



IAEA

International Atomic Energy Agency

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Radiopharmaceutical Production

QC Tests
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Chemical Purity

Chemical contaminants may arise from the procedure employed in synthesis of FDG. These include, the residual organic solvents (e.g., acetonitrile, ethanol), catalysts (e.g., Aminopolyether), reagents and the by-products, such as cold FDG, FDM, glucose and CIDG, depending upon the method applied for the synthesis of FDG. It is necessary to know the potential impurities present in the final preparation, and corresponding methods should be employed for analysis and control of the potential toxic substances. The potential chemical impurities present in the FDG preparation are discussed below.

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Chemical Purity

Kryptofix 2.2.2 (Amino polyether)

Acceptance Criteria: Not More Than 50µg/mL. This test should be performed at time of initial validation and periodically thereafter.

Procedure: 5µl each (or any suitable volume) of the test sample and the reference standard of Kryptofix 2.2.2 (50µg/mL) are spotted side-by-side on a silica gel plate (e.g., 10 cm x 2 cm). The spots are air dried without application of heat. The plate is then developed with the mobile phase composed of Methanol: 30% Ammonia (9:1, v/v). The developed plate, after drying, is exposed to iodine vapour in a closed container to visualize the spots. The size and intensity of the spot of the test sample should not exceed that of the reference standard.

Alternately, a spot test method is described in Ph.Eur. potentially allowing more sensitive detection of Kryptofix 2.2.2. An additional spot method involves spotting the test sample on the TLC plate without developing as a chromatogram; the air dried spot is exposed to iodine vapour to visualize the spots.

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Chemical Purity

Kryptofix 2.2.2 (Amino polyether)

Discussion: Although the European Pharmacopeia and International Pharmacopeia allow a higher upper limit for Kryptofix 2.2.2 in the final FDG preparation (2.2 mg/volume injected), with most of the synthesis modules this impurity is well below 50µg/mL. The test and standard samples should be applied as small spots in order to avoid spreading. The initial FDG production process validation should include testing for the presence of Kryptofix 2.2.2. and periodically thereafter to ensure that the level of this chemical impurity in the finished product remains low.



Chemical Purity

Chloro-2-deoxy-D-glucose (CIDG)

Acceptance Criteria: Not More Than 0.5 mg/volume injected. This test should be performed at time of initial validation and periodically thereafter.

Procedure: The test method requires the use of HPLC equipped with a strong basic anion exchange column. In the test, 0.1 Molar NaOH is used as the mobile phase. The mass detector should be suitable for carbohydrate detection, and may be placed in tandem with a radioactivity detector. This system is able to detect also FDG and FDM.

Discussion: 2-Chloro-2-deoxy-D-glucose is a potential contaminant in the ^{18}F -FDG product when an anion exchange resin in the chloride form is used during synthesis. For most PET centers with limited resources of staff and equipment, this test could be performed by an external lab on decayed samples.



Chemical Purity

Residual solvents

Acceptance Criteria: Not More Than 0.04% acetonitrile in the FDG. This test should be performed on every batch, or as an alternative, it may be run at time of initial validation and periodically thereafter as long there are no other changes to the system and procedures.

Procedure: The presence of acetonitrile in the FDG is readily assessed with a gas chromatograph (GC) equipped with a suitable column (e.g., Porapak-QS) and flame ionization detector. The GC equipment is readied prior to receiving the undiluted test sample. Approximately 2-5 μ l of the test sample is injected into the GC column and analysis report is generated. Prior to analyzing the test sample, verification of the proper operation of the GC system should be determined with standards of known concentration of the residual solvents being analyzed.

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Chemical Purity

Residual solvents

Discussion: Acetonitrile is used during synthesis, for reagent preparations and for conditioning of the purification cartridges. Traces of this organic solvent may potentially contaminate the FDG, and therefore, should be controlled. Only those solvents that may be present in the final preparation need to be analyzed (e.g. ethanol). When ethanol impurity in FDG is suspected, the quantity present can be measured using the same GC test method. The USP has set an upper limit of 0,5% ethanol per mL of FDG solution.

Read an example Standard Operating Procedure for the analysis of residual solvents by GC. [HERE](#)

To skip the procedure, hit the STOP sign





Example Procedure for GC Analysis

GC System Setup:

Methodology

The GC (HP model HP5890A) next to the Von Gahlen (FDG) hood in Building 901 Room 113 is used for residual solvent analysis for radiotracers synthesized in the cGMP laboratory (Room 113). Samples are injected using Injector B. An FID detector is installed as Detector A. The output of the detector is connected to the Peak Simple data acquisition system. See Working Procedure Q010 for setup of Peak Simple data acquisition system. The FID flame and injector B split vent into a white PVC pipe connected to the Von Gahlen hood using an in-line fan to create negative pressure. Supelco “green” septa are used in the injector port. The column is a Rtx®-wax (Restek), 30meter, 0.53mm ID. During analysis the column is maintained at 40 °C for two minutes, ramped to 130 °C at 20 °C/min and held at 130 °C for 6 minutes before cooling down to 40 °C for the next injection.

