Iron Sucrose Injection

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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. 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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Iron Sucrose Injection

Iron Sucrose Injection is a sterile colloidal solution containing a complex of ferric hydroxide with sucrose in Water for Injections and contains no antimicrobial agent, chelating agent, dextran, gluconate or other added substances. The pH of the solution may be adjusted by the addition of sodium hydroxide.

Iron Sucrose Injection contains not less than 95.0 per cent and not more than 105.0 per cent w/v of the stated amount of iron.

Usual strength. 100 mg per 5 ml.

Identification

A. Iron. To a quantity of injection containing an equivalent of 50 mg of iron, add 17.5 ml of *water* and 5 ml of *hydrochloric acid*, mix and heat for 5 minutes in a boiling water-bath. Cool, add dropwise *ammonia* until no further precipitate of ferric hydroxide is produced, filter and wash the precipitate with *water* to remove excess of ammonia. Dissolve the precipitate in the minimum volume of *2 M hydrochloric acid* and dilute to 20 ml with *water*. To 3 ml of the solution add 1 ml, each of, *2 M hydrochloric acid* and *potassium thiocyanate solution*; a red colour is produced (Solution A). To 1 ml of the Solution A, add 5 ml of *amyl alcohol* or *ethyl ether*, shake, and allow to stand; a pink organic layer is obtained. To 1 ml of Solution A, add 2 ml of 6.5 per cent w/v solution of *mercuric chloride*; a red colour is discharged.

B. In the Assay for sucrose, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with reference solution (e).

C. Molecular-weight determination. The molecular weight distribution curve of the injection conforms to the following; M_W: 34000 to 60000 Da, M_N: Not less than 24000 Da and M_W/M_N: Not more than 1.7 (see Tests).

Tests

pH (2.4.24). 10.5 to 11.1, at 20°.

Specific gravity (2.4.29). 1.135 to 1.165 at 20°.

Absence of low molecular weight iron (Fe^{2+} and Fe^{3+}) complexes. In the test for Limit of Iron (Fe^{2+}), no additional peaks were obtained in the polarograms.

Alkalinity. Titrate 5 ml of injection with *0.1 M hydrochloric acid* with constant stirring to a pH of 7.4 and record the volume. Not less than 0.5 ml and not more than 0.8 ml of *0.1 M hydrochloric acid* is consumed per ml of injection.

Chloride content. Not less than 0.012 per cent and not more than 0.025 per cent.

Transfer a volume containing 12 g of injection to a 50-ml beaker, add 40 ml of *water* and 0.3 ml of *nitric acid*. While stirring, titrate with *0.01 M silver nitrate*, determining the end point potentiometrically (2.4.25), using a silver-glass electrodes. Carry out a blank titration.

1 ml of *0.01 M silver nitrate* is equivalent to 0.0003545 g of Cl.

Limit of Iron (Fe^{2+}). Not more than 0.4 per cent.

Electrolyte solution. Dissolve 15.0 g of *sodium acetate* in 100 ml of *water*, adjusted to pH 7.0 with *0.1 M acetic acid*.

Test solution. Volume of injection containing the equivalent of 0.002 per cent to 0.012 per cent of elemental iron.

Transfer a suitable amount of the electrolyte solution to a polarographic cell equipped with a mercury drop electrode. With the electrode submerged in the liquid, bubble nitrogen through the liquid for 5 minutes. Avoiding any undue exposure to air, immediately transfer the test solution to the polarographic cell. The test solution must be analysed immediately upon opening the container. Record the polarogram from 0 mV and −1700 mV. The iron [Fe^{3+}/Fe^{2+}] peak is detected at −750 ± 50 mV and the iron [Fe^{2+}/Fe] peak is detected at −1400 ± 50 mV. Measure the iron [Fe^{2+}/Fe^{3+}] peak responses obtained from the polarogram. Carry out a blank determination.

Calculate the content of Iron [Fe^{+2}], using following expression:

$$\text{Iron content (per cent w/v)} = [1 - (2/R)] \times C_T$$

Where, R = peak response ratio of iron [Fe^{2+}] to iron [Fe^{3+}],

C_T = total iron concentration of the injection (per cent w/v).

Molecular-weight determination. The weight-average molecular weight (M_W) is between 34000 Da and 60000 Da; Number average molecular weight (M_N) is not less than 24000 Da and Polydispersity is not more than 1.7.

Determine by size-exclusion chromatography (2.4.16).

