High Temperature Static Headspace Sample Introduction System* Application Note 7000-021b.doc, Teledyne Tekmar Instruments, Feb. 2004.
3. Wittrig, R.E.; F.L. Dorman, C.M. English, R.D. Sachs, *J. Chromatogr. A* 1027: 75-82 (2004).

### Acknowledgement

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### Stop-Flow GC for Agilent 6890 GCs

Description	qty.	cat.#
Stop-Flow System for use with Cool On-Column EPC (includes: Stop-Flow enclosure, top mounting plate, 1-line weldment, and interface cable)	kit	21168
Stop-Flow System for use with Split/Splitless EPC (includes: Stop-Flow enclosure, top mounting plate, 2-line weldment, and interface cable)	kit	21169

### Stabilwax<sup>®</sup> Column

15-Meter, 0.25mm, ID 0.5 $\mu$ m df, cat.# 10635

### Rtx<sup>®</sup>-200 Column

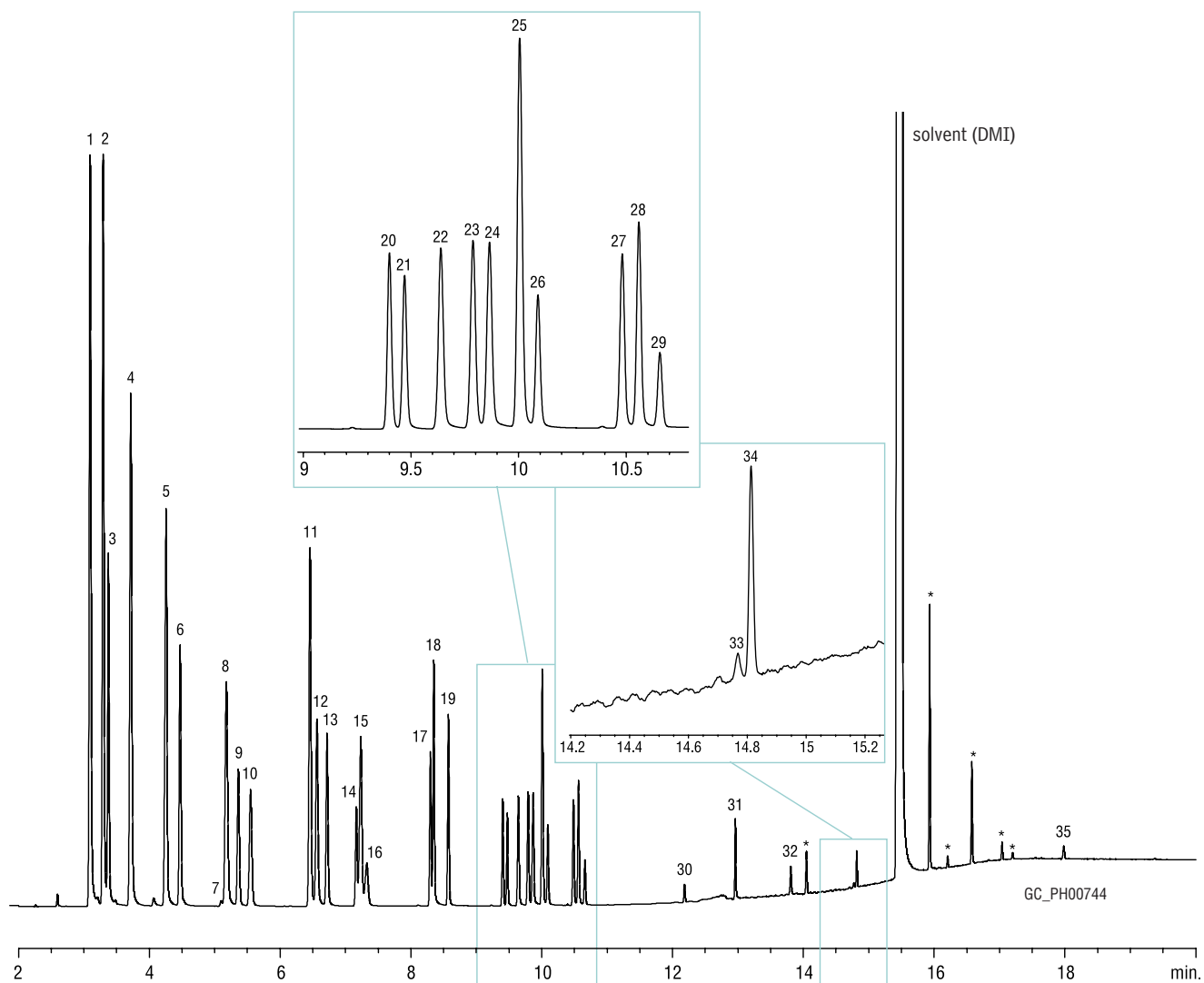
30-Meter, 0.25mm ID, 1.0 $\mu$ m df, cat.# 15053

