Solutions for organ preservation

with the following temperature programme:

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Temperature (°C)</th>
<th>Rate (°C/min)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 10</td>
<td>130</td>
<td>-</td>
<td>isothermal</td>
</tr>
<tr>
<td>10 - 30</td>
<td>130 → 190</td>
<td>3</td>
<td>linear gradient</td>
</tr>
</tbody>
</table>

Injection port 220
Detector 220

Inject 1 µl of each solution. Adjust the sensitivity of the system so that the height of the peak due to the internal standard is at least 20 per cent of the full scale of the recorder. The test is not valid unless, in the chromatogram obtained with reference solution (a), the resolution between the peaks corresponding to 2-(1-methylethyl)pentanoic acid and valproic acid is at least 3.0. In the chromatogram obtained with test solution (a): the sum of the areas of the peaks, apart from the principal peak is not greater than three times the area of the peak due to the internal standard (0.3 per cent); none of the peaks, apart from the principal peak, has an area greater than that of the peak due to the internal standard (0.1 per cent). Disregard any peak with an area less than 0.1 times the area of the peak due to the internal standard.

Chlorides (2.4.4). To 5 ml of solution S add 10 ml of water R. The solution complies with the limit test for chlorides (200 ppm).

Sulphates (2.4.13). Solution S complies with the limit test for sulphates (200 ppm).

Heavy metals (2.4.8). 1.0 g complies with limit test C for heavy metals (20 ppm). Prepare the standard using 2 ml of lead standard solution (10 ppm Pb) R.

Loss on drying (2.2.32). Not more than 2.0 per cent, determined on 1.000 g by drying in an oven at 100 °C to 105 °C.

ASSAY
Dissolve 0.1500 g in 25 ml of anhydrous acetic acid R. Titrate with 0.1 M perchloric acid determining the end-point potentiometrically (2.2.20).

1 ml of 0.1 M perchloric acid, is equivalent to 16.62 mg of C₈H₁₅NaO₂.

STORAGE
Store in an airtight container.

IMPURITIES

A. R = R' = H: pentanoic acid (valeric acid),
B. R = H, R' = CH₃CH₂: (2RS)-2-ethylpentanoic acid,
C. R = H, R' = CH(CH₃)₂: (2RS)-2-(1-methylethyl)pentanoic acid,
D. R = R' = CH₃CH₂CH₂: 2,2-dipropylpentanoic acid,
E. R = R' = H: pentanamide (valeramide),
F. R = H, R' = CH₃CH₂CH₃: 2-propylpentanamide,
G. R = R' = CH₂CH₂CH₃: 2,2-dipropylpentanamide,
H. R = R' = H: pentanenitrile (valeronitrile),
I. R = H, R' = CH₃CH₂CH₃: 2-propylpentanenitrile,
J. R = R' = CH₃CH₂CH₃: 2,2-dipropylpentanenitrile.

SOLUTIONS FOR ORGAN PRESERVATION

Solutiones ad conservacionem partium corporis

DEFINITION
Solutions for organ preservation are sterile, aqueous preparations, intended for storage, protection and/or perfusion of mammalian body organs that are in particular destined for transplantation. They contain electrolytes that are typically at a concentration close to the intracellular electrolyte composition. They may contain carbohydrates (such as glucose or mannitol), amino acids, calcium-complexing agents (such as citrate or phosphate), hydrocolloids (such as starch or gelatin derivatives) and other excipients, for example to make the preparation isotonic with blood, to adjust or buffer the pH, to prevent deterioration of the ingredients, but not to adversely affect the intended action of the preparation or, at the concentration used, to cause toxicity or undue local irritation. Solutions for organ preservation may also contain active substances or these may be added immediately before use.

Solutions for organ preservation, examined under suitable conditions of visibility, are clear and practically free from particles.

Solutions for organ preservation may also be presented as concentrated solutions. They are diluted to the prescribed volume with a prescribed liquid immediately before use. After dilution, they comply with the requirements for solutions for organ preservation.

Before use, the solutions for organ preservation are cooled below room temperature, typically to 2 °C to 6 °C, to reduce the temperature of the body organ and its metabolism.

Where applicable, the containers for solutions for organ preservation comply with the requirements for Materials used for the manufacture of containers (3.1 and subsections) and Containers (3.2 and subsections). Solutions for organ preservation are supplied in glass containers (3.2.1) or in other containers such as plastic containers (3.2.2 and 3.2.8). The tightness of the container is ensured by suitable means. Closures ensure a good seal, prevent the access of micro-organisms and other contaminants and usually permit the withdrawal of a part or the whole of the contents without removal of the closure. The plastic materials or elastomers of which the closure is composed are sufficiently firm and elastic to allow the passage of a needle with the least possible shedding of particles.

