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Original Research Article

Comprehensive physicochemical analysis of ferric carboxymaltose products marketed in India

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ABSTRACT

Background: Intravenous iron therapy is essential for managing iron-deficiency anemia (IDA). Ferric carboxymaltose (FCM), a colloidal complex of ferric oxyhydroxide within a carboxymaltose shell, enhances iron delivery and supports hemoglobin synthesis. However, stability, uniformity, shelf life and efficacy challenges persist across available FCM formulations in the Indian market. The latest Indian Pharmacopoeia (IP) guidelines emphasize evaluating key physicochemical properties to ensure the quality and safety of formulations.
Methods: This first-of-its-kind study comprehensively analyzes nine marketed injectable FCM formulations including an innovator and competing brands A-H, by evaluating their physicochemical parameters with statistical validation.
Results: The evaluation highlights significant deviations in key physicochemical parameters among the brands. Brand C exceeds acceptable density and particle size limits, leading to a high PDI and increased risk of agglomeration. Brand E shows low molecular weight and carbohydrate content with an elevated PDI, indicating instability and rapid iron release. Brand F, with a higher molecular weight, exhibits elevated PD and PDI values, reflecting molecular weight diversity. Brand H surpasses acceptable density and carbohydrate content ranges, further evidenced by its high PDI.
Conclusions: FCM is widely used for IDA and pregnancy, offering rapid iron replenishment with fewer doses and cost effectiveness. This study highlights quality and safety variations among injectable FCM brands. Brand A, with strong physicochemical properties interms of osmolality, iron core size, zeta potential, particle size, iron and carbohydrate contents comparable to the innovator, stands out as a reliable option for intravenous iron supplementation, ensuring efficacy and patient safety.

Keywords: Colloidal injection, Ferric carboxymaltose, Iron deficiency anemia, Iron oxyhydroxide complex, Physicochemical parameters

INTRODUCTION

Iron deficiency anemia (IDA) is the most common type of anemia, particularly affecting women with menorrhagia, during pregnancy and after blood loss from postpartum or surgical events. It results from insufficient iron for red blood cells and haemoglobin production, essential for oxygen transport.[1] Contributing factors include iron and vitamin deficiencies, poor nutrition and infections like malaria and hookworm, which can cause gastrointestinal bleeding. Conditions that worsen IDA include thalassemia, celiac disease, *H. pylori* infections, chronic kidney disease (CKD), congestive heart failure (CHF) and malignancies.[2,3] The World Health Organization (WHO) 2023 reports that anemia affects about 40% of children aged 6 to 59 months, 37% of pregnant women and 30% of

women aged 15 to 49 worldwide.[4] Managing IDA effectively requires addressing its causes, through iron supplementation and dietary changes. Untreated IDA can lead to fatigue and cognitive impairment. Initially, oral ferrous sulfates was the standard treatment for IDA, but its gastrointestinal side effects led to the exploration of intravenous iron formulations in 1954.[1,5] These formulations were stabilized using carbohydrates like dextran and sucrose for controlled iron release, however, they carried a high risk of anaphylactic shock.[3] Recent studies indicate that ferric carboxymaltose (FCM), which combines ferric oxyhydroxide with carboxymaltose, offers higher iron-loading capacity with fewer side effects compared to iron.[6]

In the Indian market, a variety of FCM brands are present, among which Orofer FCM® (Emcure Pharmaceuticals Ltd.) stands out as the leading brand, alongside the innovator brand and other competing brands. This research paper compares eight competing FCM formulations available in the Indian market, focusing on their quality and safety. The regulatory bodies like European Medical Agency (EMA), Food and Drug Administration (FDA) and Indian Pharmacopoeia (IP) emphasize the importance of assessing key physicochemical parameters such as particle size, molecular weight (MW), iron content, osmolality, density, iron core composition and pH levels since these factors impact bioavailability, pharmacokinetics, safety and therapeutic efficacy. This study evaluates physicochemical parameters across various FCM brands to determine their influence on stability, compatibility, solubility and effectiveness. By identifying the strengths and weaknesses of each formulation, this investigation provides a valuable resource for healthcare professionals, enhancing their understanding of FCM quality and aiding in the selection of effective options in the Indian market.

