Enhanced Residual Solvents Analysis

Enhanced Residual Solvents Analysis: A Practical Approach to Sampling, Transport, Storage and Analysis.

Residual solvents are organic volatile chemicals used or produced in the manufacture of active pharmaceutical ingredients (API), excipients or drug products, which remain in the material at the end of the manufacturing process. Their control is important in limiting exposure and guidelines exist to maintain patient safety, not just to satisfy competent authorities.

It is a requirement that all pharmaceutical substances comply with ICH limits even if not required by individual monographs or if no compendial monograph exists.

The focus of this paper is the USP general chapter, however, the experience gained and enhancements proposed can be applied to all pharmacopeias complying with the ICH guidelines for residual solvents.

Sampling, Transport and Storage Prior to Analysis

The aim of residual solvents analysis is to obtain an understanding of the materials proposed for use in the production of pharmaceutical raw materials and the finished product itself. This means that the results must reflect the bulk at the point of sampling and not at the time of analysis. Results obtained for residual solvents, even when generated by motivated and competent analysts with the latest equipment and within a GMP environment are meaningless unless sample integrity prior to analysis has been maintained.

Obviously, a representative sample must be taken from the bulk material but such consideration, although of primary importance, is out-with the scope of this paper. When affected by sampling, transportation and storage, results will generally be lower than actual fact, due to evaporative losses prior to analysis. This must be avoided if the risk to the patient is not to be increased.

It is recommended that representative samples of bulk are taken quickly and directly into glass, gas-tight containers with PTFE lined closures to avoid volatile loss while leaving minimal headspace. Plastic constructions should be avoided since these can not only absorb solvents, leading to a falsely lower result, but can also impart solvent taints on the sample from the plastic itself. Too large a container void volume above the sample material will result in any volatiles present having an increased tendency to partition into this headspace and will not be included in the subsequent analytical procedure.

Ideally, samples should be transported under refrigerated conditions and container systems evaluated to ensure that closures do not lose integrity under cooling. Samples should remain refrigerated at the testing laboratory and be carefully equilibrated to room temperature prior to analysis. This will avoid condensation of moisture which could affect sample weighing during the analytical procedure.

Obviously analysis should be initiated as soon as possible after sampling and good communication of proposed sample submission to an external laboratory is vital to this end.

The Problems:

The USP Residual Solvents general chapter includes methods based on GC headspace analysis. A full description and evaluation of is not intended here. The discussion which follows is focused on enhancements which have been applied to the basic sample preparation schemes outlined in the USP, in order to negate some significant problems, including the following:

Aqueous dilutions of hydrophobic solvents used in the preparation of working standards. This practice has led to some laboratories reporting that the method is not sensitive enough, especially for the critical class 1 components. The "lack of sensitivity" is in fact due to evaporative losses suffered during the preparation by serial dilution.

The USP default for analysis of water insoluble materials, is to use non-polar solvents, however, many substances e.g. Magnesium Stearate are not soluble in these, leading to gross inaccuracy when diluting solutions containing insoluble material.

Not all manufacturers of G43 phase columns, stipulated in the procedure, meet the resolution system suitability requirements of the method.

The inaccuracy of using water calibrated glass pipettes for preparing reference standard solutions.

The Solutions:

The following proposals were delivered to an audience of the Joint Pharmaceutical Analysis Group (JPAG) at the invitation of the USP.

Reduced Sensitivity due to Volatile Loss

Even a brief comparison of the two schemes in Figure 1 and 2 below for the water soluble articles imparts the overall simplicity of the enhanced approach. Comparing the preparation of the Class 1 working standards from the Class 1 Mix RS the following can be noted:-

The USP scheme (Figure 1.) involves 1ml of USP Class 1 RS containing the critical non-polar solvents (e.g. Benzene) being added to 9ml of DMSO contained in a 100ml flask and making to volume with water. A further 1ml to 100ml dilution with water follows. A dilution of 1ml to 10ml with water is then made. Finally 1ml of the resultant solution is added to a headspace vial containing 5ml of water ready for analysis. This scheme has four steps of serial aqueous dilution with evaporative losses at every stage. The prudent but unsuspecting analyst of course gives each volumetric many inversions with each step, driving the volatiles into the headspace which are then omitted from analysis.

