RESTEK pharmaceutical

Applications note

European Pharmacopoeia Tests—Newly Revised for Residual Solvents

Residual solvent testing in pharmaceutical formulations can be confusing. The International Conference on Harmonization (ICH) has proposed a set of guidelines that may end the confusion and the European Pharmacopoeia (EP) was the first to revise their regulations for clarity.[1,2] However, these guidelines are challenging, containing over 60 compounds of regulatory interest to manufacturers of active substances, excipients, and medicinal products. The EP methods also allow testing limits based on either a concentration limit in a product, or calculated from the maximum daily dosage of the product and the permissible daily exposure limit of the solvent. These technical challenges will affect the sampling method and capillary column needed to ensure precise and accurate results.

The two most common sampling techniques for residual solvent testing are direct injection and static headspace sampling. While the EP method lists only static headspace sampling, the ICH allows the use of any validated sampling method. Although the majority of the regulated compounds may be successfully tested by either sampling method, six of the Class 2 compounds cannot be tested by headspace. These compounds—formamide, 2-methoxyethanol, N-methylpyrrolidone, sulfolane, 2-ethoxyethanol, and ethylene glycol—are available from Restek in a separate mix at the regulatory limit for EP residual solvent testing to be analyzed by direct injection.

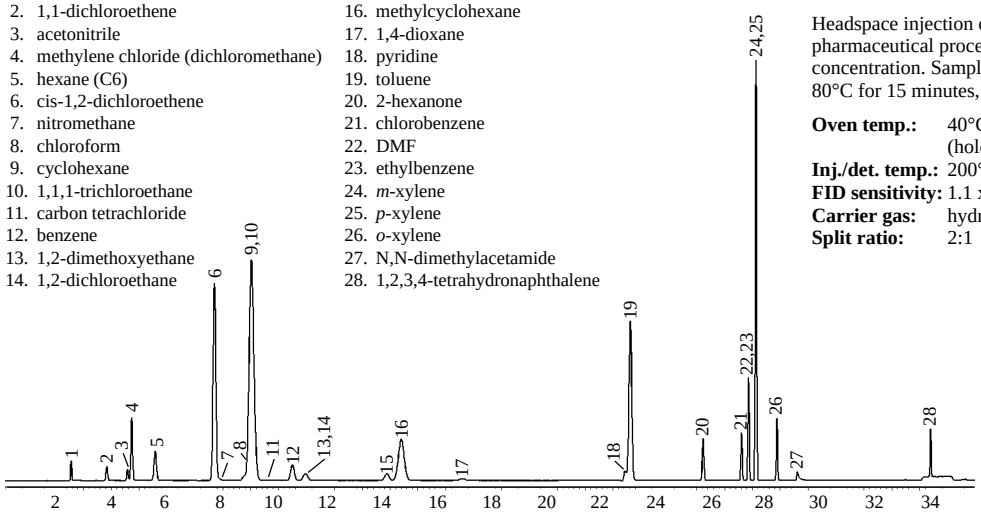
Restek sells EP calibration mixes at the regulatory concentration limit, allowing the same sample:dilutant (1:20) ratio to be used for the calibration material without any further concentration correction back to the sample concentration. *See the product listing for Class 1 and Class 2 residual solvent classifications.*

Restek sells the Class 1 and Class 2 compounds in a mix of water:dimethylsulfoxide (90:10). The use of co-solvents helps precision by limiting the loss of volatile analytes during standard preparation and handling, and product dispersion during sample preparation. Restek can provide custom analytical reference materials in N,N-dimethylformamide (DMF) or 1,3 dimethyl-2-imidazolidinone (DMI) to meet certain EP testing requirements.

The recommended capillary columns for EP residual solvent testing are the Rtx®-1301 and Stabilwax®. We can recommend other columns for customers analyzing abbreviated residual solvent lists. The Rtx®-1301 column shows excellent resolution of most European Pharmacopoeia Class 1 and 2 compounds at the regulation limit concentration (**Figure 1**). The Stabilwax® column makes an excellent confirmation column for the analysis of residual solvents (**Figure 2**). Please call us with your specific compound list and our technical representatives will find the best column for your solvent list and provide you with a price quotation for the custom analytical reference materials you need.

