RESIDUAL SOLVENTS

IDENTIFICATION, CONTROL, AND QUANTIFICATION OF RESIDUAL SOLVENTS

Whenever possible, the substance under test needs to be dissolved to release the residual solvent. Because the USP deals with drug products, as well as active ingredients and excipients, it may be acceptable that in some cases some of the components of the formulation will not dissolve completely. In those cases, the drug product may first need to be pulverized into a fine powder so that any residual solvent that may be present can be released. This operation should be as fast as possible to prevent the loss of volatile solvents during the procedure.

NOTE—The organic-free water specified in the following procedures produces no significantly interfering peaks when chromatographed.

Class 1 and Class 2 Residual Solvents

The following procedures are useful to identify and quantify residual solvents when the information regarding which solvents are likely to be present in the material is not available. When the information about the presence of specific residual solvents is available, only Procedure C is needed to quantify the amount of residual solvents present.

WATER-SOLUBLE ARTICLES

Procedure A—

Class 1 Standard Stock Solution—Transfer 1.0 mL of USP Class 1 Residual Solvents Mixture RS to a 100-mL volumetric flask, add 9 mL of dimethyl sulfoxide, dilute with water to volume, and mix. Transfer 1.0 mL of this solution to a 100-mL volumetric flask, dilute with water to volume, and mix. Transfer 1.0 mL of this solution to a 10-mL volumetric flask, dilute with water to volume, and mix.

Class 1 Standard Solution—Transfer 1.0 mL of Class 1 Standard Stock Solution to an appropriate headspace vial, add 5.0 mL of water, apply the stopper, cap, and mix.

Class 2 Standard Stock Solutions—Transfer 1.0 mL of USP Residual Solvents Class 2—Mixture A RS to a 100-mL volumetric flask, dilute with water to volume, and mix. This is Class 2 Standard Stock Solution A. Transfer 1.0 mL of USP Residual Solvents Class 2—Mixture B RS to a 100-mL volumetric flask, dilute with water to volume, and mix. This is Class 2 Standard Stock Solution B.

Class 2 Mixture A Standard Solution—Transfer 1.0 mL of Class 2 Standard Stock Solution A to an appropriate headspace vial, add 5.0 mL of water, apply the stopper, cap, and mix.

Class 2 Mixture B Standard Solution—Transfer 5.0 mL of Class 2 Standard Stock Solution B to an appropriate headspace vial, add 1.0 mL of water, apply the stopper, cap, and mix.

Test Solution—Transfer about 250 mg of the article under test, accurately weighed, to a 25-mL volumetric flask, dissolve in and dilute with water to volume, and mix.

Test Solution—Transfer 5.0 mL of Test Solution to an appropriate headspace vial, add 1.0 mL of water, apply the stopper, cap, and mix.

Class 1 System Suitability Solution—Transfer 1.0 mL of Class 1 Standard Stock Solution to an appropriate headspace vial, add 5.0 mL of Test Stock Solution, and apply the stopper, cap, and mix.

Chromatographic System (see Chromatography (621))—The gas chromatograph is equipped with a flame-ionization detector, a 0.32-mm × 30-m fused-silica 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. The carrier gas is nitrogen or helium with a linear velocity of about 35 cm per second, and a split ratio of 1:5. [NOTE—Split ratio can be modified in order to optimize sensitivity.] The column temperature is maintained at 40° for 20 minutes, then raised at a rate of 10° per minute to 240°, and maintained at 240° for 20 minutes. The injection port and detector temperatures are maintained at 140° and 250°, respectively. Chromatograph the Class 1 Standard Solution, Class 1 System Suitability Solution, and Class 2 Mixture A Standard Solution, and record the peak responses as directed for Procedure: the signal-to-noise ratio of 1,1,1-trichloroethane in the Class 1 Standard Solution is not less than 5; the signal-to-noise ratio of each peak in the Class 1 System Suitability Solution is not less than 3; and the resolution, R, between acetonitrile and methylene chloride in the Class 2 Mixture A Standard Solution is not less than 1.0.

