Introducing New Functionalities in Liquid Stationary Phases in GC Columns for Confirming Organic Volatile Impurity Testing in Pharmaceutical Products.

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Abstract

One of the most common GC testing methods used by today's pharmaceutical laboratories is the analysis of organic volatile impurities (OVIs) in finished pharmaceutical products. There are many challenges in performing OVI analyses. The most commonly used capillary GC stationary phases for OVI analysis of regulated solvents are the G27 (5% diphenyl/95%dimethyl polysiloxane) and G43 (6%cyanopropyl phenyl/94%dimethyl polysiloxane) columns. However, other stationary phases must be employed depending on the specific solvents used in the manufacturing process of a pharmaceutical compound.

Often the OVIs are low-boiling, low molecular weight compounds that are difficult to retain and resolve on capillary stationary phases. Thick stationary films (3.0µm and 5.0µm) often are used to achieve required separations at a sacrifice in analysis time and the inability to use high GC operating temperatures. Restek is developing a new stationary phase for confirming OVIs, that will resolve coeluting unregulated compounds from regulated solvents.

Retention time information on seventy-six of the most common solvents will be presented on three stationary phases. Chromatograms of these common solvents will be presented to show the utility of these phases for the OVI analysis. This data will also be used to design a new column that will attempt to resolve all 76 compounds.

Background

Residual solvents in pharmaceuticals are defined as volatile organic chemicals that are used or produced in the manufacture of drug substances or excipients, or in the preparation of drug products. The solvents are not completely removed by practical manufacturing techniques. Since there is no known therapeutic benefit from residual solvents, all residual solvents should be removed to the extent possible to meet product specifications, good manufacturing practices or other quality based requirements.

USP Compound Classes

These solvents can be characterized by toxicity in three classes as follows:

Class I – have unacceptable toxicities and should be avoided.
Class II—less severe, should be avoided if possible.
Class III—less toxic and should be used when possible.
Solvents –not classified, or isomers of analytes listed above.

USP Changes Address Challenging Separations

USP made changes in 1997 to overcome the difficulties resulting from unregulated solvents coeluting with regulated solvents and thereby causing over-representation of their concentration. These changes allow FID methods, GC/MS or a second validated column to be used. Restek is currently developing a new stationary phase, which is designed to be a confirmation column to phases such as G43 & G27.

Analysis of Common Solvents Using Two Columns

The following conditions apply to both chromatograms shown (Rtx-G27 & Rtx-VGC), the only deviation from these parameters is the film thickness of the Rtx-VGC, which is 3.0 microns. The chromatograms are Headspace injections of 24 common residual solvents for pharmaceutical processing. Prepared to equal about 500ppm in the bulk pharmaceutical. The Rtx-VGC would make a suitable confirmation column to the G27 phase for this compound set, but a column specifically engineered for these compounds could be used for a variety of methods and provide better resolution.

