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Haemodialysis Solutions

General Notices

(Solutions for Haemodialysis, Ph. Eur. monograph 0128)

Ph Eur

DEFINITION

Solutions of electrolytes with a concentration close to the electrolytic composition of plasma. Glucose may be included in the formulation.

Because of the large volumes used, haemodialysis solutions are usually prepared by diluting a concentrated solution with water of suitable quality (see the monograph *Haemodialysis solutions, concentrated, water for diluting (1167)*), using for example an automatic dosing device.

CONCENTRATED SOLUTIONS FOR HAEMODIALYSIS

Concentrated haemodialysis solutions are prepared and stored using materials and methods designed to produce solutions having as low a degree of microbial contamination as possible. In certain circumstances, it may be necessary to use sterile solutions.

During dilution and use, precautions are taken to avoid microbial contamination. Diluted solutions are to be used immediately after preparation.

Concentrated solutions for haemodialysis are supplied in:

— rigid, semi-rigid or flexible plastic containers;

— glass containers.

3 types of concentrated solutions are used:

1. Concentrated solutions with acetate or lactate

Several formulations of concentrated solutions are used. The concentrations of the components in the solutions are such that, after dilution to the stated volume, the concentrations of the components per litre are usually in the following ranges (see Table 0128.-1):

Table 0128.-1.

	Concentration (mmol/L)	Concentration (mEq/L)
Sodium	130 - 145	130 - 145
Potassium	0 - 3.0	0 - 3.0
Calcium	0 - 2.0	0 - 4.0
Magnesium	0 - 1.2	0 - 2.4
Acetate or lactate	32 - 45	32 - 45

	Concentration (mmol/L)	Concentration (mEq/L)
Chloride	90 - 120	90 - 120
Glucose	0 - 12.0	

Concentrated solutions with acetate or lactate are diluted before use.

2. Concentrated acid solutions

Several formulations of concentrated solutions are used. The concentrations of the components in the solutions are such that, after dilution to the stated volume and before neutralisation with sodium hydrogen carbonate, the concentrations of the components per litre are usually in the following ranges (see Table 0128.-2):

Table 0128.-2.

	Concentration (mmol/L)	Concentration (mEq/L)
Sodium	80 - 110	80 - 110
Potassium	0 - 3.0	0 - 3.0
Calcium	0 - 2.0	0 - 4.0
Magnesium	0 - 1.2	0 - 2.4
Acetic acid	2.5 - 10	2.5 - 10
Chloride	90 - 120	90 - 120
Glucose	0 - 12.0	

Sodium hydrogen carbonate must be added immediately before use to a final concentration of not more than 45 mmol/L. The concentrated solution of sodium hydrogen carbonate is supplied in a separate container. The concentrated acid solutions and the concentrated solutions of sodium hydrogen carbonate are diluted and mixed immediately before use using a suitable device. Alternatively, sodium hydrogen carbonate in powder form may be used to prepare the solution.

3. Concentrated solutions without buffer

Several formulations of concentrated solutions without buffer are used. The concentrations of the components in the solutions are such that, after dilution to the stated volume, the concentrations of the components per litre are usually in the following ranges (see Table 0128.-3):

Table 0128.-3.

	Concentration (mmol/L)	Concentration (mEq/L)
Sodium	130 - 145	130 - 145
Potassium	0 - 3.0	0 - 3.0
Calcium	0 - 2.0	0 - 4.0
Magnesium	0 - 1.2	0 - 2.4
Chloride	130 - 155	130 - 155
Glucose	0 - 12.0	

Concentrated solutions without buffer are used together with parenteral administration of suitable hydrogen carbonate solutions.

The following tests are carried out on the diluted, ready-to-use solutions.

IDENTIFICATION

According to the stated composition, the solution to be examined gives the following identification reactions (2.3.1):

— potassium: reaction (b);

— calcium: reaction (a);

— sodium: reaction (b);

— chlorides: reaction (a);

— lactates;

— carbonates and hydrogen carbonates;

— acetates:

— if the solution is free from glucose, use reaction (b);

— if the solution contains glucose, use the following method: to 5 mL of the solution to be examined add 1 mL of *hydrochloric acid R* in a test-tube fitted with a stopper and a bent tube, heat and collect a few millilitres of distillate; carry out reaction (b) of acetates on the distillate;

— magnesium: to 0.1 mL of *titan yellow solution R* add 10 mL of *water R*, 2 mL of the solution to be examined and 1 mL of a 4.2 g/L solution of *sodium hydroxide R*; a pink colour is produced;

— glucose: to 5 mL of the solution to be examined add 2 mL of *dilute sodium hydroxide solution R* and 0.05 mL of *copper sulfate solution R*; the solution is blue and clear; heat to boiling; an abundant red precipitate is formed.