Procedure—Separately inject (following one of the headspace operating parameter sets described in the table below) equal volumes of headspace (about 1.0 mL) of the Class 1 Standard Solution, Class 2 Mixture A Standard Solution, Class 2 Mixture B Standard Solution, and the Test Solution into the chromatogram, record the chromatograms, and measure the responses for the major peaks. If a peak response of any peak, other than a peak for 1,1,1-trichloroethane, in the Test Solution is greater than or equal to a corresponding peak in either the Class 1 Standard Solution or either of the two Class 2 Mixture Standard Solutions, or a peak response of 1,1,1-trichloroethane is greater than or equal to 150 times the peak response corresponding to 1,1,1-trichloroethane in the Class 1 Standard Solution, proceed to Procedure B to verify the identity of the peak; otherwise the article meets the requirements of this test.

Table 5. Headspace Operating Parameters

<table>
<thead>
<tr>
<th>Headspace Operating Parameter Sets</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equilibration temperature (°)</td>
<td>80</td>
<td>105</td>
<td>80</td>
</tr>
<tr>
<td>Equilibration time (min.)</td>
<td>60</td>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td>Transfer-line temperature (°)</td>
<td>85</td>
<td>110</td>
<td>105</td>
</tr>
<tr>
<td>Carrier gas: nitrogen or helium at an appropriate pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pressurization time (s)</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Injection volume (mL)</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Procedure B—

Class 1 Standard Stock Solution, Class 1 Standard Solution, Class 2 Standard Stock Solutions, Class 2 Mixture A Standard Solution, Class 2 Mixture B Standard Solution, Test Stock Solution, Test Solution, and Class 1 System Suitability Solution—Prepare as directed for Procedure A. [NOTE—Split ratio can be modified in order to optimize sensitivity.] The column temperature is maintained at 50° for 20 minutes, then raised at a rate of 6° per minute to 165°, and maintained at 165° for 20 minutes. The injection port and detector temperatures are maintained at 140° and 250°, respectively. Chromatograph the Class 1 Standard Solution and the Class 1 System Suitability Solution, and record the peak responses as directed for Procedure: the signal-to-noise ratio of benzene in the Class 1 Standard Solution is not less than 5; the signal-to-noise ratio of each peak in the Class 1 System Suitability Solution is not less than 3; and the resolution, R, between acetonitrile and dichloroethane in the Class 2 Mixture A Standard Solution is not less than 1.0.
WATER-INSOLUBLE ARTICLES

Procedure A—[NOTE—Dimethyl sulfide may be substituted as an alternative solvent to dimethylformamide.]

Class 1 Standard Stock Solution—Transfer 1.0 mL of USP Class 1 Residual Solvents Class 2—Mixture A RS to a 100-mL volumetric flask previously filled with about 80 mL of dimethylformamide, dilute with dimethylformamide to volume, and mix. Transfer 1.0 mL of this solution to a 100-mL volumetric flask, previously filled with about 80 mL of dimethylformamide, dilute with dimethylformamide to volume, and mix. [NOTE—Reserve a portion of this solution for the Class 1 System Suitability Solution.] Transfer 1.0 mL of this solution to a 10-mL volumetric flask, dilute with dimethylformamide to volume, and mix.

Class 1 Standard Solution—Transfer 1.0 mL of Class 1 Standard Stock Solution to an appropriate headspace vial, containing 5.0 mL of water, apply the stopper, cap, and mix.

Class 2 Standard Stock Solutions—Transfer 1.0 mL of USP Residual Solvents Class 2—Mixture A RS to a 100-mL volumetric flask, previously filled with about 80 mL of dimethylformamide, dilute with dimethylformamide to volume, and mix. This is Class 2 Standard Stock Solution A. Transfer 0.5 mL of USP Residual Solvents Class 2—Mixture B RS to a 10-mL volumetric flask, dilute with dimethylformamide to volume, and mix. This is Class 2 Standard Stock Solution B.

