RESIDUAL SOLVENT METHOD

FOR

DURACOR TABLETS

BY GAS CHROMATOGRAPHY

METHOD APPROVALS

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INTRODUCTION

The level of solvent used in the manufacturing of a pharmaceutical product used must be controlled to levels that are safe and have no adverse effect upon the stability or the performance of the drug. The residual solvent testing of Duracor tablets will be determined by gas chromatography (GC). GC is a separation technique that uses pressurized helium gas (mobile phase) flowing past a liquid (stationary phase) coated onto the internal walls of a capillary tube to separate complex mixtures of volatile substances such as organic solvents. Solvents present in the sample are vaporized above their boiling point before entering the capillary tube at a controlled temperature where they separate based upon the magnitude of their boiling point and/or their relative attraction to the stationary liquid. As each solvent passes out of the capillary, they are detected and quantitated by a flame ionization detector.

Acetone (dimethyl ketone, $(CH_3)_2C = O$) is used in the manufacture of Duracor Tablets. The acetone is removed from the powder mixture by drying at elevated temperature before the powder is compressed into tablets. The acetone must be removed to a level of not ore than 0.5%. To determine the level of acetone in Durocor, two tablets will be dissolved in water, a portion of which is filtered and then injected into the gas chromatograph. By comparing the acetone response of the sample solution to that of a solution of known concentration of acetone (standard solution), the amount of acetone in tablets is calculated.

TEST METHOD

Residual solvent method in Norvin Pharma monograph "Duracor", current version.

2.1 Instrumentation and Conditions:

Column: 30 m x 0.53 mm I.D capillary coated with 4% cyanophenylmethylsilicone polymer
Column Temperature: 40º C
Injector Temperature: 125º C
Detector: Flame Ionization
Detector Temperature: 250º C
Carrier Gas: Helium, 50 cm/sec
Split Flow Rate: 100 mL/minute
Injection Volume: 1.0 µL
Sample Solvent: Deionized water

2.2 Solution Preparation:

Resolution Solution (0.3 mg/mL)

1. Place approximately 2 mL of water into a weighing vial and place it on a balance and tare.
2. Fill a 1 mL syringe filled with acetone and carefully dispense 30 mg into the vial (about 2 drops). Record the weight on the worksheet.
3. Tare the balance and repeat the procedure with acetonitrile, recording the weight (about 30 mg) on the worksheet.
4. Carefully transfer the contents of this vial into a labeled 100 mL volumetric flask .
5. Rinse the vial several times with water and each time transfer the contents into the volumetric flask.
6. Dilute to volume with water and mix well.
7. Fill an autosampler vial with the solution, place a cap on the vial, seal the cap with a crimper, and label the vial.

Limit of Quantitation Solution (LOQ, 0.01 mg/mL)

1. Using an auto pipette, transfer 2.0 mL of the Resolution Solution into a 50 mL volumetric flask.
2. Dilute to volume with deionized water and mix well.
3. Fill an autosampler vial with the solution, place a cap on the vial, seal the cap with a crimper, and label the vial.

Standard Solution (0.4 mg/mL)

1. Place approximately 2 mL of water into a weighing vial and place it on the balance and tare.
2. Fill a 1 mL syringe filled with acetone and carefully dispense 40 mg into the vial (about 2-3 drops). Record the weight on the worksheet.
3. Tare the balance and repeat the procedure with acetonitrile, recording the weight (about 30 mg) on the worksheet.
4. Carefully transfer the contents of this vial into a labeled 100 mL volumetric flask .
5. Rinse the vial several times with water and each time transfer the contents into the volumetric flask.
6. Dilute to volume with water and mix well.
7. Fill an autosampler vial with the solution, place a cap on the vial, seal the cap with a crimper, and label the vial.

Check Standard Solution (0.4 mg/mL)

1. Prepare a Check Standard using the procedure for the Standard Solution.
2. Fill an autosampler vial with the solution, place a cap on the vial, seal the cap with a crimper, and label the vial.

Blank

Fill an autosampler vial with deionized water, place a cap on the vial, seal the cap with a crimper, and label the vial.

Sample Preparation

1. Weigh two tablets on a balance and record the weight on the worksheet.
2. Place the two tablets into a 50 mL vial.
3. Using an automatic pipette, transfer 20.0 mL of water into the vial and cap tightly.
4. Place the vial on the shaker and shake for 5 minutes. A fine suspension of solid in water should be observed.

5. Transfer about 2 mL of the suspension into a syringe with 0.45 µm nylon filter unit attached.
6. Filter into an autosampler vial. Place a cap on the vial, seal the cap with a crimper, and label the vial.

2.3 Gas Chromatographic Sequence:

Vial Position	Sample Identification	Number of Injections
1	Blank	1
2	Resolution Solution	1
3	Standard Solution	6
4	Check Standard	2
5	LOQ	2
6	R& D Batch	2
7	Production Batch 1	2
8	Production Batch 2	2
9	Production Batch 3	2

2.4 Procedure:

1. Set up the gas chromatograph according to the conditions described in Section 2.1 and allow the system to equilibrate to the preset conditions.
2. Set up the autosampler with all solution preparations in the order described in the sequence table described in Section 2.3.
3. Enter sample weight and standard concentration into the sequence table.
4. Start the gas chromatographic run with the Start Run command.
5. Record peak areas of acetone peaks from each chromatogram into the appropriate entries of the Excel Worksheet.
6. All system suitability requirements must be met as described in Section 2.5.
7. The average acetone assay of each batch must be not more than 0.5% and difference between the two assay results must be not more than 10%.

2.5 System Suitability Requirements:

1. The chromatogram of the blank shows no peak eluting at the retention time of the acetone peak.
2. Baseline resolution is observed between the acetone and acetonitrile peaks in the chromatogram of the resolution solution.
3. Percent residual standard deviation of the peak areas of the acetone peak from the standard solution chromatograms are not more than 2.0%.

4. The average assay of acetone in the check standard solution chromatogram is 98.0 – 102.0%.
5. The signal-to-noise ratio of the acetone peak from the LOQ solution chromatogram is not less than 10.

Calculations

The percent acetone in the Duracor tablets is calculated using the following equation:

% Acetone = (A_{sa} / A_{std}) (C_{std} / W_{sa}) (DF) (100)

Where

A_{sa} = Peak area of acetone from the sample solution
A_{std} = Average peak area of acetone from the standard solution
C_{std} = Concentration of acetone in the standard solution in mg/mL
W_{sa} = Weight of the two Duracor tablets in mg
DF = Dilution factor of sample solution = 20

The signal-to-noise ratio, S/N, is calculated from the chromatogram of the LOQ solution using the following equation:

S/N = Peak Height of Acetone / RMS noise of baseline

Peak height of acetone in millivolts, mv, is measured from the baseline to the peak of the acetone.
RMS or route mean square of the baseline noise is calculated by the data acquisition software.

Chromatograms

System Suitability Chromatogram

Standard Chromatogram

4.3 ***LOQ Chromatogram***

4.4 *Sample Chromatogram*