The enhanced scheme (Figure 2.), however, involves 1ml of USP Class 1 RS being dissolved and diluted to 100ml with DMSO. 1ul of the resultant solution is then inoculated directly into 6ml of water contained in a headspace vial ready for analysis after immediate capping. This halves the number of steps required and most significantly excludes water dilution until the final addition directly to the analytical vial. The use of calibrated syringes with positive displacement action for volumetric transfer also negates the inaccuracy of using standard laboratory water calibrated glass pipettes with DMSO.

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Similar enhancements to the sample preparation scheme for water insoluble articles have resulted in comparable improvements, especially in accuracy.

Figure 1. The USP Water Soluble Articles Procedure

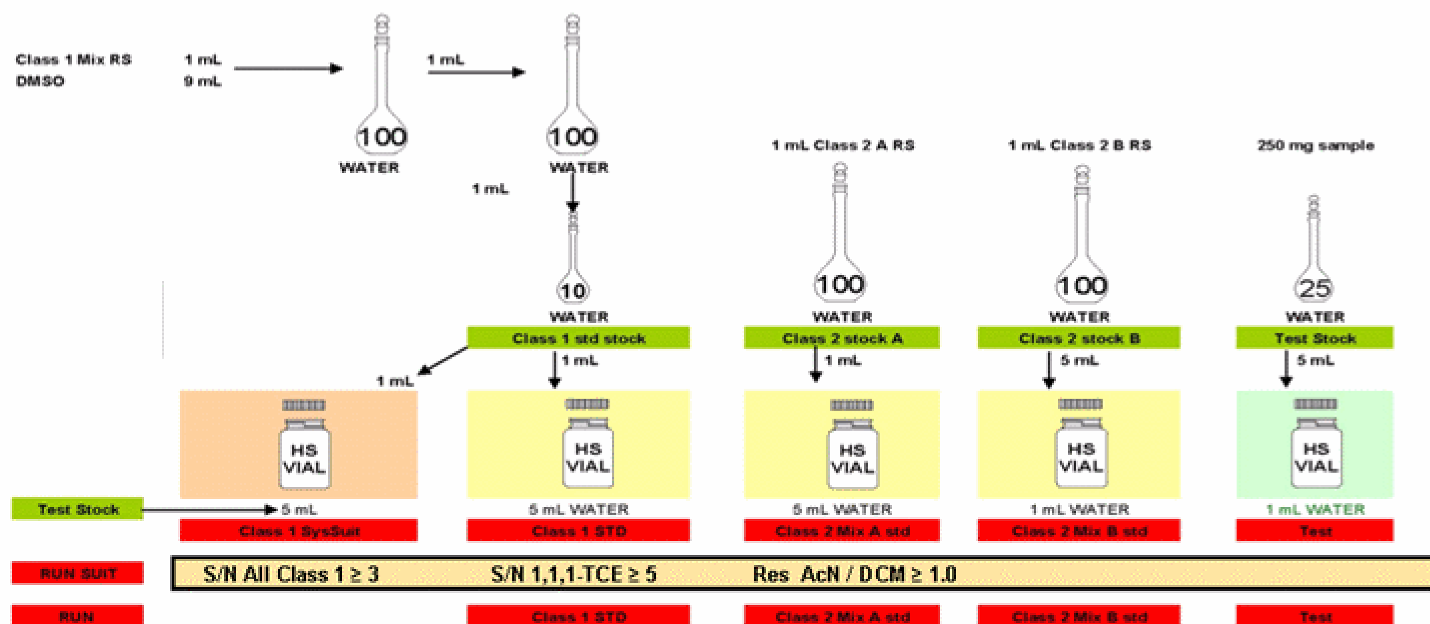
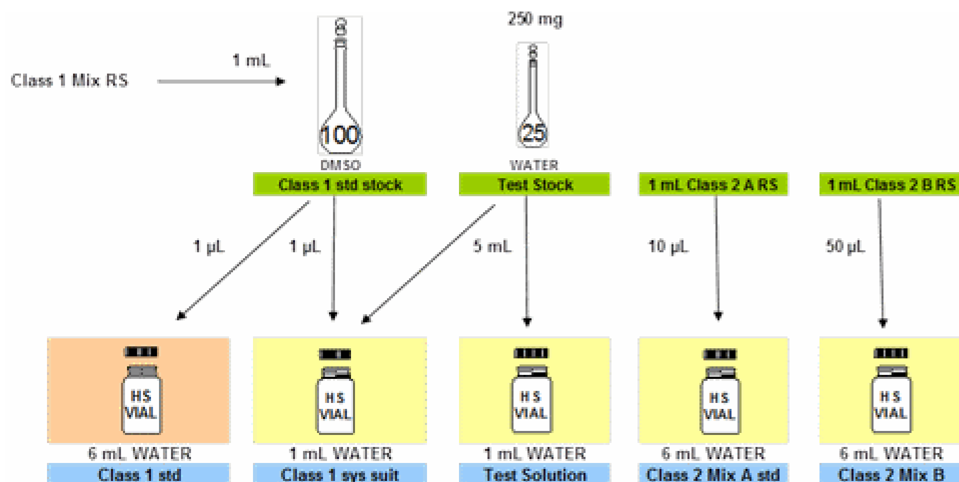