TESTS

Appearance of solution

The solution to be examined is clear (2.2.1). If it does not contain glucose, it is colourless (2.2.2, Method I). If it contains glucose, it is not more intensely coloured than reference solution Y_7 (2.2.2, Method I).

Aluminium

Maximum 10 µg/L.

Atomic absorption spectrometry (2.2.23, Method I or II). Use a matrix modifier (for example, *nitric acid R* and *magnesium nitrate R* in *water R*) in the same quantity for the test solution, the reference solutions and the blank solution.

Test solution If necessary, dilute the solution to be examined with *water R* to a concentration suitable for the instrument to be used.

Reference solutions. Method I – direct calibration.

Prepare the reference solutions by diluting, for example *aluminium standard solution (10 ppm Al) R* with acidified *water R*.

Reference solutions. Method II – standard additions.

Prepare at least 3 reference solutions in the test solution, in a range spanning the expected aluminium concentration of the test solution, for example by diluting *aluminium standard solution (10 ppm Al) R* with the test solution.

Blank solution *water R*.

Source Aluminium hollow-cathode lamp.

Wavelength 309.3 nm.

Atomisation device Graphite furnace.

Extractable volume (2.9.17)

The volume measured is not less than the nominal volume stated on the label.

Microbial contamination

TAMC: acceptance criterion 10^2 CFU/mL (2.6.12).

Sterility (2.6.1)

If the label states that the concentrated haemodialysis solution is sterile, it complies with the test for sterility.

Bacterial endotoxins (2.6.14)

Less than 0.25 IU/mL in the solution diluted for use.

Pyrogens (2.6.8)

Solutions for which a validated test for bacterial endotoxins cannot be carried out comply with the test for pyrogens. Dilute the solution to be examined with *water for injections R* to the concentration prescribed for use. Inject 10 mL of the solution per kilogram of the rabbit's mass.

ASSAY

Determine the density (2.2.5) of the concentrated solution and calculate the content in grams per litre and in millimoles per litre.

Sodium

97.5 per cent to 102.5 per cent of the content of sodium (Na) stated on the label.

Atomic emission spectrometry (2.2.22, Method I).

Test solution If necessary, dilute the solution to be examined with *water R* to a concentration suitable for the instrument to be used.

Reference solutions Prepare the reference solutions using *sodium standard solution (200 ppm Na) R*.

Wavelengths 589.0 nm or 589.6 nm (sodium emits as a doublet).

Potassium

95.0 per cent to 105.0 per cent of the content of potassium (K) stated on the label.

Atomic absorption spectrometry (2.2.23, Method I).

Test solution Dilute with *water R* an accurately weighed quantity of the solution to be examined to a concentration suitable for the instrument to be used. To 100 mL of this solution add 10 mL of a 22 g/L solution of *sodium chloride R*.

Reference solutions Prepare the reference solutions using *potassium standard solution (100 ppm K) R*. To 100 mL of each reference solution add 10 mL of a 22 g/L solution of *sodium chloride R*.

Source Potassium hollow-cathode lamp.

Wavelength 766.5 nm.

Atomisation device Air-acetylene flame.

Calcium

95.0 per cent to 105.0 per cent of the content of calcium (Ca) stated on the label.

Atomic absorption spectrometry (2.2.23, Method I).

Test solution Dilute 5.0 mL of the solution to be examined to 100.0 mL with *water R*. To 3.0 mL of this solution add 5 mL of *lanthanum chloride solution R* and dilute to 50.0 mL with *water R*.

Reference solutions Into 4 identical volumetric flasks each containing 5 mL of *lanthanum chloride solution R*, introduce respectively 2.5 mL, 5.0 mL, 7.0 mL and 10.0 mL of *calcium standard solution (10 ppm Ca) R* and dilute to 50.0 mL with *water R*.