USP <467> Common solvents

Method I: G27 30m x 0.53mm x 5.0 df , w/ 5m PM guard

Inj: Headspace at 500ppm in bulk pharm. 2:1 split

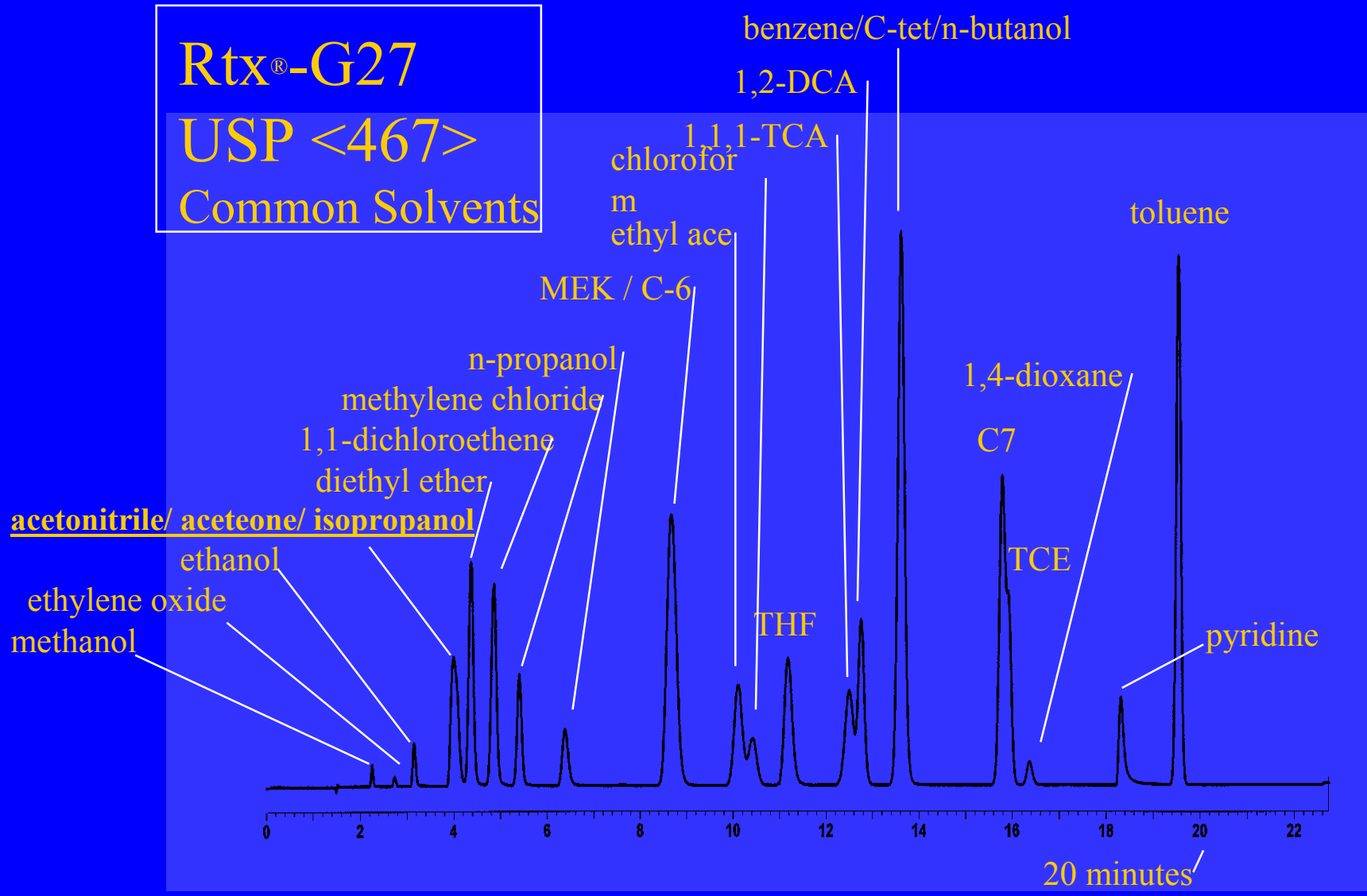
Oven Temp: 35(10)5/100 (0) 25/240(5)

Detector: FID, 260°C, 1 x 10^{-11} AFS

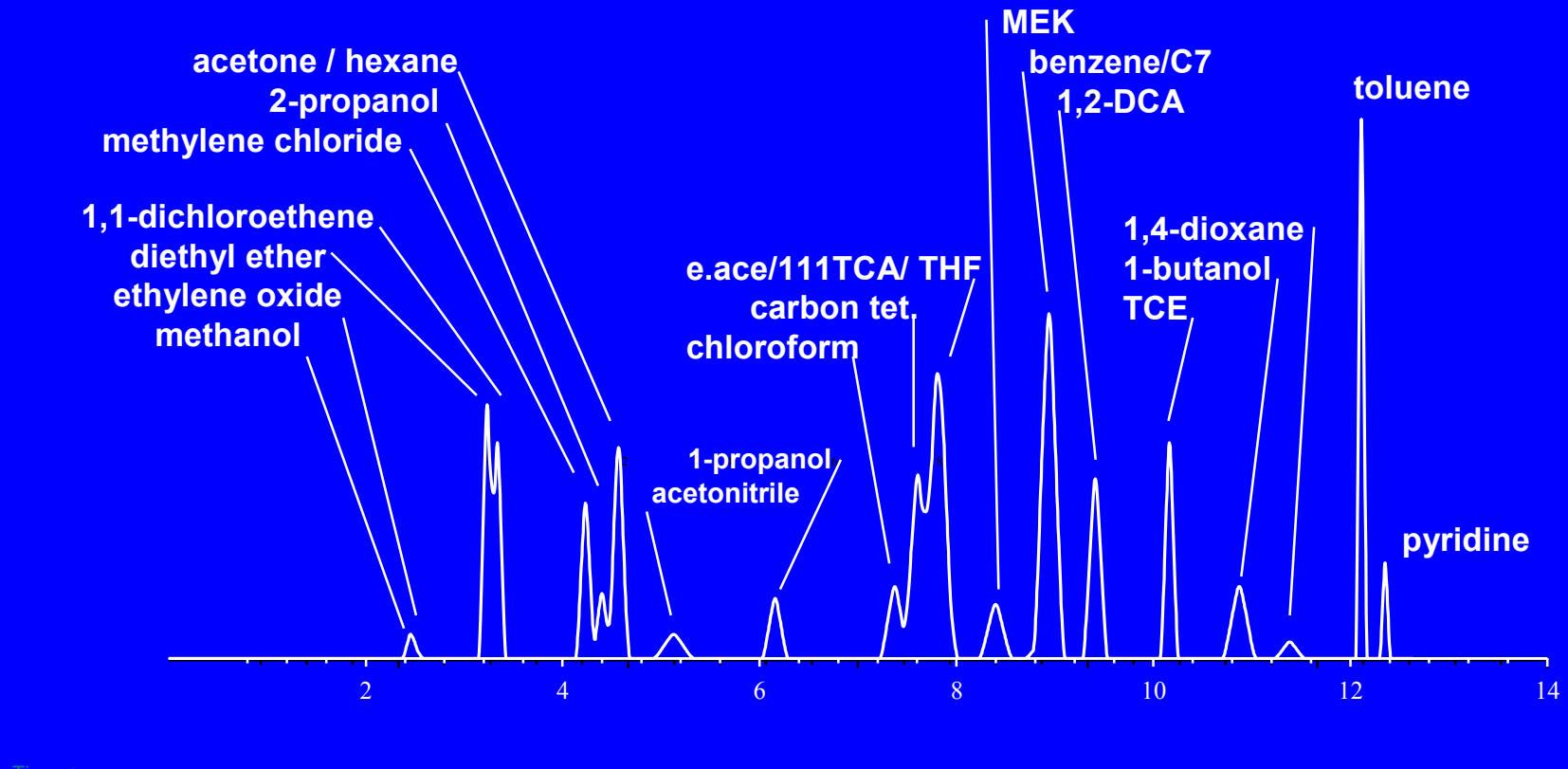
Carrier: helium, 4.1psi const, 35cm/sec @ 35°C