Figure 1: *The Rtx®-1301 column shows excellent resolution of most European Pharmacopoeia Class 1 and Class 2 compounds at the regulation limit concentration.*

1. methanol
2. 1,1-dichloroethene
3. acetonitrile
4. methylene chloride (dichloromethane)
5. hexane (C6)
6. cis-1,2-dichloroethene
7. nitromethane
8. chloroform
9. cyclohexane
10. 1,1,1-trichloroethane
11. carbon tetrachloride
12. benzene
13. 1,2-dimethoxyethane
14. 1,2-dichloroethane
15. trichloroethylene (1,1,2-trichlorethene)
16. methylcyclohexane
17. 1,4-dioxane
18. pyridine
19. toluene
20. 2-hexanone
21. chlorobenzene
22. DMF
23. ethylbenzene
24. *m*-xylene
25. *p*-xylene
26. *o*-xylene
27. N,N-dimethylacetamide
28. 1,2,3,4-tetrahydronaphthalene



30m x .53mm ID x 3.0mm Rtx®-1301 (cat.# 16085-126)

Headspace injection of 28 Class 1 and 2 residual solvents for pharmaceutical processing. Prepared at the regulatory limit concentration. Samples shaken and heated at 80°C for 15 minutes, 1mL headspace injection.

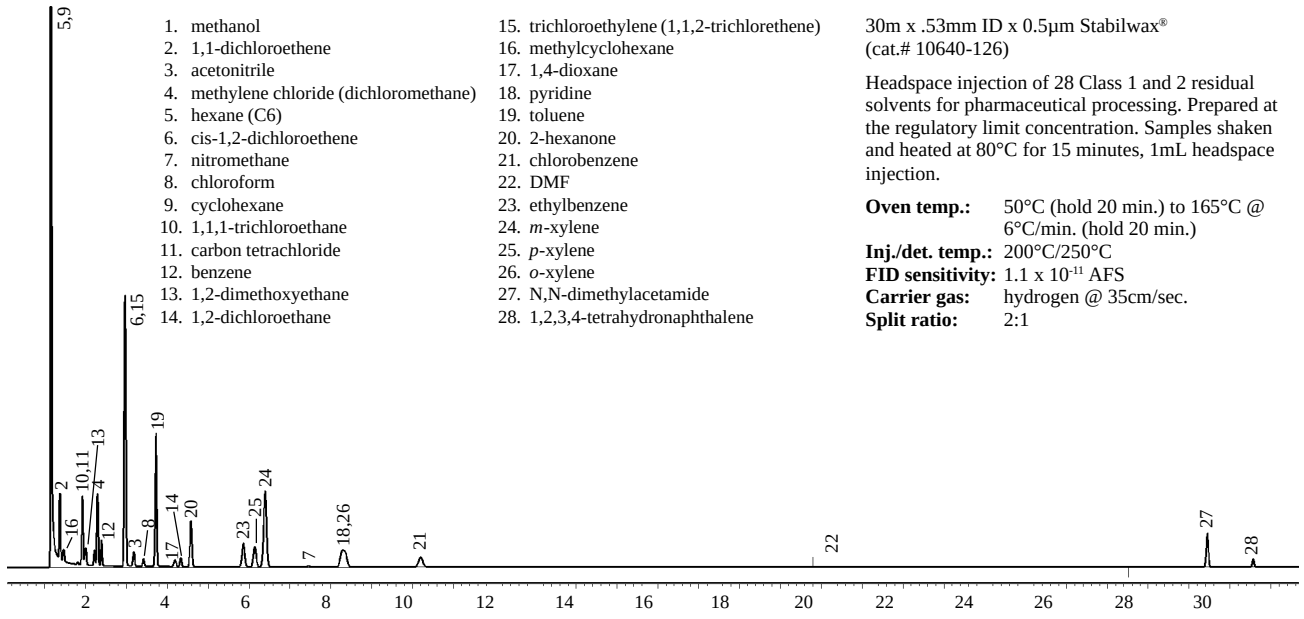
Oven temp.: 40°C (hold 20 min.) to 240°C @ 10°C/min. (hold 20 min.)
Inj./det. temp.: 200°C/250°C
FID sensitivity: 1.1 x 10^{-11} AFS
Carrier gas: hydrogen @ 35cm/sec.
Split ratio: 2:1

To place an order: call your local Restek representative.

