



Tips to Meeting the Criteria of the Upcoming Revised USP Monograph <467>: Residual Solvents

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On July 1, 2008, the United States Pharmacopoeia (USP) is adopting a slightly modified version of International Conference for Harmonization (ICH) Quality-3C (Q3C) methodology. This revision provides a risk-based approach to residual solvent analysis that considers a patient's exposure to a solvent residue in the drug product (1). Solvents have been classified based on their potential health risks into three main classes:

Class 1: Solvents should not be used because of the unacceptable toxicities or deleterious environmental effects

Class 2: Solvents should be limited because of inherent toxicities

Class 3: Solvents may be regarded as less toxic and of lower risk to human health

Testing is only required for those solvents used in the manufacturing or purification process of drug substances, excipients, or products. This allows each company to determine which solvents it uses in production and develop testing procedures that address their specific needs. Herein, we discuss the main advantages and disadvantages of using headspace vs. direct liquid injection techniques to meet the <467> guidelines.

A Strategic Approach to the Testing of Residual Solvents That Meets <467> Guidelines

Although the number of solvents now requiring testing has increased, a company is only required to test for those solvents that are likely to be present in the drug formulation. Since the solvents used in process development at each company are likely to be different, a company should consider developing a chromatographic testing system that addresses their specific needs.

In general, the strategy should be to develop a testing method for residual solvents that:

- Resolves all solvents of interest likely to be present in their drug substances, excipients, and/or products
- Reduces analysis time for maximum sample throughput
- Obtains high accuracy and precision independent of the matrix
- Detects compounds at or below their control limits
- Provides qualitative and quantitative data that is consistent with USP/PhEur testing requirements

To determine the solvents that will be relevant to your company, you must interview your scientists involved in process development and any vendors for excipients and/or drug substances that are included in your formulation. Compare these results to the USP <467> list of solvents to determine what Class 1, 2, and 3 solvents are likely to be present. This information will help you design a strategy to accurately determine the level of residual solvents in your drug formulation.

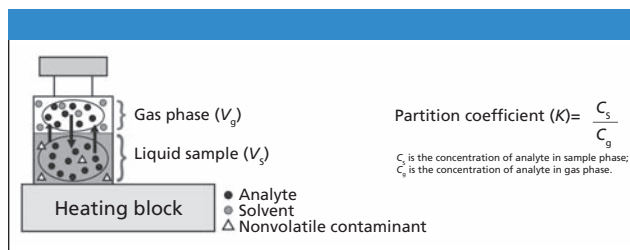


Figure 1.

Injection Techniques – Headspace vs. Direct Liquid

The main advantage of using headspace injection technique is that only the volatile portion of the sample is introduced into the column, thereby avoiding the non-volatile components that can damage the GC column and cause problems with the analysis. However, there are certain Class 2 solvents that are not detected via headspace injection, making liquid injections necessary (2).

Direct Liquid Injection

There are three forms of direct liquid injection: split, splitless, and on-column. Both splitless and on-column transfer the entire injected sample onto the column and both techniques provide high sensitivity. However, these techniques are not recommended when working with dirty samples because all of the contaminants will be transferred onto the column as well.

Split injection techniques significantly reduce the amount of contamination that enters the column and decreases the residence time of the sample in the injection port. The split ratio should be adjusted to reduce the amount of contamination that is injected onto the column while still achieving the required sensitivity limits.

In a liquid injection, a relatively small sample amount is introduced into a heated injection port where it is instantaneously vaporized. The resulting gas volume is referred to as the expansion volume and it is unique for each solvent. The volume of the sample should not exceed the volume of the GC liner because this can cause reproducibility problems.

