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RESIDUAL SOLVENTS METHOD FOR D-GALACTOSE

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1. **PURPOSE:**

   1.1. To provide a procedure for the assessment of Residual Solvent Analysis for solvents in compliance with USP<467> and <1467> for Galactose.

2. **SCOPE:**

   2.1. This method applies to the analysis of residual solvents in water and in 10% w/v solutions of Galactose.

3. **RESPONSIBILITIES:**

   3.1. The Quality Control Manager, or other qualified designated individual, is responsible for the control, implementation, training, and maintenance of this Protocol.
   3.2. The QC Analysts are responsible for complying with the requirements of this method.
   3.3. If any abnormalities are determined during routine use or during calibration, the QC Manager shall be promptly notified. If necessary, the GC-FID will be serviced.

4. **REFERENCES:**

   4.1. BSI-RPT-0781, Analytical Method Validation Report: Aqueous Soluble Residual Solvents USP 1467- Galactose
   4.2. BSI-SOP-0098, Balance SOP
   4.3. BSI-SOP-0126, Laboratory Notebooks
   4.4. BSI-SOP-0134, Pipette SOP
   4.5. BSI-SOP-0316, Shimadzu QP2010S GC SOP
   4.6. BSI-SOP-0436, Analytical Methods Validation Master Plan
   4.7. ICH Q3A
   4.8. USP NF <467>
   4.9. USP NF <621>
   4.10. USP NF <1467>

5. **MATERIALS AND EQUIPMENT:**

   5.1. Equipment
      5.1.1. Analytical Balance
      5.1.2. Shimadzu QP2010S GC/MS with FID Detector
   5.2. Reagents/Reference Standards
      5.2.1. Galactose
      5.2.2. Purified Water/MilliQ Water (Type 1 Ultrapure)
      5.2.3. Methanol Reference Standard
      5.2.4. Ethanol (SDA 3C)
      5.2.5. 2-Propanol (IPA)
      5.2.6. Methyl Isobutyl Ketone (MIBK)
   5.3. Consumable Supplies
      5.3.1. 20mL vertex Headspace Vial
      5.3.2. Verex Seal Vial Cap
      5.3.3. 150mL Beakers
      5.3.4. Volumetric Flasks, Class A
      5.3.5. Vesel Graphite Ferrule
      5.3.6. Metal Encapsulated Vespel Graphite Ferrule

Method Parameters

HS-20	
Parameter	**Requirement**
Oven Temperature	80.0°C
Sample Line Temperature	150.0°C
Transfer Line Temperature	155.0°C
Shaking Level	1
Injection Count	1
Pressurizing Gas	176.2 kPa
Equilibrating Time	15.00 min.
Pressurization Time	0.50 min.
Pressure Equilibration Time	0.50 min.
Load Time	1.00 min.
Load Equilibration Time	0.50 min.
Injection Time	1.00 min.
Needle Flush Time	1.00 min.
GC Cycle Time	7.00 min.
Check System Ready	Off
Extended System Ready Check	Off
Check GC Ready	Off
Extended GC Ready Check	Off
Needle Check	Yes
Action on Leak Check Error	Stop
Action with No Vial in Tray	Stop
GC-2010	
Column Oven Temperature	80.0°C
Injection Mode	Split
Flow Control Mode	Linear Velocity
Pressure	176.2 kPa
Total Flow	50.7 mL/min.
Column Flow	2.32 mL/min.
Linear Velocity	47.6 cm/sec

GC-2010		
Purge Flow	2.0mL/min.	
Split Ratio	20	
High Pressure Injection	Off	
Carrier Gas Saver	Off	
Splitter Hold	Off	
Oven Temp Program		
Rate °C per min	Temperature °C	Hold Time (min)
--	80.0	6.00
Ready Checks		
Column Oven	Yes	
HS	No	
FID	Yes	
HS Carrier	Yes	
HS Purge	Yes	
APC1	Yes	
FID Makeup	Yes	
FID1 H2	Yes	
FID1 Air	Yes	
External Wait	No	
Auto Flame On	Yes	
Auto Flame Off	Yes	
Reignite	Yes	
Auto Zero After Ready	Yes	
Equilibrium Time	3.0 min.	
CRG (INJ)	Off	
APC1	176.2kPa	

6. PROCEDURE:

6.1. Residual Solvent Stock Solutions:

6.1.1. Prepare individually a 1,000mg/L (ppm) solution of Methanol, Ethanol (SDA 3C), and Methyl Isobutyl Ketone (MIBK) in purified water by weighing approximately 0.50g of standard directly into a 500mL volumetric flask and dilute to volume. Mix thoroughly. Calculate actual concentrations based off CoA/purity.

6.1.2. Prepare individually a 10,000mg/L (ppm) solution of 2-Propanol (IPA) in purified water by weighing 0.50g of standard directly into a 50mL volumetric flask and dilute to volume. Calculate actual concentrations based off CoA/purity.

