Ferric Carboxymaltose

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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.

Document History and Schedule for the Adoption Process

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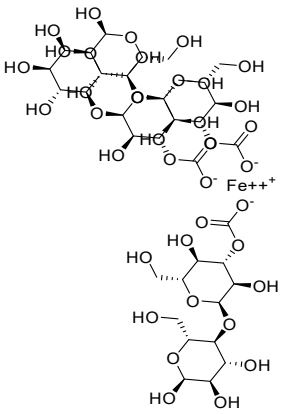
Ferric Carboxymaltose



[FeOx(OH)y(H_2O)z]n [{($C_6H_{10}O_5$)m ($C_6H_{12}O_7$)}l]k

[Where n ≈ 103, m ≈ 8, l ≈ 11, and k ≈ 4 (l represents the mean branching degree of the ligand). Relative Molecular weight 130000 to 200000 Da]

Ferric Carboxymaltose is polynuclear iron (III)-hydroxide-4(R)-(poly-(1→4)-O-α-D-glucopyranosyl)-oxy-2(R),3(S),5(R),6-tetrahydroxy-hexanoate

Ferric Carboxymaltose contains not less than 24.0 per cent and not more than 30.0 per cent of Iron, Fe^{+3}.

Category. Haematinic.

Description. A brown to dark brown amorphous powder. It has colloidal particle size (D_{50}), not less than 20 nm and not more than 30 nm.

Identification

A. To 1 ml of the test solution containing 5 per cent w/v 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. Dissolve 5 mg in 10 ml of *water*. Dilute 1 ml of the solution to a test-tube, add 10 ml of *anthrone solution*; a dark green colour is produced.

Tests

Chloride content. Not more than 6.0 per cent w/w, calculated as sodium chloride (NaCl), determine by the following method.

Dissolve 0.2 g of the substance under examination in 5.0 ml of *water*, add 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 0.05844 g of NaCl.

Dextrin content. 32.0 per cent w/w to 45.0 per cent w/w.

Test solution. Dissolve 0.5 g of the substance under examination in *water* and dilute to 250.0 ml with *water*.

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

Blank solution. Use *water* as blank.

Transfer 1.0 ml, each of, test solution, reference solution and blank solution to three separate test-tubes, add 10.0 ml of *anthrone solution* slowly to each of the test-tube and 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.
Calculate the dextrin content.

Limit of Iron (Fe^{+2}). Not more than 1.2 per cent.

Dissolve 1.0 g of substance under examination in 10 ml of *water* add slowly 5 ml of *sulphuric acid* with stirring and titrate with *0.01 M cerric sulphate,* using 0.1 ml of *ferroin solution* as indicator, until colour changes from dark red to greenish yellow. Carry out a blank titration.

1 ml of *0.01 M cerric sulphate* is equivalent to 0.05585 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 index is not more than 1.9.

Determine by size-exclusion chromatography (2.4.16).

Test solution. Heat the substance under examination containing 5.0 per cent w/v of iron, in an oil-bath at 85° for 2 hours. Cool the solution to room temperature. Dilute 1.0 ml of the solution to 10.0 ml with *water.*

Reference solution (a). Weigh and transfer 20 mg, each of, *polysaccharide molecular weight-5900 Da IPRS, polysaccharide molecular weight-11800 Da IPRS, polysaccharide molecular weight-22800 Da IPRS, polysaccharide molecular weight-47300 Da IPRS, polysaccharide molecular weight-112000 Da IPRS, polysaccharide molecular weight-212000 Da IPRS, polysaccharide molecular weight-404000 Da IPRS* and *polysaccharide molecular weight-788000 Da IPRS,* 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 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-270000 Da IPRS* and 0.5 per cent w/v of *glucose IPRS* in the mobile phase.

Chromatographic system
- a guard column: a stainless steel column 4 cm x 6.0 mm, packed with hydrophilic polyhydroxymethacrylate gel of totally porous spherical resin (6 µm),
- Column: a stainless steel column 30 cm x 7.8 mm, 1000 Å packed with hydrophilic polyhydroxymethacrylate gel of totally porous spherical resin (12 µm) in series with a stainless steel column 30 cm x 7.8 mm, 120 Å packed with hydrophilicpolyhydroxymethacrylate gel of totally porous spherical resin (6 µm) (Such as Ultrahydrogel),
- 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 to generate a third order (cubic) calibration curve. 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 index (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 calibration curve.

Number Average Molecular Weight (Mn) using following expression:

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

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.

$$\text{Polydispersity Index} = M_W / M_N$$

Where,

M_W : Weight average molecular weight,

M_N : Number average molecular weight.

Water (2.3.43). Not more than 8.0 per cent, determined on 0.2 g.

Bacterial endotoxins (2.2.3). Not more than 1.0 Endotoxins Unit per mg of iron.

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. Dissolve 50 mg of the substance under examination in 15 ml of *hydrochloric acid* and dilute to 100.0 ml with *water*. Dilute 5.0 ml of the solution to 50.0 ml with *water*.

Reference solution. Dissolve 0.121 g of *ferric ammonium sulphate* in 15 ml of *hydrochloric acid* and dilute to 100.0 ml with *water*. Dilute 5.0 ml of the solution to 50.0 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, test-tube. Shake and wait for 5 minutes, add 5 ml of the buffer solution and add 1.0 ml of 1.0 per cent w/v solution of *1,10 phenanthroline* in *water* to each test-tube. Measure the absorbance at the maximum at about 511 nm (2.4.7),

Calculate the content of Iron Fe^{+3}.

Storage. Store protected from moisture, at a temperature not exceeding 30°.