Headspace Injection

To remain consistent with <467> methodology, headspace injection should be used whenever possible. Since many of the regulated solvents and drug components are more soluble in an organic solvent, an organic dilution solvent is usually recommended for the general method. Sample preparation

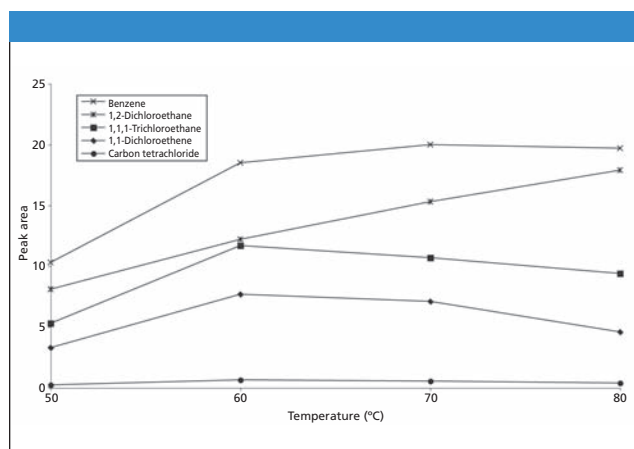


Figure 2.

using water should be made available for use with samples that are not miscible in organic solvents.

When working with headspace injection techniques, the sample matrix can significantly affect the quantitative performance of the GC method. In a given matrix, each analyte will have a unique partition coefficient (K), which is an equilibrium distribution of the analyte between the liquid phase and the gas phase (Figure 1).

Sensitivity is largely affected by the concentration of the analyte in the gas phase. To achieve the detection limits required by <467>, it is important to drive as much analyte out of solution into the headspace as possible. This can be done by (1) increasing the vial temperature, (2) increasing the equilibration time, and/or (3) adding matrix modifiers (salts) to increase the ionic strength of the solvent.

Experimental evidence has shown that increasing the temperature of the headspace vial above a certain level does not significantly increase the amount of analyte in the gas phase (Figures 2 and 3). The same is also true for the equilibration time, time points longer than 30 minutes are not necessary for many of the Class 1 and 2 solvents.

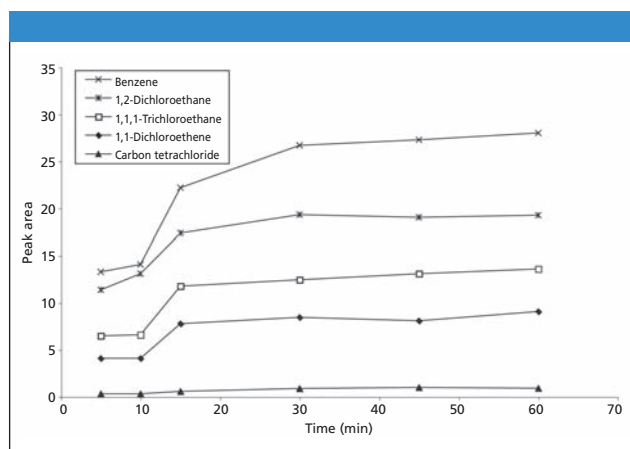


Figure 3.

Conclusion

The new USP regulations are aimed at improving patient safety and will need to be implemented for all existing or new products. Although the USP has provided a testing method that can be used to identify and quantitate Class 1 & 2 solvents, the method can be improved based on each company's needs.

The changes to the <467> monograph will not be official until July 2008, but it is important to start formulating a strategy now to become compliant. The USP, in partnership with Phenomenex, will be hosting a series of comprehensive hands-on courses to help people fully understand the new revisions and how to become compliant to the revised USP <467> methodology. For more information about these courses, or to learn about additional ways to become compliant, contact Ngoc Nguyen at ngocn@Phenomenex.com.

References

- (1) Osterberg, R.E. Impurities: Residual Solvents ICH: Q3C. 2007 USP/PDA Joint Conference, Maryland, 2007.
- (2) <467> Organic Volatile Impurities. General Notices and Requirements: Applying to Standards, Tests, Assays, and Other Specifications of the United States Pharmacopeia. 2007 USP/PDA Joint Conference, Maryland, 2007.

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