METHODS

FCM (50 mg/ml in 10 ml vials of 9 marketed brands) was purchased from the local market. The acquired FCM vials were designated as an innovator brand, along with brand A (Orofer FCM®) to H for the purpose of analysis. Ferric ammonium sulfate dodecahydrate (FAS), hydroxylamine hydrochloride, ammonium acetate, 1,10-Phenanthroline, concentrated hydrochloric acid (conc. HCl), anthrone, sulphuric acid, dextrose (D (+) Glucose) standard, dibasic sodium phosphate dihydrate, monobasic sodium phosphate monohydrate, sodium azide reagents were of analytical reagent (AR) grade and were purchased from LOBA Chemie. D-Glucose anhydrous was purchased from Qualigens SQ grade. The High MW dextran (2,70,000 Da) standard was purchased from Sigma-Aldrich.

This physicochemical analysis was conducted in accordance with lab standard operating procedures and in compliance with protocol during period of March 2024 to November 2024 at the pharmaceutical chemistry department of the Bombay College of Pharmacy-Autonomous, Mumbai, India.

pH

A pH meter measures hydrogen ion concentration in a solution, affecting formulation solubility, stability and bioavailability. A calibrated universal pH meter was used to measure pH of nine brands.[9,10]

Density

The density of FCM samples was determined by placing the sample in a pycnometer, weighing it and determining its specific gravity using a calibration factor.[11]

Osmolality

Osmolality is a key parameter for assessing the stability of colloid and nanoparticle formulations, as it evaluates solute-solvent interactions based on colligative properties.[12] An osmometer from Agilus Path Lab in Mumbai, Maharashtra, was used to analyze 2 ml sample from each vial to determine osmolality.

MW

Gel permeation chromatography (GPC), a type of size exclusion chromatography, efficiently evaluates MW distribution in polymers based on hydrodynamic volume. Key parameters include number average molecular weight (Mn), weight average molecular weight (Mw) and polydispersity index (PD=Mw/Mn).[13]

The apparent MW was measured using a Waters Alliance GPC system with a 2414 refractive index (RI) detector. Calibration of the 1000 Å ultra hydrogel column was performed with shodex pullulan standards P-82 (Mw=6300 Da, 21900 Da, 50100 Da, 110000 Da, 231000 Da, 375000 Da). The calculated Mw values for these standards were validated against European Pharmacopeia and USP standards.[14,15]

For analysis, 1 ml samples were diluted with 10 ml distilled water and 25 µl was injected. The analysis ran for 55 minutes at a flow rate of 0.5 ml/min, with the column oven and detector maintained at 45±2°C. Sodium phosphate buffer was used as the mobile phase and data were processed using Empower 3 software.[10]

Elemental iron content

Ultraviolet-visible (UV-Vis) spectrophotometry is a method for measuring iron concentrations, enabling precise quantification of elemental iron in solution for accurate dosing.[16]

To prepare the standard solution, 863 mg of FAS was dissolved in 500 ml of water with 25 ml of conc. HCl and heated to 90°C for 15 minutes. For each FCM brand

sample, 2 ml of injection sample was similarly treated. For absorbance analysis, 2 ml of the standard or sample solution was mixed with 1 ml of 10% hydroxylamine HCl, 5 ml of ammonium acetate buffer (pH 4.75) and 1 ml of O-phenanthroline reagent. Absorbance was measured at 511 nm using a Shimadzu UV spectrometer.[17]

Carbohydrate content

Carbohydrate concentration was determined using UV-vis spectrophotometry, correlating absorbance with analyte concentration via single-point standardization.[18] A standard solution (50 mg dextrose in 250 ml distilled water) was prepared, with distilled water as the blank.