Figure 2. The Enhanced Water Soluble Articles Procedure



The Use of Non-Polar Solvents for the Preparation of Water Insoluble Substances

The problem noted for substances which are water and DMF (USP default) insoluble, stems from the USP preparation scheme which attempt to disperse 500mg of sample made up in a 10ml volumetric flask. This is followed by transfer of multiple 1ml sub-aliquots to a number of required solutions in separate headspace vials.

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For specific substances such as Magnesium Stearate, mentioned above, the ability to obtain several headspace vials containing precisely the same mass of sample using this procedure is simply impossible. It is also likely that the analyst will over-mix in an attempt to disperse the non-soluble sample material and will produce evaporative loss of residual solvents present into the headspace of the volumetric flask.

The enhanced procedure proposed simply weighs 50mg of sample directly into each of the required headspace vials with solvent then being added before immediate capping. Sample homogeneity concerns raised by the smaller sample size are addressed by assessment of the precision of agreement following duplicate analysis.

Choice of USP G43 Column Phase

At the heart of the GC analysis is the analytical column. Chromatographic problems are solved in 90% of cases by the selection of the correct column in good condition. In the case of headspace analysis in general, detrimental chromatographic effects caused by direct injection are not significant because the sample is already in the vapour phase on entering the injector and does not undergo flash expansion. This means that the choice of column is fundamental.

The chemistry of the USP G43 stationary phase is based on 6% Cyanopropylphenyl, 94% Dimethyl Polysiloxane, however, all column manufacturers use slightly different bonding chemistries. It is also the case that different cross-linking molecules are added in order to increase the thermal stability of the stationary phase film. Unfortunately, such modifications can have a significant effect on chromatographic performance. Manufacturers do not publish precise details but it is clear that the G43 is a generic label applied to many slightly different phases.

Butterworth Laboratories has beta-tested proposed new G43 variants from two manufacturers and completed an extensive selection process before implementing the use of those which fully satisfy system suitability requirements. The USP allows a column dimension choice of either a 0.32-mm × 30-m column coated with a 1.8-µm layer of phase G43 or a 0.53-mm × 30-m wide-bore column coated with a 3.0-µm layer of phase G43.

Given this allowed choice, it is surprising that no 0.53mm column was found to comply with the required system suitability in terms of resolution of class 1 components benzene and 1,2-dichloroethane. The 0.53mm columns tested also gave lower sensitivity due to band broadening. After much trial, the only column which met all requirements was a 0.32mm column from one specific manufacturer.

The chromatographic performance of USP compliant G43 columns can differ to the extreme. An example of the chromatography obtained for the Class 1 USP RS using two different G43 columns is shown in the following two chromatograms (Figures 3 and 4).

The second chromatogram illustrates not only the higher efficiency of specific VF-624 phases with respect to the resolution of peaks 4 and 5 but also that the signal to noise ratio of Carbon Tetrachloride is greatly enhanced with the application of the Butterworth modified preparation scheme.

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Figure 3: Class 1 std. USP Preparation. Column: Phase G43 – 30m x 0.32mm x 1.8µm

