Ferric Carboxymaltose 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. 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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Ferric Carboxymaltose Injection

Ferric Carboxymaltose Injection is a terminally sterilized colloidal solution of Ferric Carboxymaltose in Water for Injection.

Ferric Carboxymaltose Injection contains Ferric Carboxymaltose equivalent to elemental iron, Fe+3 not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of Iron, Fe+3.

Usual strength. 50 mg iron per ml.

Description. A brown to dark brown colour solution.

Identification

A. For Iron-Place a volume of the injection containing 50 mg of Iron content on a watch-glass, add 2 drops of *ammonium hydroxide*; no precipitate is formed. Add 2 ml of *hydrochloric acid*, mix and add 2 ml of *ammonium hydroxide*, a brown precipitate is formed, which gets dissolved slowly.

B. For Dextrin-Dilute a volume of the injection containing 50 mg Iron to 250 ml with *water*. Transfer 1 ml of the solution to a test-tube, add 10 ml of the (0.2 per cent w/v solution of *anthrone* in a mixture of 95 volumes of *sulphuric acid* and 5 volumes of *water*, mix well, a dark green colour is produced.

Tests

pH(2.4.24). 5.0 to 7.0.

Weight per ml (2.4.29).1.05 g per ml to 1.15 g per ml, at 25°.

Chloride content. Not less than 0.45 per cent w/w and not more than 0.55 per cent w/w, determine by the following method.

Weight and transfer 0.75 g of the injection to a titration flask, add 50 ml of *water* and 2 ml of *nitric* acid. Titrate with *0.01 M silver nitrate*, determining the end-point potentiometrically (2.4.25). Carry out a blank titration.

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

Dextrin content. 5.5 per cent w/w to 8.5 per cent w/w.

Test solution. Weigh and transfer0.5 g of the injection to a 250-ml volumetric flask, add 50 ml of *water*, shake to dissolve and dilute to volume with *water*.

Reference solution. A 0.02 per cent w/v solution of *dextrose IPRS* in *water*.

Blank. Use *water* as blank.

Transfer 1.0 ml, each of, the test solution, reference solution and blank to three separate test-tubes, slowly and carefully add 10.0 ml of 0.2 per cent w/v solution of *anthrone* in a mixture of 95 volumes of *sulphuric acid* and 5 volumes of *water* in a cold condition. Heat on water-bath at 80° for 10 minutes. Cool to room temperature. Measure the absorbance at the maximum at about 625 nm (2.4.7), using blank as compensation liquid.

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

Weight and transfer 2.0 g of the injection a to beaker, add 10 ml of *water* and slowly add 5 ml of *sulphuric acid* with stirring. Titrate with *0.01 M ceric sulphate* by potentiometrically (2.4.25). Carry out a blank titration.

1 ml of *0.01 M ceric sulphate* is equivalent to 0.0005585 g of Iron (Fe^{+2}).

Molecular-weight determination. The weight average molecular weight (Mw) is between 130000 and 200000 Da; Number average molecular weight (Mn) is not less than 70000 Da and Polydispersity is not more than 1.5.

Determine by size-exclusion chromatography (2.4.16).

Test solution. Transfer 1.0 ml of the injection to a 10-ml volumetric flask, add 5 ml *water*, shake and dilute to volume with *water.*

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, polysaccharide molecular weight standard-404000 Da* and *polysaccharide molecular weight standard -788000 Da, (NOTE-Certified Standards (POLLULANS) 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. *(After the agglomerate particles of each reference solution have swelled to their fullest extent, gently swirl each reference solution until dissolved.)*

NOTE – The chromatograms of freshly prepared reference solution regularly shows a small unidentified secondary peaks 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 *glucose IPRS* in the mobile phase.

Chromatographic system

- guard column: a stainless steel column 4 cm x 6.0 mm, 200 A° packed with hydrophilic polyhydroxymethacrylate gel of totally porous spherical resin (6 µm),
- column: a stainless steel column 30 cm x 7.8 mm, 1000 A° packed with hydrophilic polyhydroxymethacrylate gel of totally porous spherical resin (12 µm) in series with stainless steel column 30 cm x 7.8 mm, 120 A° packed with hydrophilic polyhydroxymethacrylate gel of totally porous spherical resin (6 µm),
- 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 monohydrate* 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 glucose and dextran 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.

Calculate the weight-average molecular weight (Mw), number average molecular weight (Mn) and Polydispersity (Mw/Mn) using following expression;

$$\text{Weight average molecular weight (Mw)} = \frac{\Sigma\left(A_T M_T\right)}{\Sigma A_T}$$

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.

Number Average Molecular Weight (Mn) using following expression:

$$\text{Number Average Molecular Weight (Mn)} = \frac{\sum(A_T)}{\sum(A_T / M_T)}$$

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.