samples shaken and heated at 90°C for 15 minutes, 1mL headspace injection.

Rtx®-G27
USP <467>
Common Solvents



Rtx®-VGC
USP <467>
Common Solvents

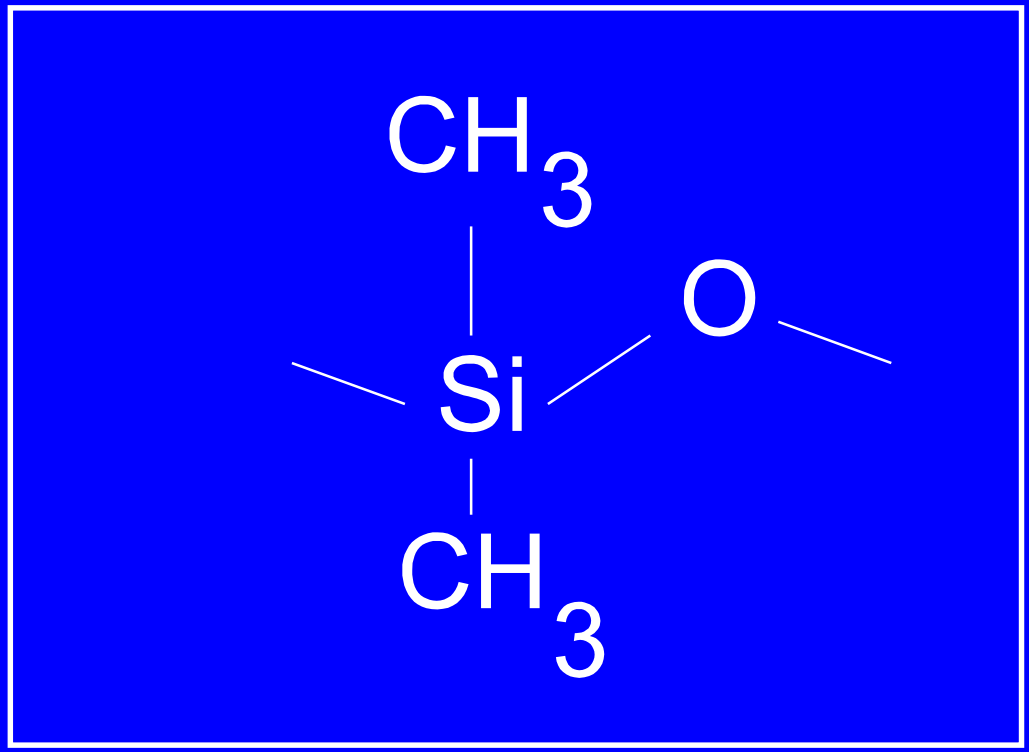


Chromatograms of the 76 Solvents Using the Rtx-1, Rtx-200 and an Experimental Fluorinated Polymer.

The three chromatograms are run under the exact same conditions. These analytes can be modeled allowing predictions of retention time under any set of conditions, such as, column diameter, column length, film thickness, temperature, detector considerations, injection techniques, and flow. This allows subsets of the compound list to be resolved using specific conditions. Contact Restek for more information.