Test solution. Dilute 5.0 ml of injection to 10.0 ml with the mobile phase.

Reference solution (a). Weigh and transfer 20 mg, each of, *polysaccharide molecular weight standard-5900 Da*, *polysaccharide molecular weight standard-11800 Da*, *polysaccharide molecular weight standard-22800 Da*, *polysaccharide molecular weight standard-47300 Da*, *polysaccharide molecular weight standard-112000 Da*, *polysaccharide molecular weight standard-212000 Da*, and *polysaccharide molecular weight standard-404000 Da (NOTE — Certified Standards (PULLULANS) Kit may be used)* to separate 5-ml volumetric flasks, add 4.0 ml of mobile phase to each flask and allow each containing aliquot to stand at or below 25° for at least 12 hours.

NOTE —1. After the agglomerate particles of each reference solution have swelled to their fullest extent, gently swirl each reference solution until dissolved.

2. The chromatograms of freshly prepared reference solution regularly show a small unidentified secondary peak following the main peak. Discard the reference solutions if the secondary peak reaches half the height of the main peak.

Reference solution (b). A solution containing 1.0 per cent w/v of *dextran molecular weight standard-270000 Da* and 0.5 per cent w/v of *dextrose IPRS* in the mobile phase.

Chromatographic system

- a stainless steel column 30 cm × 7.8 mm, 1000 Å packed with hydrophilic polyhydroxymethacrylate gel of totally porous spherical resin connected in series with a stainless steel column 30 cm × 7.8 mm, 120 Å packed with hydrophilic polyhydroxymethacrylate gel of totally porous spherical resin,
- column temperature: 45°,
- mobile phase: a buffer solution prepared by dissolving 3.56 g of *disodium hydrogen phosphate dihydrate*, 2.76 g of *sodium dihydrogen phosphate* and 0.2 g of *sodium azide* in 1000 ml of *water*,
- flow rate: 0.5 ml per minute,
- refractive index detector, at temperature: 45°,
- injection volume: 25 µl.

Inject reference solution (b). The test is not valid unless the resolution between the peaks due to dextran and dextrose is not less than 4.0.

Inject reference solution (a) (each reference solution individually) and the test solution. The correlation coefficient obtained should not be less than 0.98 for plot of reference solutions. Use test chromatogram to determine weight average molecular weight (Mw) of test solution. Using a suitable program, plot the retention times of reference solution (a) and their molecular weights (Mp) to generate a third order (cubic) calibration curve. *(NOTE — Use actual molecular weight values (Mp) of the standards from the certificate of analysis)*. Calculate the molecular weight from the calibration curve using suitable gel permeation chromatography (GPC) software.

NOTE — Integrate the peak base-to-base, and ignore shoulder peak.

Calculate the weight-average molecular weight (M_W), Number average molecular weight (M_N) and Polydispersity (M_W/M_N) using following expression:

$$\text{Weight-average molecular weight } (M_W) = \frac{\sum(A_T M_T)}{\sum(AT)}$$

where,

A_T = area of each fraction of the test distribution,

M_T = corresponding mean molecular weight of each fraction as determined from its retention time on calibration curve.

Number Average Molecular Weight (M_N) using following expression:

$$\text{Number average molecular weight } (M_N) = \frac{\sum(A_T)}{}$$

$$\sum(A_T/M_T)$$

where,

A_T = area of each fraction of the test distribution,

M_T = corresponding mean molecular weight of each fraction as determined from its retention time on the calibration curve.

$$\text{Polydispersity} = \frac{Mw}{M_N}$$

where,

M_W = weight average molecular weight,

M_N = number average molecular weight.

Osmolality (2.4.23). 1150 mOsmol per litre to 1350 mOsmol per litre, in a 10 per cent v/v solution in *water*.

Turbidity. 4.4 to 5.3.

Weigh and transfer 0.5 g of the injection to a 150-ml beaker, add 100 ml of *water*, and with constant stirring, adjusted to pH 6.0 with *0.1 M hydrochloric acid*. Remove the pH electrode from the solution. Adjust a light source such that the beam hits the beaker at a parallel angle 2 cm below the surface of the liquid. The light must shine through to the surface, and the solution must not have any turbidity. Measurement must be carried out in a room as dark as possible. Add dropwise, *0.1 M hydrochloric acid* until a slight but lasting turbidity develops. Record the pH of the solution as the turbidity point of the injection.