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Example Procedure for GC Analysis

Daily Performance Check

GC performance is checked daily (if in use) by injection of a known amount of a standard solution of acetonitrile and ethanol. Acquire the data in 10 Hz. **Daily Setup:**

Turn on Power

Turn on the GC using the switch located on the right side on the back panel of the GC

Turn on Supply Gases

Turn on the air and hydrogen valves on the panel mounted on the wall behind the GC. Check pressures setting, H₂ 20psi, air 40psi, He 90psi.

Turn on Oven

After the GC self-test (< 1 minute), turn on the oven (set to 40 °C) using the front panel controls of the GC. Using the same controls turn on Injector B temperature (250 °C) and Detector A (300 °C).

Set Helium Flow

Set the Helium flow to 50 mL/min using knob at bottom left front of GC.



Example Procedure for GC Analysis

Turn on FID

Wait for temperatures to come up then turn on Detector A (FID)

Helium flow

Re-check Helium flow and adjust to 45-55 mL/min.

Light the flame:

Purge air and hydrogen supplies about 1 minute with valves full open (control knobs at top left front of GC) then close off hydrogen while leaving air full open. Hold igniter switch down while slowly opening hydrogen flow until flame is lit (you will hear a small pop sound when flame lights). Release igniter switch after flame is lit. Turn H2 full open.

Signal Stabilization

Watch Signal A (FID) until output is stable. This usually takes about 5 minutes. Normal baseline value is 20 – 40 on GC display.

Helium Flow

Re-check Helium flow and adjust to 45 – 55 mL/min.

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Example Procedure for GC Analysis

Injection of Standard:

Standard Preparation

See SOP Q025 for the procedure to prepare standards. Standards are stored in refrigerator in Room 112. Let standard warm to room temperature before opening. Standards contain mixtures of acetonitrile and ethanol and may also contain butanol used as an internal standard.

Syringe Preparation

Use a 10uL syringe and rinse 5 –10x with water. Load 1-2 uL of water and then withdraw air until front of water bolus is at ~2 uL mark on syringe.

Load Syringe

Load about 1 to 2 uL of standard (usually STD #7 – 0.025% butanol; 0.05% ethanol; 0.005% acetonitrile). Read volume by withdrawing air with syringe out of standard so that volume of bolus can be determined using syringe markings.



Example Procedure for GC Analysis

Sample Injection

Inject sample into Injector B and hold for 3-5s to allow full vaporization of sample from syringe needle. At the time of injection depress the start button on the GC front panel. This will automatically start data acquisition by the Peak Simple system.

Calculation of standard concentrations:

Integrate peaks using the Peak Simple software.

Determine nL injected either directly from Peak Simple if calibration curves have been entered or using the appropriate calibration factors found in the residual solvents Excel spreadsheet.

Percentage Solvent Calculation

Calculate % solvent using the following equation:

$$\% \text{ solvent} = [(\text{nL in sample}) / \text{nL injection}] * 100$$

where “nL in sample” is determined using the latest calibration curve and “nL injected” is either the value read from the injection syringe or that determined from the internal standard.



Example Procedure for GC Analysis

Validation of Calibration

If the standard agrees within 20% of the value indicated on the label then the current calibration is valid and continue with the analysis. Otherwise re-calibration of the GC is required.

Sample Analysis:

Sample Dilution

Dilute (usually 1:1) an aliquot from the production QC sample (typically 0.05 – 0.1mL) with 0.1 % butanol standard.

Prepare Syringe

Rinse a 10 uL syringe 5 – 10x with water. Load 1-2 uL of water and then withdraw air until front of water bolus is at ~2 uL mark on syringe.

Load Sample

Load about 1 uL of the diluted sample into the syringe. Read the volume by withdrawing air so that volume of bolus can be determined using syringe markings.



Example Procedure for GC Analysis

Inject Sample

Inject sample into Injector B and hold for 3-5s to allow full vaporization of sample from syringe needle. At the time of injection depress the start button on the GC front panel. This will automatically start data acquisition by the Peak Simple system.

Calculation of sample solvent concentrations:

Peak Integration

Integrate peaks using the Peak Simple software. Determine nL injected either directly from Peak Simple if calibration curves have been entered or using the appropriate calibration factors found in the residual solvents Excel spreadsheet.

Percentage Solvent Calculation

Calculate % solvent using the following equation:

$$\% \text{ solvent} = \text{Dilution Factor} * [(\text{nL in sample}) / \text{nL injection}] * 100$$

where “nL in sample” is determined using the latest calibration curve and “nL injected” is either the value read from the injection syringe or that determined from the internal standard. The Dilution Factor is usually 2.

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Example Procedure for GC Analysis

Record Results and Limits

Record the values in the Quality Control Report of the production batch record. The batch is rejected if the ethanol concentration is $> 0.5\%$ w/v or the acetonitrile concentration is $> 0.04\%$ w/v.

Maintenance and Cleaning

Cleaning of this device is not required. Change septa regularly (10 to 20 punctures) as indicated by abnormal daily check results. Check and clean the injection liner annually or as needed.

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