Stationary Phases Used for Modeling

Dimethyl-polysiloxane

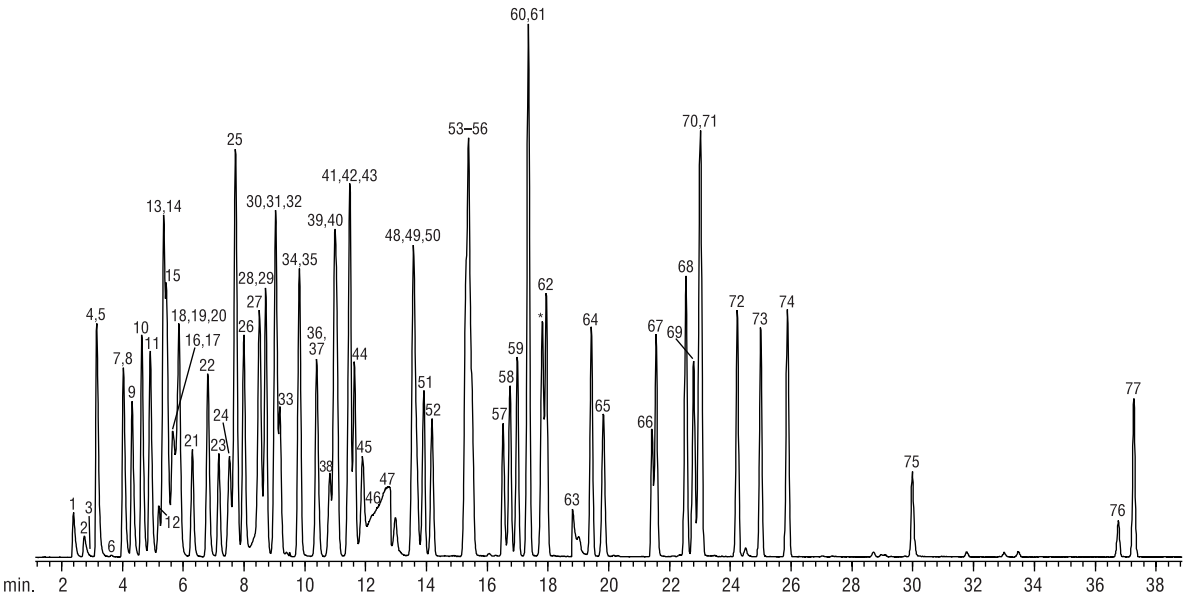


Rtx-1

Rtx-1

OVI methods allow for GC/MS confirmational analysis to identify complex chromatograms. GC/MS compound identification errors are common since ketones & acetates share parent ions (43). Alkanes & alkenes also present challenges since these compounds contain the 57 ion. The chromatogram shown illustrates the problems with non-polar phase with this compound list. Polar compound such as ethylene glycol have poor solubility in the dimethyl-polysiloxane phase resulting in poor sensitivity & linearity. The alcohols are retained less relative to the non-polar analytes.