Bacterial endotoxins (2.2.3). Not more than 3.7 Endotoxin Units per mg of iron.

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

Assay.

For sucrose — Not less than 26.0 per cent and not more than 34.0 per cent.

Determine by liquid chromatography (2.4.14).

Test solution. Pool the contents of 3 vials and prepare a composite sample. Transfer 1.875 g of pooled sample to a 25-ml volumetric flask, add 1.25 ml of *water*, mix, add 1.25 ml of sodium dihydrogen phosphate solution prepared by dissolving 30 g of *sodium dihydrogen phosphate* in 50 ml of *water*, and mix. Allow the resulting solution to stand for 10 minutes to precipitate the colloidal ferric hydroxide. Dilute to volume with *water*. Centrifuge the solution at 3000 rpm for 15 minutes, filter the supernatant liquid, discarding the first 2 ml of filtrate.

Reference solution (a). A 1.3 per cent w/v solution of *sucrose IPRS* in *water*.

Reference solution (b). A 1.6 per cent w/v solution of *sucrose IPRS* in *water*.

Reference solution (c). A 1.8 per cent w/v solution of *sucrose IPRS* in *water*.

Reference solution (d). A 2.1 per cent w/v solution of *sucrose IPRS* in *water*.

Reference solution (e). A 2.3 per cent w/v solution of *sucrose IPRS* in *water*.

Chromatographic system

- a stainless steel column 25 cm × 4.0 mm, packed with monomolecular layer of aminopropylsilane bonded to porous silica (1.5-10 µm) (such as Zorbax NH_2),
- column temperature: 25°,
- mobile phase: a mixture of 21 volumes of *water* and 79 volumes of *acetonitrile*,
- flow rate: 2 ml per minute,
- refractive index detector maintained at 25°,
- injection volume: 20 µl.

Inject reference solutions (a), (b), (c), (d) and (e). The correlation coefficient obtained should not be less than 0.998 from the linear regression of reference solutions.

Inject reference solutions (a), (b), (c), (d), (e) and the test solution. Plot the peak area for each reference solutions versus concentration of sucrose (in mg per ml) in the test solution.

Calculate the content of $C_{12}H_{22}O_{11}$, using following expression:

$$\text{Sucrose content (in mg)} = (C_U \times D \times G)/W$$

Where, C_U = concentration of sucrose in the test solution (mg per ml),

D = dilution volume of the test solution (ml),

G = density of injection (g per ml),

W = weight of injection (g).

For iron — Determine by atomic absorption spectrophotometry (2.4.2).

Solvent mixture. Dissolve 2.64 g of *calcium chloride* in 500 ml of *water*, add 5.0 ml of *hydrochloric acid* and dilute to 1000.0 ml with *water*.

Test solution. Pool the contents of 3 vials and prepare a composite sample. Transfer 2 ml of the pooled sample to a 100-ml volumetric flask, add 5 ml of *hydrochloric acid*, swirl until the solution turns yellow, cool and dilute to volume with the solvent mixture. *(NOTE – Rinse the pipette several times with the solvent mixture)*. Transfer 2.0 ml of the solution to a 100-ml volumetric flask and dilute to volume with the solvent mixture.

Reference solution. A 0.005 per cent w/v solution of iron, prepared by dissolving 350 mg of *ferrous ammonium sulphate* in 1000.0 ml of *water*. Dilute the solution to obtain the concentrations of 0.0002 per cent w/v, 0.0004 per cent w/v, 0.0006 per cent w/v, 0.0008 per cent w/v and 0.001 per cent w/v of iron with the solvent mixture.

Set the zero of the instrument using the solvent mixture as blank. Measure the absorbance at 248.3 nm using an iron hollow-cathode lamp as source of radiation and an air-acetylene flame.

Plot the absorbance of each reference solution versus concentration (in µg per ml) of Iron and draw the straight-line best fitting of five plotted points. From the graph, determine the concentration (in µg per ml) of Iron in the test solution.

Calculate the content of Iron, (Fe) (in per cent) in each ml of the injection taken.

Storage. Preserve in a single dose container, preferably of Type I glass. Store at a temperature not exceeding 30°. Do not freeze.

Labelling. The label states (1) indicate that it is for intravenous use only; (2) that when administered by intravenous infusion, the injection must be diluted with 0.9 per cent sodium chloride injection to a concentration of 1.0 mg per ml to 2.0 mg per ml of elemental iron; (3) that the total osmolarity of the solution expressed in mOsmol per litre.