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

Where,

Mw = Weight average molecular weight,

Mn = Number average molecular weight.

Osmolality(2.4.23). 270mOsmol/kg to 390mOsmol/kg.

Particulate contamination (2.5.9). Determine by Method 1. Microscopic particle count test.

Particle of more than or equal to 10 µm size should not be more than 3000 particles per vial and particles of more than or equal to 25 µm size should not be more than 300 particles per vial.

Test solution. Dilute a suitable volume of injection with equal volume of *water*, filter.

Zeta Potential. Should be positive.

Test solution. Transfer 0.5 ml of the injection to a 100-ml volumetric flask, add 50 ml of *water* and shake for 3 to 4 minutes, dilute to volume with *water*.

Determine the Zeta potential using dip cell with suitable zeta potential analyzer.

Colloidal particle size (Z-Average) and Polydispersity index (2.5.13).

Test solution. Transfer 1.0 ml of the injection to a 100-ml volumetric flask, add 50 ml of *water* and shake for 3 to 4 minutes, dilute to volume with *water*.

Determine the Colloidal particle size (Z-Average) and Polydispersity index using quartz cuvette with suitable Zetasizer.

Colloidal particle size Z-Average: Not less than 20 nm and not more than 30 nm.

Polydispersity index: Not more than 0.15.

Sodium content. Not more than 0.55per cent w/w.

Determine by atomic absorption spectrophotometry (2.4.2), equipped with a sodium hollow-cathode lamp and an air-acetylene flame.

Solvent mixture. Dilute 1.0 ml of *nitric acid* and 1.0 ml of *hydrochloric acid* to a 1000-ml volumetric flask containing 400 ml *water*, and dilute to volume with *water*.

Test solution. Weigh and transfer 1.0 g of the injection to a 100-ml volumetric flask, add 10 ml of *hydrochloric acid*, shake to dissolve completely till clear solution observed, then add 10 ml *nitric acid*, and dilute to volume with *water*. Dilute 1.0 ml of the solution to 100.0 ml with *water.*

Reference solution. Dilute 10.0 ml of the *sodium standard solution* (1000 ppm) to 100.0 ml with *water*. Transfer 0.1 ml, 0.3 ml, 0.5 ml, 0.7 ml and 1.0 ml of the solution to separate 100-ml volumetric flasks and dilute to volume with the solvent mixture to obtain solution containing 0.1 ppm, 0.3 ppm, 0.5 ppm, 0.7 ppm and 1.0 ppm sodium, respectively.

Determine the absorbance of the *reference solutions* and the *test solution at 589 nm*. Plot the absorbances of the *reference solutions* versus their concentrations, in µg/ml, of sodium, and draw the straight line. From the graph so obtained, determine the concentration, *C*, in µg/ml, of sodium in the test *solution.*

Calculate the sodium content.

Where,

I = Mean corrected Intensity of sodium in test preparation.
M = Slope of the line.
W = Weight of test (in gm)

$$\% \text{ sodium content} = \frac{\mu g/ml \text{ of sodium}}{10000}$$

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

Bacterial endotoxins (2.2.3). Not more than 0.33 Endotoxins Unit per mg of iron.

Uniformity of dosage unit (2.5.4.(I)). Complies with the test for uniformity of dosage unit.

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

Assay.

Buffer solution. Dissolve 32 g of *ammonium acetate* in *water*, add 1 ml of *glacial acetic acid* and dilute to 100.0 ml with *water*.

Test solution. Pool the contents of 3 vials and prepare a composite sample. Transfer 2.0 ml of the pooled sample to a 200-ml volumetric flask, add 30 ml of *hydrochloric acid*, mix and dilute to volume with *water*. Dilute 4.0 ml of the solution to a 100.0 ml with *water.*

Reference solution. Weigh and transfer 432.5 mg of *ammonium iron (III) sulphate dodecahydrate* to a 100-ml volumetric flask, add 15 ml of *hydrochloric acid*, mix and dilute to volume with *water*. Dilute 4.0 ml of the solution to a 100.0 ml with *water.*

Blank. Use *water* as blank.

Transfer 1.0 ml, each of, reference solution, test solution and blank in to three separate test-tubes, add 1 ml of 10 per cent w/v solution of *hydroxylamine hydrochloride* in *water* to, each of, the test-tube. Shake and wait for 5 minutes, add 5 ml of the buffer solution and add 1.0 ml of 0.1 per cent w/v solution of *1,10 phenanthroline* in *water* to each test-tube, mix. Measure the absorbance at the maximum at about 511 nm (2.4.7).

Calculate the Iron (III) content.

Storage. Store protected from light, at a temperature not exceeding 30°. Do not refrigerate.

Labelling. The label states the quantity of, ferric carboxymaltose in terms of the equivalent amount of elemental Iron.