USP Solvents
Rtx®-1



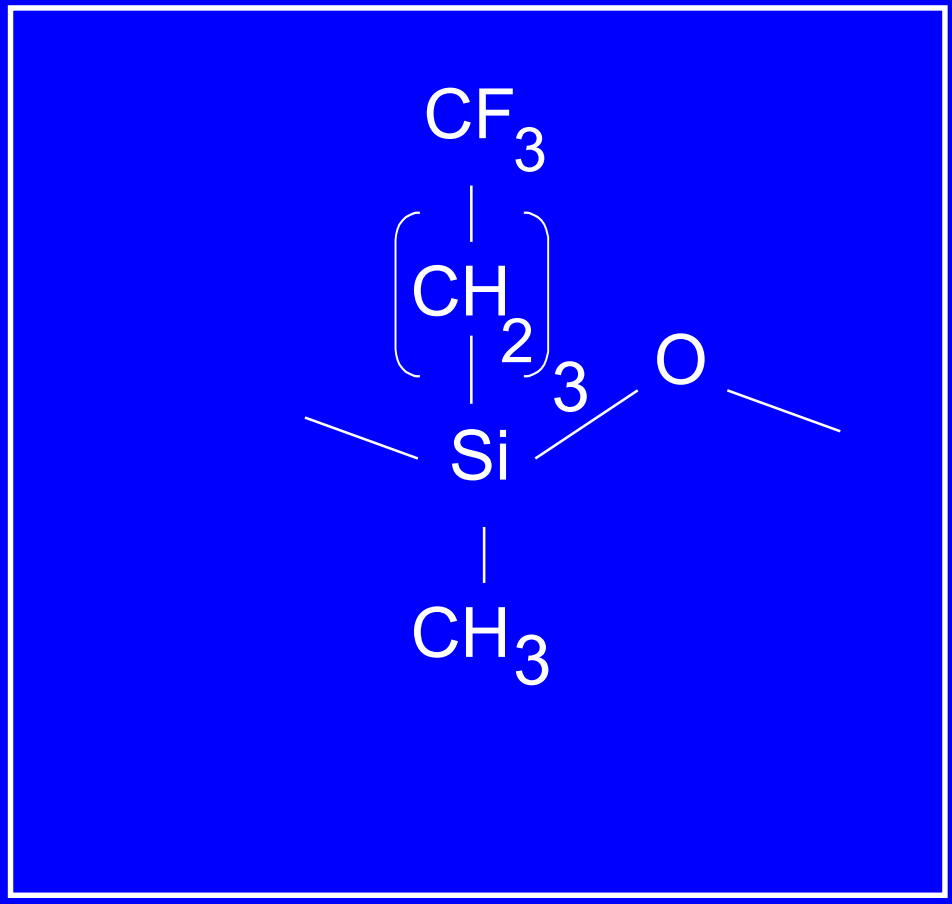
GC_EV00463

Rtx®-1 60m, 0.53mm, 3.00µm (cat.# 10188)
Sample: solvents
Conc.: solventless mixture ~1.3% each*
Sample size: needle vapor
Inj.: split, 250°C
Septa purge: 5mL/min.
Split vent flow: 100mL/min. ~1:13 split
Carrier: helium
Head pressure: 11.0psi constant pressure
Linear velocity: 45.6 cm/sec @ 35°C
Det: Mass Selective
Scan range: 10amu to 260amu
MS interface: open split interface ~1:7 split
Oven temp.: 35°C (hold 4 min.) to 250°C @ 4°/min.

1. formaldehyde
2. water
3. chloromethane
4. methanol
5. acetaldehyde
6. ethylene oxide
7. chloroethane
8. ethanol
9. acetonitrile
10. acetone
11. 2-propanol
12. 2-chloropropane
13. diethylether
14. pentane
15. ethyl formate
16. formic acid
17. methylal
18. 1,1-dichloroethene
19. methyl acetate
20. methylene chloride
21. nitromethane
22. 1-propanol
23. *trans*-1,2-dichloroethene
24. methyl *tert*-butyl ether
25. 2-methylpentane (spiked at 9%)
26. 2-butanone (MEK)
27. 2-butanol
28. *cis*-1,2-dichloroethene
29. acetic acid
30. isopropyl ether
31. ethyl acetate
32. hexane
33. chloroform
34. tetrahydrofuran
35. 2-methoxyethanol
36. 1,2-dichloroethane
37. methyl cyclopentane
38. 1,1,1-trichloroethane
39. 1,2-dimethoxyethane
40. methyl isopropyl ketone
41. 2,2-dimethoxypropane
42. isopropyl acetate
43. 1-butanol
44. benzene
45. carbon tetrachloride
46. ethylene glycol
47. formamide
48. 1,4-dioxane
49. trichloroethene
50. isooctane
51. 2-ethoxyethanol
52. *n*-heptane (C7)
53. isoamyl alcohol
54. hexanone (MIBK)
55. pyridine
56. methyl cyclohexane
57. dimethyl formamide (DMF)
58. 1,1,2-trichloroethane
59. 1-pentanol
60. isobutyl acetate
61. toluene
62. 2-hexanone (MBK)
63. dimethyl sulfoxide
64. butyl acetate
65. 1,1-diethoxypropane
66. N,N-dimethylacetamide
67. chlorobenzene
68. ethylbenzene
69. isoamyl acetate
70. *p*-xylene
71. *m*-xylene
72. *o*-xylene
73. anisole
74. isopropylbenzene (cumene)
75. 1-methyl-2-pyrrolidinone
76. sulfolane
77. 1,2,3,4-tetrahydronaphthalene