PRODUCTION
Solutions for organ preservation are prepared using materials and methods designed to ensure their sterility and to avoid the introduction of contaminants and the growth of micro-organisms; recommendations on this aspect are provided in the text on Methods of preparation of sterile products (5.1.1).
Unless otherwise justified and authorised, solutions for organ preservation are prepared from water for injections R and do not contain antimicrobial preservatives.

TESTS

pH (2.2.3). Carry out the test at room temperature. The pH of the solution is 5.0 to 8.0.

Osmolality (2.2.35). The osmolality of the solution is 250 mosmol/kg to 380 mosmol/kg.

Hydroxymethylfurfural. If the solution contains glucose, it complies with the following test: to a volume of the preparation to be examined containing the equivalent of 25 mg of glucose, add 5.0 ml of a 100 g/l solution of glacial acetic acid R and 1.0 ml of a 5 g/l solution of p-toluidine R in 2-propanol R containing 10 per cent V/V of glacial acetic acid R and 1.0 ml of a 5 g/l solution of barbituric acid R. The absorbance (2.2.25), determined at 550 nm after allowing the mixture to stand for 2 min to 3 min, is not greater than that of a standard prepared at the same time in the same manner using a solution containing 10 µg of hydroxymethylfurfural R in the same volume as the preparation to be examined.

Particulate contamination. Carry out the test for sub-visible particles (2.9.19) using 50 ml of preparation to be examined. The solution contains not more than 50 particles per millilitre larger than 10 µm and not more than 5 particles per millilitre larger than 25 µm.

Products for which the label states that the solution is to be used with a final filter are exempted from these requirements.

Sterility (2.6.1). The solution complies with the test for sterility.

Bacterial endotoxins (2.6.14): less than 0.5 IU/ml.

Pyrogens (2.6.8). Solutions for which a validated test for bacterial endotoxins cannot be carried out comply with the test for pyrogens. Inject per kilogram of the rabbit’s mass 10 ml of the solution, unless otherwise justified and authorised.

LABELLING

The label states:

– that the solution is not to be used for injection,
– the formula of the solution for organ preservation expressed in grams per litre and in millimoles per litre,
– the nominal volume of the solution for organ preservation in the container,
– the osmolality, expressed in milliosmoles per kilogram,
– that any unused portion of the ready-to-use solution, of the concentrated solution or of the diluted solution must be discarded,
– the storage conditions,
– if applicable, that the solution is to be used in conjunction with a final filter.

In addition, for concentrated solutions the label states that the solution must be diluted with a suitable liquid immediately before use.

**Somatostatinum**

DEFINITION

Somatostatin is a cyclic tetradecapeptide having the structure of the hypothalamic hormone that inhibits the release of human growth hormone. It is obtained by chemical synthesis. It contains a variable amount of acetic acid. It is available in the freeze-dried form.

Content: 95.0 per cent to 103.0 per cent of somatostatin (anhydrous and acetic acid-free substance).

CHARACTERS

Appearance: white, amorphous powder.

Solubility: freely soluble in water and in acetic acid, practically insoluble in methylene chloride.

IDENTIFICATION

A. Thin-layer chromatography (2.2.27).

Test solution. Dissolve 1.0 mg of the substance to be examined in 1.0 ml of water R.

Reference solution. Dissolve the contents of a vial of somatostatin CRS in water R and dilute with the same solvent to obtain a final concentration of 1 mg/ml.

Plate: TLC silica gel plate R.


Application: 20 µl.

Development: over a path of 15 cm.

Drying: in a current of warm air.

Detection: spray with a 1 g/l solution of ninhydrin R and heat the plate in an oven at 110 °C for about 5 min.

Results: the principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with the reference solution.

B. Examine the chromatograms obtained in the assay.

Results: the principal peak in the chromatogram obtained with the test solution is similar in retention time to the principal peak in the chromatogram obtained with the reference solution.

TESTS

Specific optical rotation (2.2.7): from −37 to −47 (anhydrous and acetic acid-free substance).

Dissolve 2.0 mg in 1.0 ml of a 1.0 per cent V/V solution of glacial acetic acid R.

Absorbance (2.2.25): maximum 0.20 at 280 nm (calculated with reference to the peptide content as determined in the assay).

Dissolve 5.0 mg in a 9 g/l solution of sodium chloride R and dilute to 100.0 ml with the same solvent.

Amino acids. Examine by means of an amino-acid analyser. Standardise the apparatus with a mixture containing equimolar amounts of ammonia, glycine and the L-form of the following amino acids:

- Lysine
- Threonine
- Alanine
- Leucine
- Histidine
- Serine
- Valine
- Tyrosine
- Arginine
- Glutamic acid
- Methionine
- Phenylalanine
- Aspartic acid
- Proline
- Isoleucine

together with half the equimolar amount of L-cystine. For the validation of the method, an appropriate internal standard, such as DL-norleucine R, is used.

Test solution. Place 1.0 mg of the substance to be examined in a rigorously cleaned hard-glass tube 100 mm long and 6 mm in internal diameter. Add a suitable amount of a