6.1.2.1. Note: SDA 3C also contains ~5% of IPA and needs to be factored for the total IPA Concentration.

6.1.3. Stock Solution Concentration Calculation:

$$\text{Stock Solution Concentration (ppm)} = \frac{(Solution\ weight\ (mg)}{Stock\ Solution\ Volume\ (L)} \text{ x } CoA\ Purity$$

6.2. Calibration Standard Preparation:

6.2.1. Calibration Standard 1: 0 ppb (Blank): Purified Water or equivalent.

6.2.2. Calibration Standard 2 (50% Level):

6.2.2.1. In a 100mL volumetric flask add the following:

6.2.2.1.1. 0.50mL of 1,000ppm Methanol Stock Solution
6.2.2.1.2. 2.50mL of 1,000ppm Ethanol (SDA 3C) Stock Solution
6.2.2.1.3. 2.50mL of 1,000ppm MIBK Stock Solution
6.2.2.1.4. 2.50mL of 10,000ppm IPA Stock Solution

6.2.2.2. Dilute to volume with purified water and mix thoroughly.

6.2.3. Calibration Standard 3 (80% Level):

6.2.3.1. In a 100mL volumetric flask add the following:

6.2.3.1.1. 0.80mL of 1,000ppm Methanol Stock Solution
6.2.3.1.2. 4.00mL of 1,000ppm Ethanol (SDA 3C) Stock Solution
6.2.3.1.3. 4.00mL of 1,000ppm MIBK Stock Solution
6.2.3.1.4. 4.00mL of 10,000ppm IPA Stock Solution

6.2.3.2. Dilute to volume with purified water and mix thoroughly.

6.2.4. Calibration Standard 4 (100% Level):

6.2.4.1. In a 100mL volumetric flask add the following:

6.2.4.1.1. 1.00mL of 1,000ppm Methanol Stock Solution
6.2.4.1.2. 5.00mL of 1,000ppm Ethanol (SDA 3C) Stock Solution
6.2.4.1.3. 5.00mL of 1,000ppm MIBK Stock Solution
6.2.4.1.4. 5.00mL of 10,000ppm IPA Stock Solution

6.2.4.2. Dilute to volume with purified water and mix thoroughly.

6.2.5. Calibration Standard 5 (120% Level):

6.2.5.1. In a 100mL volumetric flask add the following:

6.2.5.1.1. 1.20mL of 1,000ppm Methanol Stock Solution
6.2.5.1.2. 6.00mL of 1,000ppm Ethanol (SDA 3C) Stock Solution
6.2.5.1.3. 6.00mL of 1,000ppm MIBK Stock Solution
6.2.5.1.4. 6.00mL of 10,000ppm IPA Stock Solution

6.2.5.2. Dilute to volume with purified water and mix thoroughly.

6.2.6. Calibration Standard 5 (150% Level):

6.2.6.1. In a 100mL volumetric flask add the following:

6.2.6.1.1. 1.50mL of 1,000ppm Methanol Stock Solution

6.2.6.1.2. 7.50mL of 1,000ppm Ethanol (SDA 3C) Stock Solution
6.2.6.1.3. 7.50mL of 1,000ppm MIBK Stock Solution
6.2.6.1.4. 7.50mL of 10,000ppm IPA Stock Solution
6.2.6.2. Dilute to volume with purified water and mix thoroughly.

6.2.7. Calibration Standard Concentration Calculation:

$$\text{Standard Concentration (ppm)} = \frac{(Stock\ Solution\ Concentration\ (\frac{mg}{L}))(Volume\ of\ Stock\ solution\ (mL))}{100\ mL}$$

6.2.8. Calibrate the GC-FID instrument using calibration levels 1-6 by pipetting 10mL of the blank and each standard to headspace vials. Crimp to seal, mix thoroughly.
6.2.8.1. An r^2 of NLT 0.95 is required for each solvent of interest.

6.3. **Sample Preparation**
6.3.1. Weigh approximately 1.0g of the sample to a head space vial.
6.3.2. Add 10mL of purified water to the head space vial.
6.3.3. Crimp to Seal, mixed thoroughly.
6.3.4. Enter the dilution factor: 10 in the software
6.3.5. Report the results.

7. REPORTING:

7.1. For Methanol, determined during the method validation, the method LOQ is the 80% calibration level after applying the dilution factor.
7.1.1. For analysis results: Report any value below this value as less than the 80% calibration standard concentration multiplied by the dilution factor of the sample.
7.1.2. For values greater than the 80% calibration standard concentration multiplied by the dilution factor of the sample, report the result to 1 decimal place.
7.2. For Ethanol, MIBK, and IPA determined during the method validation, the method LOQ is the 50% calibration level after applying the dilution factor.
7.2.1. For analysis results: Report any value below this value as less than the 50% Calibration standard concentration multiplied by the dilution factor of the sample.
7.2.2. For values greater than the 50% calibration standard concentration multiplied by the dilution factor of the sample, report the result to 1 decimal place.