*paraldehyde

Trifluoropropyl-methyl

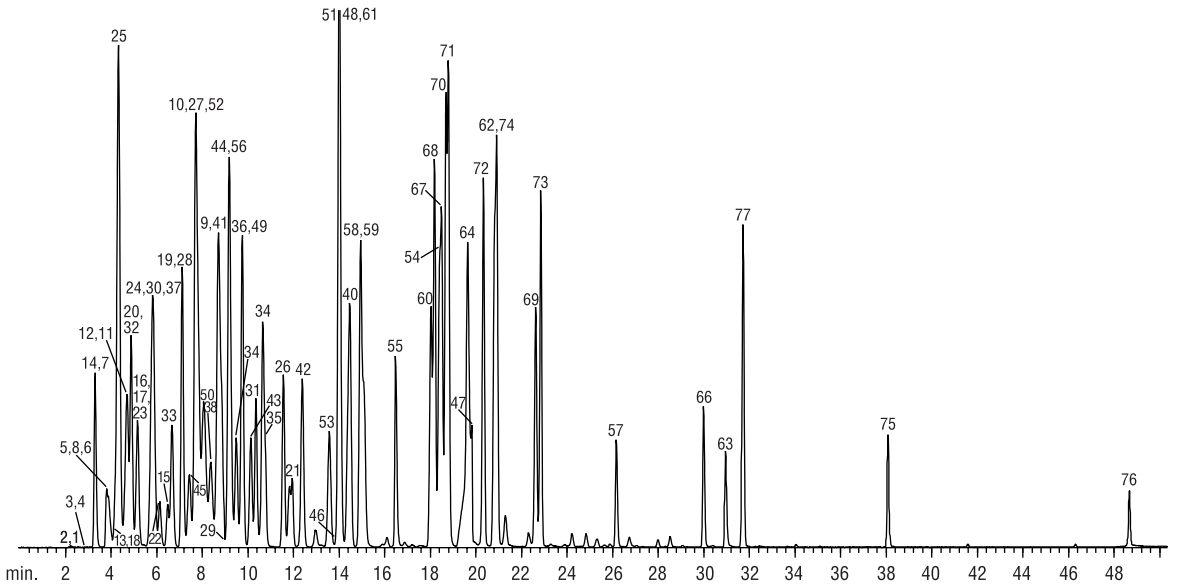


Rtx-200

Rtx-200

Like the Rtx-1 the Rtx-200 column is low bleed and is offered in thick films (3.0 micron). It has better peak shapes for glycols and other polar analytes. The Rtx-200 still lacks the “polarity” necessary to better retain compounds, such as alcohols, ketones and glycols. A phase that can withstand higher temperatures and yet have wax-like characteristics would allow for better retention.

USP Solvents
Rtx®-200



GC_EV00464

Rtx®-200 60m, 0.53mm, 3.00µm (cat.# 15088)

Sample:	solvents
Conc.:	solventless mixture ~1.3% each*
Sample size:	needle vapor
Inj.:	split, 250°C
Septa purge:	5mL/min.
Split vent flow:	100mL/min. ~1:13 split
Carrier:	helium
Head pressure:	11.0psi constant pressure
Linear velocity:	45.6 cm/sec @ 35°C
Det:	Mass Selective
Scan range:	10amu to 260amu
MS interface:	open split interface ~1:7 split
Oven temp.:	35°C (hold 4 min.) to 250°C @ 4°/min.

1. formaldehyde
2. water
3. chloromethane
4. methanol
5. acetaldehyde
6. ethylene oxide
7. chloroethane
8. ethanol
9. acetonitrile
10. acetone
11. 2-propanol
12. 2-chloropropane
13. diethylether
14. pentane
15. ethyl formate
16. formic acid
17. methylal
18. 1,1-dichloroethene
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20. methylene chloride
21. nitromethane
22. 1-propanol
23. *trans*-1,2-dichloroethene
24. methyl *tert*-butyl ether
25. 2-methylpentane (spiked at 9%)
26. 2-butanone (MEK)
27. 2-butanol
28. *cis*-1,2-dichloroethene
29. acetic acid
30. isopropyl ether
31. ethyl acetate
32. hexane
33. chloroform
34. tetrahydrofuran
35. 2-methoxyethanol
36. 1,2-dichloroethane
37. methyl cyclopentane
38. 1,1,1-trichloroethane
39. 1,2-dimethoxyethane
40. methyl isopropyl ketone
41. 2,2-dimethoxypropane
42. isopropyl acetate
43. 1-butanol
44. benzene
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47. formamide
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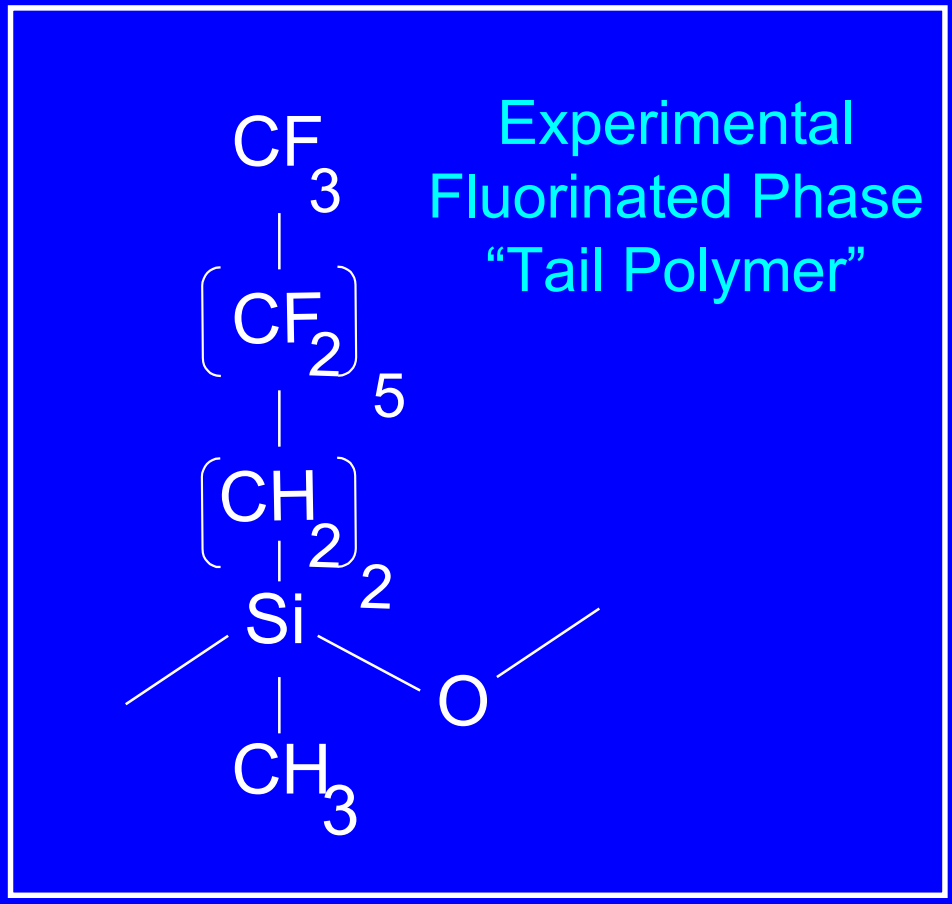
72. *o*-xylene
73. anisole
74. isopropylbenzene (cumene)
75. 1-methyl-2-pyrrolidinone
76. sulfolane
77. 1,2,3,4-tetrahydronaphthalene