Class 2 Mixture A Standard Solution—Transfer 1.0 mL of Class 2 Standard Stock Solution A to an appropriate headspace vial, containing 5.0 mL of water, apply the stopper, cap, and mix.

Class 2 Mixture B Standard Solution—Transfer 1.0 mL of Class 2 Standard Stock Solution B to an appropriate headspace vial, containing 5.0 mL of water, apply the stopper, cap, and mix.

Test Solution—Transfer about 500 mg of the article under test, accurately weighed, to a 10-mL volumetric flask, dissolve in and dilute with dimethylformamide to volume, and mix.

Test Solution—Transfer 1.0 mL of the Test Stock Solution to an appropriate headspace vial, containing 5.0 mL of water, apply the stopper, cap, and mix.

Class 1 System Suitability Solution—Mix 5 mL of the Test Stock Solution with 0.5 mL of the intermediate dilution reserved from Class 1 System Suitability Solution, and transfer 1.0 mL of this solution to an appropriate headspace vial, containing 5.0 mL of water, apply the stopper, cap, and mix.

Chromatographic System (see Chromatography (621)).—The gas chromatograph is equipped with a flame-ionization detector, a 0.53-mm × 30-m wide-bore column coated with a 3.0-μm layer of phase G43 or a 0.53-mm × 30-m wide-bore column coated with a 0.3-μm layer of phase G43. The carrier gas is nitrogen or helium with a linear velocity of about 35 cm per second, and a split ratio of 1:5. [NOTE—Split ratio can be modified in order to optimize sensitivity.] The column temperature is maintained at 40° for 20 minutes, then raised at a rate of 10° per minute to 240°, and maintained at 240° for 20 minutes. The injection port and detector temperatures are maintained at 140° and 250°, respectively. Chromatograph the Class 1 Standard Solution, the Class 1 System Suitability Solution, and the Class 2 Mixture A Standard Solution, and record the peak responses as directed for Procedure A. The column temperature is maintained at 40° for 20 minutes, then raised at a rate of 10° per minute to 240°, and maintained at 240° for 20 minutes. The injection port and detector temperatures are maintained at 140° and 250°, respectively. Chromatograph the Class 1 Standard Solution, Class 1 System Suitability Solution, and Class 2 Mixture A Standard Solution, and record the peak responses as directed for Procedure A. The column temperature is maintained at 40° for 20 minutes, then raised at a rate of 10° per minute to 240°, and maintained at 240° for 20 minutes. The injection port and detector temperatures are maintained at 140° and 250°, respectively. Chromatograph the Class 1 Standard Solution, Class 1 System Suitability Solution, and Class 2 Mixture A Standard Solution, and record the peak responses as directed for Procedure A. The column temperature is maintained at 40° for 20 minutes, then raised at a rate of 10° per minute to 240°, and maintained at 240° for 20 minutes. The injection port and detector temperatures are maintained at 140° and 250°, respectively. Chromatograph the Class 1 Standard Solution, Class 1 System Suitability Solution, and Class 2 Mixture A Standard Solution, and record the peak responses as directed for Procedure A.

Procedure—Separately inject (following one of the headspace operating parameter sets described in Table 5) equal volumes of headspace (about 1.0 mL) of the Class 1 Standard Solution, the Class 2 Mixture A Standard Solution, the Class 2 Mixture B Standard Solution, and the Test Solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the amount, in ppm, of each residual solvent found in the article under test by the formula:

\[5(C/W)(r_i/(r_{CV} - r_i))\]

where C is the concentration, in μg per mL, of the appropriate USP Reference Standard in the Standard Solution; W is the weight, in g, of the article under test taken to prepare the Test Stock Solution; and \(r_{CV}\) and \(r_i\) are the peak responses of each residual solvent obtained from the Test Solution and the Spiked Test Solution, respectively.
Procedure B—
Class 1 Standard Stock Solution, Class 1 Standard Solution, Class 1 System Suitability Solution, Class 2 Standard Stock Solutions, Class 2 Mixture A Standard Solution, and Class 2 Mixture B Standard Solution, Test Stock Solution, and Test Solution—Proceed as directed for Procedure A.