Anthrone was used as a chromogenic reagent, producing a green color after polysaccharide hydrolysis. Three solutions were prepared, each containing 1 ml of distilled water, the standard solution and FCM samples. Anthrone was added to the test tubes, which were then heated in a water bath at 80°C for 10 minutes and cooled for 15 minutes and measured for absorbance at 625 nm using a Shimadzu UV-Vis spectrometer.[19]

Particle size

The particle size distribution and polydispersity index (PDI) of nanoparticles in FCM samples were analyzed using dynamic light scattering (DLS). A 1 ml sample was diluted in a 100 ml volumetric flask, agitated for 3-4 minutes and diluted to the mark with water, avoiding sonication. Cleaned cuvettes were used for analysis. Scattering data were collected at a 173° angle using a Zeta Sizer Nano S (Malvern Instruments Ltd.) with non-invasive backscatter technology and processed with Zeta Sizer Software Version 7.12 to determine intensity- based size distribution.[20,21]

Iron core size analysis by transmission electron microscopy

Transmission electron microscopy (TEM) is an advanced imaging technique that uses a focused electron beam to pass through a thin specimen, creating an image based on electron interactions, which is then projected onto a detection medium like a fluorescent screen, photographic film or CCD camera.[13] For nine FCM samples, 2 µl of each sample was diluted with 4.0 ml of distilled water. From each dilution, 0.5 µl was drop-cast onto a 200-mesh copper-carbon grid and dried under an infrared lamp for 10 minutes. The samples were analyzed using the TECNAI G2 SPIRIT BIOTWIN at 100 kV, with data processed using Tecnai Imaging & Analysis software.[22]

Zeta potential

Zeta potential, a measure of the surface charge of iron colloidal products, is analyzed using DLS. It is determined by measuring electrophoretic mobility, the velocity of charged particles in an electric field.[23] For sample preparation, 0.5 ml of each FCM sample was transferred into nine labelled 100 ml volumetric flasks, mixed with 50 ml of Milli-Q water, shaken for 3-4 minutes and diluted to volume. Zeta potential was measured using a dip cell and a Zeta Sizer Nano S (Malvern Instruments Ltd.).[10]

Statistical analysis

The data is presented as mean±standard deviation and statistical analyses were performed using GraphPad Prism 8. For normal distribution datasets, one-way ANOVA was used, with a 5% significance threshold. Post-hoc Dunnett's test was used for multiple comparisons and a $p<0.05$ was considered a significant difference.

RESULTS

An evaluation of nine FCM brands showed pH levels ranging from 5.0 to 7.0 (Table 1), which is within the acceptable range set by the IP for solubility and stability.[10] A significant difference was found between the brand A and the innovator brand ($p<0.05$). While other brands also varied in pH compared to the innovator, all remained within acceptable limits. This underscores the importance of maintaining pH within the standard range to minimize adverse reactions and ensure safety and compatibility at physiological blood pH levels (approximately 7.35-7.45). Brand H's density exceeds IP limits and very significantly differs from the innovator brand ($p<0.05$), as shown in table 1 potentially affecting efficacy. In contrast, brand D's density is slightly above the range but shows no significant variation, suggesting a minimal impact on the formulation.

Table 1 shows that the osmolality of the nine brands is within the IP range.[10] Brand A and brands C, D and F have $p>0.05$, indicating compatibility and safety for patients. In contrast, brand B displayed extremely significant differences from the innovator brand, while brands E, G and H have $p<0.05$, suggesting potential risks due to osmolality variability. MW and its distribution are crucial for assessing the quality and stability of iron colloids.[8] Table 1 shows that brands B and F have higher Mw, while brand E has a lower Mw, but all brands display Mw within IP limits. Brand A and brand B show no significant difference from the innovator brand ($p>0.05$), while brands B, E and G differ extremely significantly ($p<0.05$), potentially affecting efficacy, stability or safety.

Table 1 also reveals that Mn values for all brands fall within the acceptable range, but brands B and E exhibit significant differences ($p<0.05$), likely due to random fluctuations in MW distribution, meaning the samples may contain both smaller and larger carboxymaltose polymer. PD indicates the uniformity of polymeric structures in the solution.[24] The PD data indicates that all brands, except B and F, fall within defined limits, although brand F very significantly differs from the innovator brand.

Table 1: Physicochemical properties and statistical significance of pH, density, osmolality, Mw, Mn and PD of innovator brand and brand A-H.