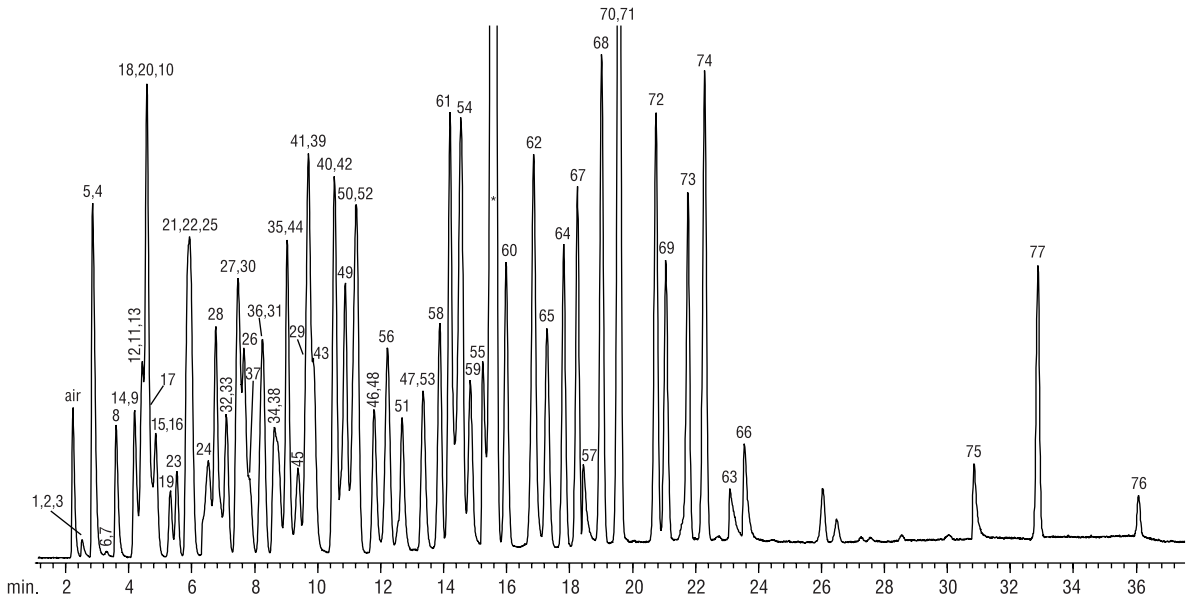
Tridecafluoro-1,1,2,2-tetrahydrooctyl-methyl



Experimental "Tail" Polymer

This is one of a series of experimental columns currently under investigation. Understandably, this polymer has similar characteristics to the Rtx-200. Direct comparisons, which maintain equal amounts of fluorine atoms, indicate that nitrogen containing compounds & ketones have less retention on this phase than the trifluoropropyl phase. This can also be seen in the chromatograms shown.