Did you  
know?



We offer many reference mixes of residual solvents for EP and USP methods. For descriptions, please refer to our chromatography supplies catalog, or visit our website.

**Figure 1** Stop-Flow GC provides a rapid, sensitive analysis for ICH Class I and Class II residual solvents.



1. 2-methylpentane
2. hexane
3. 1,1-dichloroethene
4. methyl cyclopentane
5. methanol
6. *trans*-1,2-dichloroethene
7. carbon tetrachloride
8. methyl cyclohexane
9. methylene chloride

10. 1,1,1-trichloroethane
11. benzene
12. 1,2-dimethoxyethane
13. *cis*-1,2-dichloroethene
14. trichloroethene
15. acetonitrile
16. chloroform
17. 1,2-dichloroethane
18. toluene

19. 1,4-dioxane
20. nitromethane
21. 2-methoxyethanol
22. 2-hexanone (MBK)
23. *p*-xylene
24. *m*-xylene
25. pyridine
26. 2-ethoxyethanol
27. *o*-xylene

28. chlorobenzene
29. 1,1,2-trichloroethane
30. dimethyl formamide (DMF)
31. N,N-dimethylacetamide
32. 1,2,3,4-tetrahydronaphthalene
33. formamide
34. 1-methyl-2-pyrrolidinone
35. sulfolane
- \* impurities in solvent

**Headspace Conditions**

Instrument: Teledyne Tekmar 7000HT high temperature static headspace unit  
 Platen temp.: 140°C  
 Sample equilibration: 5 min.  
 Mixing time: 10 min.  
 Mixing power: 2  
 Mixture stabilization: 1 min.  
 Pressure time: 0.2 min.  
 Pressure equilibration: 0.3 min.  
 Vial vol.: 22mL (high temperature vials)  
 Sample loop vol.: 1mL (standard size, Silcosteel® treated)  
 Loop/line temp.: 250°C  
 Loop fill time: 0.1 min.  
 Loop equilibration: 0.05 min.  
 Inj. time: 1.0 min.  
 Static vial press.: 3.5psi helium  
 Vial press.: 8psi helium  
 Variable inj. press. (VIPR): 5psi helium  
 Interface: plumbed through injection port, 1:20 split

**GC Conditions**

Column #1: Stabilwax®, 15m x 0.25mm x 0.5µm (cat. # 10635)  
 Column #2: Rtx®-200, 30m x 0.25mm x 1.0µm (cat. # 15053)  
 Sample: 200ppm each component in 1,3-dimethyl-2-imidazolidinone (DMI)  
 Instrument: Agilent 6890  
 Inj. port temp.: 250°C  
 Carrier gas: helium, constant flow  
 Flow rate: 1.9mL/min., 25.6psi @ 40°C  
 Oven temp.: 40°C (hold 2 min.) to 55°C @ 4°C/min., to 110°C @ 25°C/min. (hold 2 min.) to 250°C @ 25°C/min. (hold 5 min.)  
 Det.: FID #1 at column junction, FID #2 at sample outlet (equal settings)  
 Det. temp.: 250°C  
 Reaction gas: hydrogen, 40mL/min.  
 Air flow: 400mL/min.  
 Makeup: helium, 40mL/min.  
 Data collection rate: 100Hz

**Stop-Flow Conditions**

Instrument: Restek Stop-Flow System for Agilent 6890 GC with cool on-column injector (cat. #21168)  
 Inj. port connection: cool on-column injector  
 Pressure: 31.0psi, constant pressure  
 Pulses: valve opened 3.00 - 3.15 min., 4.65 - 5.02 min., 5.10 - 5.40 min.  
 Total analysis time: 20.55 min.