Chromatographic System—Proceed as directed for Procedure B under Water-Soluble Articles with a split ratio of 1:3. [NOTE—Split ratio can be modified in order to optimize sensitivity.]

Procedure—Separately inject (use headspace operating parameters 3 in Table 5 with a vial pressure of 10 psi) equal volumes of headspace (about 1.0 mL) of the Class 1 Standard Solution, Class 2 Mixture A Standard Solution, Class 2 Mixture B Standard Solution, and the Test Solution, into the chromatograph, record the chromatograms, and measure the responses for the major peaks. If the peak responses in the Test Solution of the peak(s) identified in Procedure A is/are greater than or equal to a corresponding peak(s) in either the Class 1 Standard Solution or any of the two Class 2 Mixture Standard Solutions, proceed to Procedure C to quantify the peak(s); otherwise the article meets the requirements of this test.

Procedure C—
Class 1 Standard Stock Solution, Class 1 Standard Solution, Class 1 System Suitability Solution, Class 2 Standard Stock Solution A, and Class 2 Mixture A Standard Solution—Proceed as directed for Procedure A.

Standard Stock Solution—[NOTE—Prepare a separate Standard Solution for each peak identified and verified by Procedures A and B.] Transfer an accurately measured volume of each individual USP Reference Standard corresponding to each residual solvent peak identified and verified by Procedures A and B to a suitable container, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a final concentration of 1/20 of the value stated in Table 1 or Table 2 (under Concentration Limit).

Standard Solution—Transfer 1.0 mL of the Standard Stock Solution to an appropriate headspace vial, containing 5.0 mL of water, apply the stopper, cap, and mix.

Test Stock Solution—Proceed as directed for Procedure A.

Test Solution—Transfer 1.0 mL of the Test Stock Solution to an appropriate headspace vial, containing 5.0 mL of water, apply the stopper, cap, and mix.

Spiked Test Solution—[NOTE—Prepare a separate Spiked Test Solution for each peak identified and verified by Procedures A and B.] Transfer 1.0 mL of the Test Stock Solution to an appropriate headspace vial, add 1 mL of the Standard Stock Solution and 4.0 mL of water, apply the stopper, cap, and mix.

Chromatographic System—Proceed as directed for Procedure C under Water-Soluble Articles.

Procedure—Separately inject (use headspace operating parameters 3 in Table 5 with a vial pressure of 10 psi) equal volumes of headspace (about 1.0 mL) of the Standard Solution, the Test Solution, and the Spiked Test Solution into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the amount, in ppm, of each residual solvent found in the article under test by the formula:

\[
10 \left( \frac{C}{W} \right) \frac{r_{ST}}{r_{U}} \left( \frac{r_{ST} - r_{i}}{r_{U}} \right)
\]

in which C is the concentration, in µg per mL, of the appropriate USP Reference Standard in the Standard Solution; W is the weight, in g, of the article under test taken to prepare the Test Solution and the Spiked Test Solution, respectively.

Class 3 Residual Solvents

*If Class 3 solvents are present, the level of residual solvents may be determined as directed under Loss on Drying (731) when the monograph for the article under test contains a loss on drying procedure, or a specific determination of the solvent may be made. If there is no loss on drying procedure in the monograph for the article under test or if a Class 3 solvent limit in an individual monograph is greater than 50 mg per day (corresponding to 5000 ppm or 0.5% under Option 1), the individual Class 3 residual solvent or solvents present in the article under test should be identified and quantified, and the procedures as described above, with appropriate modifications to the standard solutions, are to be applied wherever possible. Otherwise an appropriate validated procedure is to be employed. *USP Reference Standards, when available, should be used in these procedures. A flow diagram for the application of residual solvent limit tests is shown in Figure 1.
Figure 1. Diagram relating to the identification of residual solvents and the application of limit tests.