FCM brands	pH	Density	Osmolality	Mw	Mn	PD
Acceptable range[10]	**5.0-7.0**	**1.05-1.15 g/ml**	**270-390 mOsm**	**130000-200000 Da**	**NLT 70000 Da**	**NMT 1.50**
A	5.876*	1.10$^{\#}$	340.33$^{\#}$	182724$^{\#}$	136623.5$^{\#}$	1.33$^{\#}$
Innovator brand	5.895	1.105	319	181419.5	135123	1.34
B	6.005****	1.071$^{\#}$	368****	233433****	190509*	1.21$^{\#}$
C	6.31****	1.019$^{\#}$	313.5$^{\#}$	176903$^{\#}$	127829$^{\#}$	1.38$^{\#}$
D	6.19****	1.19$^{\#}$	311.5$^{\#}$	199705.5**	150003$^{\#}$	1.33$^{\#}$
E	6.13****	1.08$^{\#}$	352*	122787****	92876*	1.32$^{\#}$
F	6.07****	1.13$^{\#}$	318$^{\#}$	201915.5**	130909$^{\#}$	1.54**
G	6.5****	1.07$^{\#}$	351.5*	142594****	104388$^{\#}$	1.32$^{\#}$
H	6.31****	1.24**	349*	155875.5***	112023$^{\#}$	1.39$^{\#}$

$^{\#}$: No significant difference, *: p<0.05 (significant), **: p<0.01 (very significant), ***: p<0.001 (highly significant), ****: p<0.0001 (extremely significant). In the current study, FCM brands were compared with the innovator brand. Data presented in the table is the average of three readings.

Table 2: Physicochemical properties and statistical significance of elemental iron content, carbohydrate content, zeta potential, particle size, PDI and Iron core size of innovator brand and brand A-H.

FCM brands	Elemental iron content	Carbohydrate content	Particle size	PDI	Iron core size	Zeta potential
Acceptable Range[10]	**95%-105% w/v**	**5.5-8.5% w/w**	**20-30 nm**	**NMT 0.15**	**11.7±4.4 nm**	**NLT 3 (should be +)**
A	95.48$^{\#}$	6.89$^{\#}$	25.24*	0.081$^{\#}$	9.46	4.6
Innovator brand	99.7	7.49	26	0.097	9.77	6.55
B	101.08$^{\#}$	7.01$^{\#}$	27.135*	0.119$^{\#}$	9.54	-4.33
C	102.8$^{\#}$	6.10*	27.775***	0.219****	8.83	-12.9
D	96.52$^{\#}$	6.34*	30.205****	0.229****	8.93	-11.4
E	97.62$^{\#}$	4.92***	21.66****	0.164**	8.64	-18.2
F	104.32$^{\#}$	6.05**	29.76****	0.193***	8.34	-17.1
G	106.72$^{\#}$	7.18$^{\#}$	25.12*	0.24****	9.96	-15.9
H	99.78$^{\#}$	5.14**	29.2****	0.265****	9.41	-15.1

$^{\#}$: No significant difference, *: p<0.05 (significant), **: p<0.01 (very significant), ***: p<0.001 (highly significant), ****: p<0.0001 (extremely significant). In the current study, FCM brands were compared with the innovator brand. Data presented in the table is the average of three readings.

The comparative study presented in Table 2 shows that the elemental iron contents of FCM brands fall within the label claim range (95-105% w/v), except for brand G with no significant difference (p>0.05) from the innovator brand, its iron content is 106.72%w/v, slightly exceeding the specified range outlined by IP.[10] The iron content in other brands was found comparable to that of the innovator brand, indicating that the elemental iron content in these FCM formulations is meeting the expected standards. Carbohydrate levels in most FCM brands, except E and H, range from 5.5-8.5% w/w (Table 2).

Brand A shows no significant difference in carbohydrate content compared to the innovator brand. However, brands E, F and H have high and very significant differences respectively, in carbohydrate levels relative to the innovator, while brands C and D show a less significant difference compared to these brands. These variations suggest that brands D, E and H may have unique carbohydrate formulations, thereby it may potentially impact the stability, iron release, efficacy, bioavailability or safety.[14] Table 2 shows that all brands, except brand D, exceed IP particle size limits. Brand D demonstrates 30.205 nm particle size, which is slightly higher than the 30 nm threshold. Brands A, B and G show minimal differences when compared to the innovator brand, while brands C, D and H show extremely significant differences in their p values. The PDI ranges from 0.0 (uniformity) to 1.0 (high polydispersity).[25] PDI values of 0.2 or less are acceptable for polymer-derived nanoparticles.[24] Table 2 shows that only brand A and B fall within the acceptable range (p>0.05), indicating a more consistent size distribution compared to other brands (p<0.05).