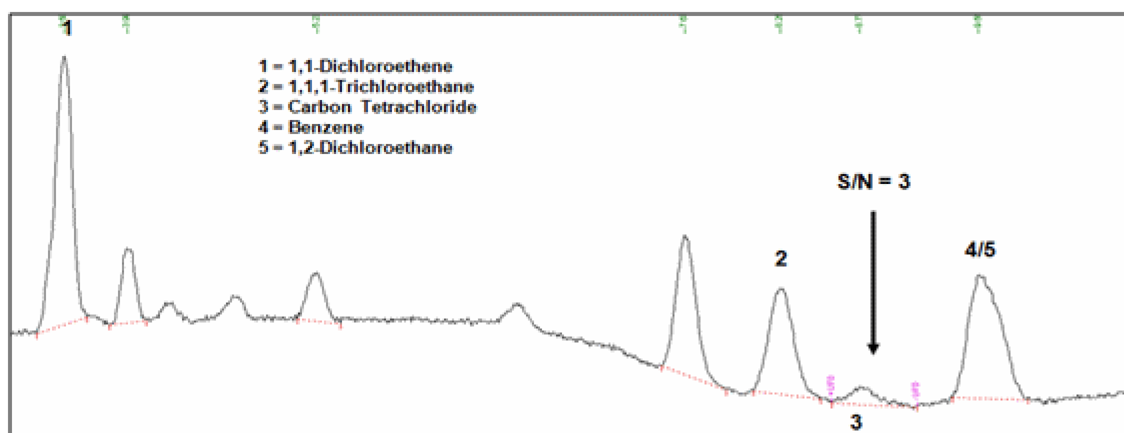
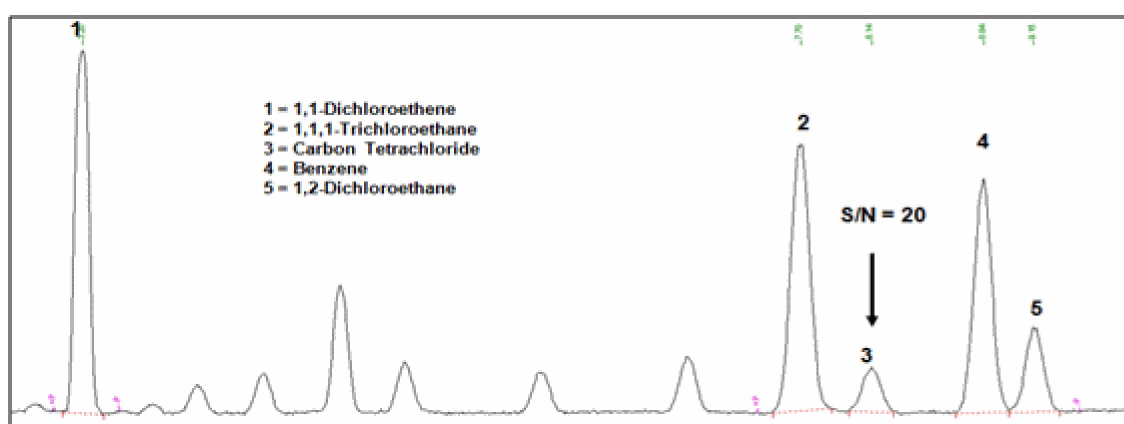


Figure 4: Class 1 std. Butterworth Laboratories Preparation. Column: VF-624ms 30m x 0.32mm x 1.8µm



Compliance of Proposed USP Enhancements

The prescription of analytical solutions required in USP monographs, is now given in terms of concentration of the component of interest in a specified solvent, rather than giving a specific dilution scheme. It is clear however that any measurements made in the preparation of solutions must be carried out in accordance with precision and accuracy requirements of USP general chapters.

All of the final analytical solutions prepared using the enhanced USP procedures are identical in concentration and final composition to solutions prepared by the published USP dilution schemes. Alternative but equivalent dilution schemes have always been allowed by guidance given in the general chapters of the USP. This has been confirmed to the author in writing by the FDA.

The enhancements proposed are not therefore considered to be deviations. In practice, due to the simpler preparation schemes with related reduction of volatile loss, a significant improvement in accuracy has been demonstrated.

Benefits Beyond Accuracy

Because the enhanced procedures are simpler and require less individual dilutions steps, there are obvious time saving benefits. It is also likely that there will be a significant reduction in non-conforming analysis, reducing time consuming and costly investigations due to errors resulting from the un-necessarily more intense USP procedures.

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Author Biography

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Frank started his career at Kings and Co Ltd as a Senior Technician before joining Berridge Environmental Labs as Organic Analysis Team Leader in 1990. After a short spell with Pharmaco LSR in their Department of Aquatic Toxicology Studies, he joined the Chromatography Department of Butterworth Laboratories in 1994 and has progressed through various roles to his current position.

Frank has spoken at JPAG meetings on Organic Volatile Impurities analysis and has been trained in preparing expert witness statements

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