Haemodialysis Solutions

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Manufacturers, regulatory authorities, health authorities, researchers, and other stakeholders are invited to provide their feedback and comments on this draft proposal. Manufacturers are also invited to submit samples of their products to the IPC to ensure that the proposed monograph adequately controls the quality of the product(s) they manufacture. Comments and samples received after the last date will not be considered by the IPC before finalizing the monograph.

Please send any comments you may have on this draft document to lab.ipc@gov.in, with a copy to Dr. Gaurav Pratap Singh (email: gpsingh.ipc@gov.in) before the last date for comments.

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Haemodialysis Solutions

Haemodialysis Fluids

Haemodialysis 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.

Haemodialysis Solutions contain not less than 97.5 per cent and not more than 102.5 per cent of the stated amount of sodium, Na, not less than 95.0 per cent and not more than 105.0 per cent of the stated amounts of potassium, K, calcium, Ca, magnesium, Mg, chloride, Cl, acetate, $C_2H_3O_2$, lactate, $C_3H_5O_3$, sodium bicarbonate, $NaHCO_3$, and glucose, $C_6H_{12}O_6$.

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.

Three types of concentrated solutions are used:

1. Concentrated solutions with acetate or lactate

Usual strengths: 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.

	Concentration in mmol per litre
Sodium	130 – 145
Potassium	0 – 3.0
Calcium	0 – 2.0
Magnesium	0 – 1.2
Acetate or Lactate	32 – 45
Chloride	90 – 120
Glucose	0 – 12.0

Concentrated solutions with acetate or lactate are diluted before use.

2. Concentrated acid solutions

Usual strengths: 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 bicarbonate*, the concentrations of the components per litre are usually in the following ranges.

	Concentration in mmol per litre
Sodium	80 – 110
Potassium	0 – 3.0
Calcium	0 – 2.0
Magnesium	0 – 1.2
Acetic acid	2.5 – 10
Chloride	90 – 120
Glucose	0 – 12.0

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

3. Concentrated solutions without buffer

Usual strengths: 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.

	Concentration in mmol per litre
Sodium	130 – 145
Potassium	0 – 3.0
Calcium	0 – 2.0
Magnesium	0 – 1.2
Chloride	130 – 155
Glucose	0 – 12.0

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

NOTE- The following tests are carried out on the diluted solutions.

Identification

A. 20 ml gives reactions (A) of chlorides, reactions (B) of sodium salts, reactions (A) of potassium salts and reactions (A) of calcium salts (2.3.1).

B. To 5 ml add 1 ml of *hydrochloric acid* in a test-tube fitted with a stopper and a bent tube, heat and collect a few ml of the distillate. The distillate gives reaction (A) of acetates (2.3.1).

C. To 0.1 ml of titan yellow solution add 10 ml of *water*, 2 ml of the solution under examination and 1 ml of *1 M sodium hydroxide*; a pink colour is produced if magnesium salts are present.

D. To 5 ml of the solution under examination, add 2 ml of *dilute sodium hydroxide* solution and 0.05 ml of *copper sulphate solution*; the solution remains blue and clear. Heat to boiling; a copious red precipitate is formed if glucose is present.

E. Lactates are identified together with the Assay for lactate.

Tests

Appearance of solution. The solution under examination is clear (2.4.1), if it does not contain glucose, it is colourless. If it contains glucose, it is not more intensely coloured than reference solution YS5 (2.4.1).

Aluminium. Not more than 10 µg per liter. Determine by atomic absorption spectrophotometry (2.4.2), measuring at 309.3 nm using graphite furnace and aluminium hollow- cathode lamp.

Atomic absorption spectrometry (2.4.2, Method A or B). Use a matrix modifier (for example, *nitric acid* and *magnesium nitrate* in *water*) in the same quantity for the test solution, the reference solution and the blank solution.

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

Reference solution. Method A – direct calibration.

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

Reference solution. Method B – standard additions.

Prepare at least 3 reference solution 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)* with the test solution.

Other tests. Comply with the tests stated under Parenteral Preparations (Injections).

Bacterial endotoxins (2.2.3). Not more than 0.25 Endotoxin Unit per ml.

Microbial contamination (2.2.9). Total aerobic viable count is not more than 100 CFU per ml.

Pyrogens (2.2.8). 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* to the concentration prescribed for use. Inject 10 ml of the solution per kg of the rabbit's body weight.

Sterility (2.2.11). Complies with the test for sterility.

