# Ferric Carboxymaltose

**Published on:** 01.08.2024 **Last date for comments:** 14.09.2024

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**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

| Description | Details |
|---|---|
| Document version | 2.0 |
| Monograph proposed for inclusion | IP 2026 |
| Tentative effective date of monograph | July, 2026 |
| First draft published on IPC website for public comments | 18.01.2024 |
| Draft revision published on IPC website for public comments | 01.08.2024 |
| Further follow-up action as required. | |

# Ferric Carboxymaltose

$[FeO_x(OH)_y(H_2O)_z]_n\ [\{(C_6H_{10}O_5)_m\ (C_6H_{12}O_7)\}_l]_k$

[Where $n \approx 10^3$, $m \approx 8$, $l \approx 11$, and $k \approx 4$ (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.

## Identification

**A. Iron**. Dissolve a quantity of the substance under examination containing 5 per cent w/v of Iron content in 80 ml of *water*. Heat at 70° to dissolve. Cool to room temperature and dilute to 100.0 ml with *water* mix and filter (Solution A). To 1 ml of the filtrate on a watch glass, add 2 drops of *ammonium hydroxide*; No precipitate is formed. Add 2 ml of *hydrochloric acid*, and 2 ml of *ammonium hydroxide*; a brown precipitate is formed, which gets dissolved slowly.

**B. Dextrin**. Dissolve 5 mg in 10 ml of *water*. Pipette 1 ml of the solution to a test-tube, add 10 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*, 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 50 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 0.0005844 g of NaCl.

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

*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, adjusted to pH 6.0 with 10 per cent solution of *sodium hydroxide* and filter. Transfer 1.0 ml of the filtrate to a 100-ml volumetric flask, add 50 ml of *water*, shake for 3 to 4 minutes and dilute to volume with *water*.

Determine the Colloidal particle size (Z-Average) and Polydispersity index using Zeta sizer.

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

Polydispersity index: Not more than 0.15.

**Zeta potential.** Limit not less than +3.0.

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

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

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

*Test solution.* Dissolve 0.5 g of solution A 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.* Use *water* as blank.

Transfer 1.0 ml, each of, test solution, reference solution and blank solution 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.

**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*. Heat the substance under examination containing 5 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 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 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 *glucose IPRS* in the mobile phase.

Chromatographic system

- a 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 a 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 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.

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

Where,

$M_W$ = weight average molecular weight,

$M_N$= number average molecular weight.

**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 ceric sulphate*, using 0.1 ml of *ferroin solution* as indicator, until colour changes from dark red to greenish yellow. Carry out a blank titration. At the end point solution changes from dark red to blue for blank titration.

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

**Total reducing sugars.** Not more than 1.0 per cent.

*Dinitrosalicylic acid reagent.* Weigh and transfer 0.65 g of *3,5-dinitrosalicylic acid* to a 100-ml volumetric flask, add 50 ml of *water* and sonicate to dissolve, add 32.5 ml *0.05 M sodium hydroxide* solution and 4.5 g *glycerol*, cool and dilute to volume with *water*.

*Test solution.* Transfer 1.5 ml of solution A to a 50-ml centrifuge tube, add 1 ml of *0.05 M sodium hydroxide* and vertex for about 2 minutes. Add 12.5 ml *ethanol* and vertex for about 5 minutes and mix. Centrifuge at 5000 rpm for 15 minutes. Filter the supernatant. Pipette out 10 ml of the filtrate to a glass tube and evaporate to dryness by keeping in water-bath at 90°. After evaporation add 1.0 ml *water* and mix.

*Reference solutions (a).* A 0.0015 per cent w/v solution of *D-Dextrose IPRS* (anhydrous) in *water*.

*Reference solutions (b).* A 0.005 per cent w/v solution of *D-Dextrose IPRS* (anhydrous) in *water*.

*Reference solutions (c).* A 0.008 per cent w/v solution of *D-Dextrose IPRS* (anhydrous) in *water*.

*Reference solutions (d).* A 0.010 per cent w/v solution of *D-Dextrose IPRS* (anhydrous) in *water*.

*Reference solutions (e).* A 0.012 per cent w/v solution of *D-Dextrose IPRS* (anhydrous) in *water*.

*Reference solutions (f).* A 0.015 per cent w/v solution of *D-Dextrose IPRS* (anhydrous) in *water*.

Transfer1.0 ml, each of blank (*water*), reference solution (a), (b), (c), (d), (e), (f) and the test solution to separate test tubes, add 4.0 ml of the dinitrosalicylic acid reagent to each test tube and shake. Stopper the test tube and heat at 80° for 30 minutes in a water-bath. Immediately cool in ice-bath for 10 minutes. Keep the solution to reach room temperature and filter. Measure the absorbance of each reference solutions and the test solution at 540 nm, using blank (*water*) as a compensation liquid.

Plot the calibration curve of absorbance Vs the concentration of reference solution. Determine the correlation coefficient, slope and Y-intercept of the line. Correlation coefficient should be not less than 0.99. Calculate the concentration of total reducing sugar in the test solution.

**Water** (2.3.43). Not more than 10.0 per cent, determined on 0.2 g.

**Bacterial endotoxins** (2.2.3). Not more than 0.2 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 dodecahydrate* 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, 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. Measure the absorbance at the maximum at about 511 nm (2.4.7).

Calculate the Iron (III) content.

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

## Solubility.

**Ferric Carboxymaltose.** Freely soluble in hot *water* and insoluble in *ethanol*, in *acetone* and in *ether*.

**4.2 General Reagents**

**Anthrone Solution.** Dissolve 0.2 g of *anthrone* in 100.0 ml of cool mixture of 95 volumes of *sulphuric acid* and 5 volumes of *water*.