



ANALYSIS OF RESIDUAL SOLVENTS

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INTRODUCTION

Residual solvents are organic volatile impurities arising from the manufacture of drug products. While it is impossible to eliminate all solvents from production processes, manufacturers minimize the use of solvents where possible. As solvents can potentially cause adverse health effect, the content of solvents in final drug products must be known. In this context, ICH guidelines have been introduced into the European Pharmacopeia (EP) and United States Pharmacopeia (USP) in order to harmonize how to deal with the analysis of residual solvents.

Firstly, all solvents do not have the same degree of toxicity. Authorities class them into three categories:

Class 1 Solvents: these are the solvents to be avoided Class 2 Solvents: these are the solvents to be limited Class 3 Solvents: these are the solvents with low toxic potential

In USP, Chapter <467> describes several methods using GC/FID with headspace injection mode. These methods are generally applied by SGS and permit the analysis of most solvents (Classes 1, 2 and 3).

I. OBJECTIVES

To address limitations laboratories may encounter in performing residual solvent analyses. Specifically:

- Several Class 2 Solvents cannot be analyzed using head-space analysis because they are not volatile enough for head-space testing
- How to differentiate foreign peaks due to matrices from sample peaks

2. METHODS

 Liquid injection method based on USP <467> procedure B Column type: G16 (CP wax 52 CB) 30m x 0.32mm Helium flow: 2.1mL/min Temperatures: FID: 250°C Injector: 140°C Column: 50°C for 20 min, 50°C to 165°C at 6°C/min, 165°C for 20 min Injection volume: 1µL GC/MS method based on USP <467> procedure A Column type: G43 (VF-624ms) 30m x 0.32mm Helium flow: 1.5mL/min Temperatures: Detector: source: 230°C quadrupole: 150°C interface: 260°C Injector: 250°C Column: 40°C for 18 min, 40°C to 250°C at 10°C/min, 250°C for 20 min Injection volume: 1µL

3. RESULTS

System suitability tests were performed as described in the compendia. Results reveal system suitability (data not shown).

1 – LIQUID INJECTION METHOD

One problem for certain Class 2 Solvents is that these cannot be analysed with headspace injection. These compounds are formamide, 2-ethoxyethanol, 2-methoxyethanol, ethylene glycol, N-methylpyrrolidone, sulfolane, N,N-DMAC and N,N-DMF. A method with liquid injection has been developed by our laboratory to analyse 2-ethoxyethanol, 2-methoxyethanol and ethylene glycol. Chromatogram show that we can detect all of the eight Class 2 solvents above. (Figure 1)



FIGURE 1: Chromatogram obtained with standard solution as describe in the method developed for liquid injection

2-MATRIX PEAKS (E.G. EXCIPIENTS, ETC.)

Another major problem that can arise using the GC/FID involves foreign peaks due to the matrix. In this example, we tested paraffin. Using the GC/FID liquid injection method, a paraffin alone sample was run and one containing the solvents methylethylketone (MEC), methylisobutylketone (MIBK) and Nmethylpyrrolidone (NMP). The resulting profiles (Figures 2 and 3) are typical of hydrocarbons. The chromatograms reveal that this method is not suitable due to the numerous foreign peaks with the same retention time as NMP.



FIGURE 2: Chromatogram obtained with a sample solution of paraffin analysed by GC/FID and liquid injection method

3-USING GC/MS FOR RESOLUTION

To address the problems with resolution, we developed a method using GC/MS, also using liquid injection.

a) Identification of MEC, MIBK and NMP

First we performed GC/MS runs using solutions containing standards alone and also containing paraffin. (Figures 4 and 5)



FIGURE 4: Chromatogram obtained with standard solution by GC/MS method

COMPONENT	RETENTION TIME (MIN)
MEC	4.9
MIBK	15.3
NMP	29.4



The method has been validated. LOD and LOQ for 2-ethoxyethanol, 2-methoxyethanol and ethylene glycol have been determined.

SOLVENT	LOD (ppm)	LOQ (ppm)
2-ethoxyethanol	6.4	20.8
2-methoxyethanol	5.0	15.0
Ethylene glycol	5.0	16.1





b) Determination of target ions

From the total ion current (TIC) chromatogram (Figure 4), mass spectra from components of interest are extracted by selecting the correspond peak on the chromatogram. The mass spectrum of the component is compared automatically to mass spectra from an official library, (here NIST02), to identify the component. (Figure 6)

FIGURE 6: Mass spectra of NMP

From the mass spectra, target ion and qualifier(s), when possible, are defined. Here, we have defined from NMP mass spectrum (Figure 6):

c) Selected Ion Monitoring

Finally, the analysis is performed in selected ion monitoring (SIM) acquisition mode. (Figures 7 to 9). The quantitation is performed on the target ion, and therefore must be specific to the component in order not to over-estimate the solvent concentration. Here we see the chromatograms of the target and qualifier ions for MEC, MIBK and NMP. The ratio indicates if there are ions coming from another component. The ratio must be constant.



FIGURE 7: SIM chromatogram for methylethylketone (MEC) in standard solution



4 - CONCLUSION

15.3

29.4

MIBK

NMP

Our laboratories have performed many analyses using the compendia methods for residual solvents by headspace/FID gas chromatography. In order to respond to client issues, we have also developed methods using liquid injection with GC/FID and GC/MS. However liquid injection is more likely to generate matrix problem than headspace injection. GC/MS is an alternative for adverse matrix effects. With this in mind, methods should be developed for analysing all solvents that need liquid injection by GC/MS. The methods must then be validated according to ICH guidelines.

ION	M/Z RATIO
Target	99.1
Qualifier 1	98.1
Qualifier 2	44.1





FIGURE 8: SIM chromatogram for methylisobutlketone (MIBK) in standard solution

FIGURE 9: SIM chromatogram for N-methylpyrrolidone (NMP) in standard solution

Specifications for Class 3 solvents like MEC and MIBK are not more than 5000 ppm and not more than 530 ppm for NMP (Class 2 solvent). Limits of detection and quantification (LOD, LOQ) have been evaluated (less than 1 ppm). They are much lower than the specifications.