Source Calcium hollow-cathode lamp.

Wavelength 422.7 nm.

Atomisation device Air-acetylene flame.

Magnesium

95.0 per cent to 105.0 per cent of the content of magnesium (Mg) stated on the label.

Atomic absorption spectrometry (*2.2.23, Method I*).

Test solution Dilute 5.0 mL of the solution to be examined to 100.0 mL with *water R*. To 2.0 mL of this solution add 5 mL of *lanthanum chloride solution R* and dilute to 50.0 mL with *water R*.

Reference solutions Into 4 identical volumetric flasks each containing 5 mL of *lanthanum chloride solution R*, introduce respectively 1.0 mL, 2.0 mL, 3.0 mL and 4.0 mL of *magnesium standard solution (10 ppm Mg) R* and dilute to 50.0 mL with *water R*.

Source Magnesium hollow-cathode lamp.

Wavelength 285.2 nm.

Atomisation device Air-acetylene flame.

Total chloride

95.0 per cent to 105.0 per cent of the content of chloride (Cl) stated on the label.

Dilute an accurately measured volume of the solution to be examined containing the equivalent of about 0.68 mEq of chloride with an appropriate volume of *water R* in order to immerse the electrode. Carry out a potentiometric titration (*2.2.20*), using *0.1 M silver nitrate*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M silver nitrate* is equivalent to 3.545 mg of Cl.

Acetate

95.0 per cent to 105.0 per cent of the content of acetate stated on the label.

To a volume of the solution to be examined, corresponding to about 0.7 mmol of acetate, add 10.0 mL of *0.1 M hydrochloric acid*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 0.1 mmol of acetate.

Lactate

95.0 per cent to 105.0 per cent of the content of lactate stated on the label.

To a volume of the solution to be examined, corresponding to about 0.7 mmol of lactate, add 10.0 mL of *0.1 M hydrochloric acid*. Then add 50 mL of *acetonitrile R*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 0.1 mmol of lactate.

Sodium hydrogen carbonate

95.0 per cent to 105.0 per cent of the content of sodium hydrogen carbonate stated on the label.

Titrate with *0.1 M hydrochloric acid* a volume of the solution to be examined corresponding to about 0.1 g of sodium hydrogen carbonate, determining the end-point potentiometrically (*2.2.20*).

1 mL of *0.1 M hydrochloric acid* is equivalent to 8.40 mg of $NaHCO_3$.

Reducing sugars

(expressed as glucose): 95.0 per cent to 105.0 per cent of the content of glucose stated on the label.

Transfer a volume of the solution to be examined containing the equivalent of 25 mg of glucose to a 250 mL conical flask with a ground-glass neck and add 25.0 mL of *cupri-citric solution R*. Add a few grains of pumice, fit a reflux condenser, heat so that boiling occurs within 2 min and maintain boiling for exactly 10 min. Cool and add 3 g of *potassium iodide R* dissolved in 3 mL of *water R*. Carefully add, in small amounts, 25 mL of a 25 per cent *m/m* solution of *sulfuric acid R*. Titrate with *0.1 M sodium thiosulfate* using *starch solution R*, added towards the end of the titration, as indicator. Carry out a blank titration using 25.0 mL of *water R*.

Calculate the content of reducing sugars, expressed as glucose ($C_6H_{12}O_6$), using Table 0128.-4.

Table 0128.-4.

Volume of *0.1 M sodium thiosulfate* (mL)	Glucose (mg)
8	19.8
9	22.4
10	25.0
11	27.6
12	30.3
13	33.0
14	35.7
15	38.5
16	41.3

STORAGE

At 4 °C or above.

LABELLING

The label states:

— the formula of the concentrated solution for haemodialysis expressed in grams per litre and in millimoles per litre;

— the nominal volume of the solution in the container;

— where applicable, that the concentrated solution is sterile;

— the storage conditions;

— that the concentrated solution is to be diluted immediately before use;

— the dilution to be made;

— that the volume taken for use is to be measured accurately;

— the ionic formula for the diluted solution ready for use in millimoles per litre;

— that any unused portion of solution is to be discarded;

— where applicable, that sodium hydrogen carbonate is to be added before use;

— that the solution is not to be used for intraveneous infusion.

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