References:
1. "ICH Harmonized Tripartite Guideline, Impurities: Guideline for Residual Solvents," The Fourth International Conference on Harmonization, July 17, 1997.
2. European Pharmacopoeia Supplement, January 1999, pp.14-15, 208.

pharmaceutical

Figure 2: *The Stabilwax® column makes an excellent confirmation column for the analysis of residual solvents.*



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9. cyclohexane
10. 1,1,1-trichloroethane
11. carbon tetrachloride
12. benzene
13. 1,2-dimethoxyethane
14. 1,2-dichloroethane
15. trichloroethylene (1,1,2-trichlorethene)
16. methylcyclohexane
17. 1,4-dioxane
18. pyridine
19. toluene
20. 2-hexanone
21. chlorobenzene
22. DMF
23. ethylbenzene
24. *m*-xylene
25. *p*-xylene
26. *o*-xylene
27. N,N-dimethylacetamide
28. 1,2,3,4-tetrahydronaphthalene

30m x .53mm ID x 0.5µm Stabilwax®
(cat.# 10640-126)

Headspace injection of 28 Class 1 and 2 residual solvents for pharmaceutical processing. Prepared at the regulatory limit concentration. Samples shaken and heated at 80°C for 15 minutes, 1mL headspace injection.

Oven temp.: 50°C (hold 20 min.) to 165°C @ 6°C/min. (hold 20 min.)
Inj./det. temp.: 200°C/250°C
FID sensitivity: 1.1 x 10^{-11} AFS
Carrier gas: hydrogen @ 35cm/sec.
Split ratio: 2:1

Product Listing

European Pharmocopoeia/ICH Class 1 Mix

benzene	2µg/mL	1,1-dichloroethene	8µg/mL
carbon tetrachloride	4	1,1,1-trichloroethane	1500
1,2-dichloroethane	5		

Prepared in water:dimethylsulfoxide 90:10, 1mL/ampul

Ea.: 36228 **5-pk.: 36228-510** **10-pk.: 36328**

European Pharmocopoeia/ICH Class 2 Mix A

chlorobenzene	360µg/mL	N,N-dimethylformamide	880µg/mL
cyclohexane	3,880	toluene	890
cis-1,2-dichloroethene	1,870	1,1,2-trichloroethene	80
dichloromethane	600	*m*-xylene	1,302
ethylbenzene	369	*o*-xylene	195
hexane	290	*p*-xylene	304
methylcyclohexane	1,180		

Prepared in water:dimethylsulfoxide 90:10, 1mL/ampul

Ea.: 36229 **5-pk.: 36229-510** **10-pk.: 36329**

European Pharmocopoeia/ICH Class 2 Mix B

acetonitrile	410µg/mL	2-hexanone	50µg/mL
chloroform	60	methanol	3,000
1,2-dimethoxyethane	100	nitromethane	50
N,N-dimethylacetamide	1,090	pyridine	200
1,4-dioxane	380		
1,2,3,4-tetrahydronaphthalene (tetraline)	100		

Prepared in water:dimethylsulfoxide 90:10, 1mL/ampul

Ea.: 36230 **5-pk.: 36230-510** **10-pk.: 36330**

European Pharmocopoeia/ICH Class 2 Mix C

2-ethoxyethanol	160µg/mL	N-methylpyrrolidone	4,840µg/mL
ethylene glycol	620	sulfolane	160
formamide	220		
2-methoxyethanol	50		

Prepared in water, 1mL/ampul

Ea.: 36231 **5-pk.: 36231-510** **10-pk.: 36331**

Rtx®-1301 Columns

Length	ID	df (µm)	cat.#
30m	0.32mm	1.5	16069
30m	0.53mm	3.0	16085

Stabilwax® Columns

Length	ID	df (µm)	cat.#
30m	0.32mm	0.25	10624
30m	0.53mm	0.50	10640

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