USP Solvents
Experimental Fluorinated Polymer "Tail"



GC_EV00589

Experimental Fluorinated Polymer "Tail" 60m, 0.53mm, 3.00µm

Sample:	solvents
Conc.:	solventless mixture ~1.3% each*
Sample size:	needle vapor
Inj.:	split, 250°C
Septa purge:	5mL/min.
Split vent flow:	100mL/min. ~1:13 split
Carrier:	helium
Head pressure:	11.0psi constant pressure
Linear velocity:	45.6 cm/sec @ 35°C
Det:	Mass Selective
Scan range:	10amu to 260amu
MS interface:	open split interface ~1:7 split
Oven temp.:	35°C (hold 4 min.) to 250°C @ 4°/min.

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35. 2-methoxyethanol
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37. methyl cyclopentane
38. 1,1,1-trichloroethane
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68. ethylbenzene
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70. *p*-xylene
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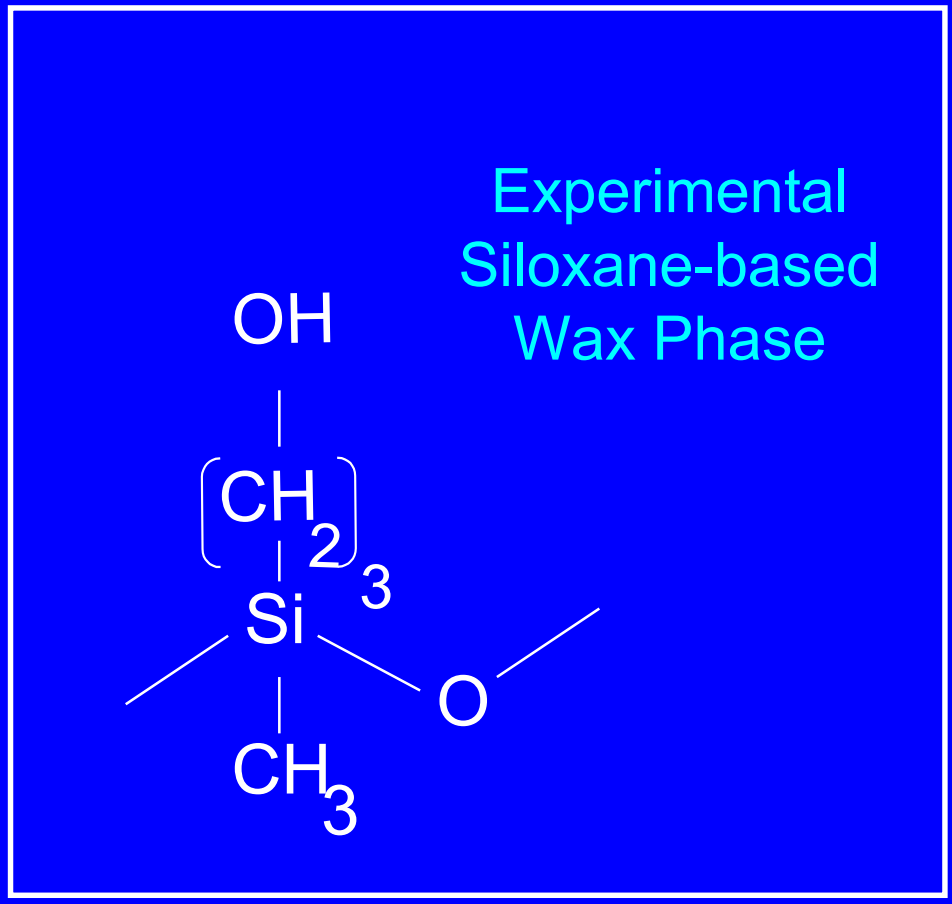
72. *o*-xylene
73. anisole
74. isopropylbenzene (cumene)
75. 1-methyl-2-pyrrolidinone
76. sulfolane
77. 1,2,3,4-tetrahydronaphthalene

*paraldehyde

1-hydroxypropyl-methyl



Experimental Siloxane-Based Wax Phase

Years ago Restek attempted to fill the gap in polarity between polyethylene-glycol phases and bonded siloxane-based polymers by mixing the two phases together. The effects gave favorable retention of complex compound mixtures, such as the one presented in the chromatograms, but suffered many other problems. The bleed was high and the selectivity of these phases changed over time since the polyethylene-glycol bled at a higher rate than the dimethylpolysiloxane. These phases do not mix well, which compromised the coating efficiency of the column. Development of a bonded siloxane wax-like phase could solve these problems and aid in the development of a successful solution to the OVI column.

New OVI Column

Restek is developing a stationary phase that will resolve the Class I compounds from the Class II & III analytes at the concentrations required by the USP. The second goal is to resolve the Class II from the Class III, as well as added solvents and their isomers. Conventional polysiloxanes will not meet the design criteria.

For More Information...

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