Assay. *For sodium* — Determine by atomic emission spectrometry (2.4.3) using Method A, measuring at 589.0 nm or 589.6 nm.

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

Reference solution. A 0.02 per cent w/v solution of *sodium standard solution* in *water*.

For potassium — Determine by for atomic absorption spectrophotometry (2.4.2) using Method A, measuring at 766.5 nm using air-acetylene flame and potassium hollow-cathode lamp.

Test solution. Dilute with *water* accurately weighed quantity of the solution to be examined to a concentration suitable for the instrument to be used. To 100 ml of the solution, add 10 ml of a 0.0022 per cent w/v solution of *sodium chloride solution*.

Reference solution. A 0.01 per cent w/v solution of *potassium solution AAS* in *water*. To 100 ml of each the solutions add 10 ml of a 0.0022 per cent w/v solution of *sodium chloride solution*.

For calcium — Determine by atomic absorption spectrometry (2.4.2) using Method A, measuring at 422.7 nm using air-acetylene flame and calcium hollow-cathode lamp

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

Reference solution. Into 4 identical volumetric flasks each containing 5 ml of *lanthanum chloride solution*, and add respectively 2.5 ml, 5.0 ml, 7.0 ml and 10.0 ml of 0.001 per cent w/v solution of *calcium solution AAS* in *water* and dilute to 50.0 ml with *water*.

For magnesium — Determine by for atomic absorption spectrophotometry (2.4.2) using Method A, measuring at 285.2 nm using air-acetylene flame and magnesium hollow-cathode lamp.

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

Reference solution. Into 4 identical volumetric flasks each containing 5 ml of *lanthanum chloride solution*, and add respectively 1.0 ml, 2.0 ml, 3.0 ml and 4.0 ml of 0.001 per cent w/v solution of *magnesium solution AAS* in *water*. and dilute to 50.0 ml with *water*.

For total chloride — Dilute a measured volume containing about 68 mg of chloride to 50.0 ml with *water*. Titrate with *0.1 M silver nitrate*, determining the end-point potentiometrically (2.4.25). Read the volume added between the two points of inflexion.

1 ml of *0.1 M silver nitrate* is equivalent to 0.003545 g of total chloride, calculated as Cl.

For acetate — Dilute a measured volume containing about 0.7 mmol of acetate, add 10 ml of *0.1 M hydrochloric acid*. Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (2.4.25). Read the volume added between the two points of inflexion.

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

For lactate — Dilute a measured volume containing about 0.7 mmol of lactate, add 10 ml of *0.1 M hydrochloric acid*. Then add 50 ml of *acetonitrile.* Titrate with *0.1 M sodium hydroxide*, determining the end-point potentiometrically (2.4.25). Read the volume added between the two points of inflexion.

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

For sodium bicarbonate — Titrate with *0.1 M hydrochloric acid* a volume of the preparation under examination containing about 0.1 g of *sodium bicarbonate*, determining the end-point potentiometrically (2.4.25).

1 ml of *0.1 M hydrochloric acid* is equivalent to 0.0084 g of $NaHCO_3$.

For glucose — Transfer a volume of the preparation under examination containing about 25 mg of Glucose to a 250-ml conical flask with a ground-glass neck and add 25.0 ml of *cupri-citric solution*. Add a few grains of pumice, fit a reflux condenser, heat so that boiling occurs within 2 minutes and boil for exactly 10 minutes. Cool and add 3 g of *potassium iodide* dissolved in 3 ml of *water*. Carefully add, in small amounts, 25 ml of a 25 per cent w/w solution of *sulphuric acid*. Titrate with *0.1 M sodium thiosulphate* using *starch solution* as indicator. Carry out a blank titration using 25 ml of *water*.

Calculate the content of anhydrous glucose, $C_6H_{12}O_6$, from the following Table.

Volume of *0.1 M sodium thiosulphate* (ml)	Anhydrous 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. Store at a temperature 4º or above.

Labelling. The label states (1) the formula of the concentrated solution for haemodialysis, expressed in grams per litre and in millimoles per litre; (2) the nominal volume of the solution in the container; (3) where applicable, that the concentrated solution is sterile; (4) that the concentrated solution is to be diluted immediately before use; (5) the dilution to be made; (6) that the volume taken for use is to be measured accurately; (7) the ionic formula for the diluted solution ready for use in millimoles per litre; (8) that any unused portion of the solution is to be discarded; (9) where applicable, that sodium bicarbonate is to be added before use; (10) that the solution is not to be used for intravenous infusion; (11) the storage conditions.