The TEM analysis at 50 nm scale of akageneite (β-FeOOH) revealed the structure of its iron core, as shown in Figure 1. FCM consists of rod-shaped iron cores with iron crystals.[26] Brands A, B, C and F show structural uniformity, whereas brands D, G and H show noticeable agglomeration of iron crystals as compared to the innovator brand.

The surface charge or ζ potential on FCM formulations is crucial for predicting efficacy, safety and potential for side effects, particularly in terms of targeted delivery and reduced adverse reactions. A strong positive or negative ζ-potential helps to maintain the physical stability of nanoparticles in suspension by preventing aggregation.[21] Table 2 shows that brand A and innovator brand exhibited a positive ζ-potential under constant pH conditions, brands B to H demonstrated negative ζ-potential.

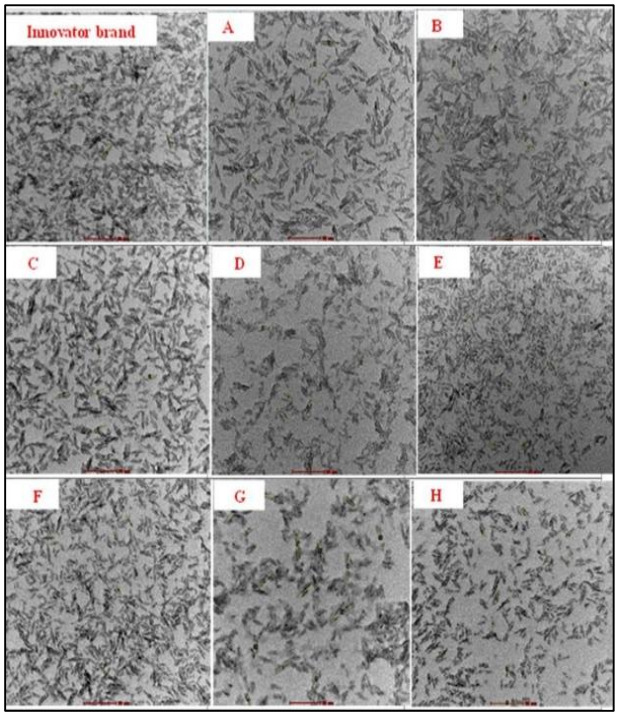

Figure 1: (A-H) TEM image of iron oxide cores of innovator brand, brands.

DISCUSSION

FCM is a safe and effective iron replacement therapy for pregnant and postpartum women, essential for fetal development and oxygen transport. Its nanoparticle structure consists of a polynuclear ferric oxyhydroxide core and a carboxymaltose shell (Figure 2), enabling controlled bioavailable iron release and high-dose administration in a single infusion, enhancing IDA treatment efficiency.[17]

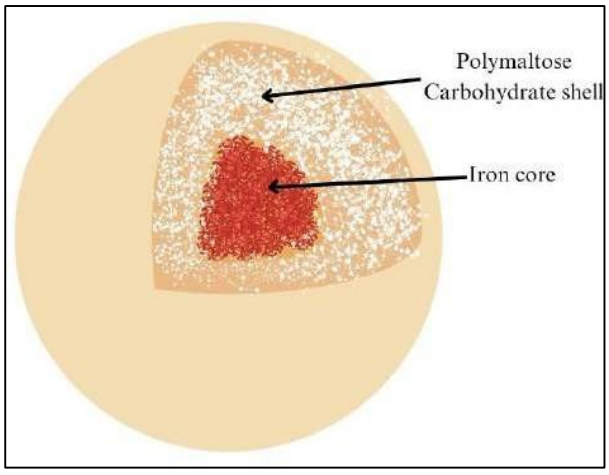

Figure 2: Diagrammatic representation of FCM.

While various FCM formulations are available in India, challenges persist regarding stability, consistency, free iron release, shelf life and overall quality. To ensure safety and efficacy, it is essential to assess parameters such as pH, density, osmolality, ferric ion content, MW, carboxymaltose content and particle characteristics.[27] The studies show that pH is essential for FCM complex solubility, with an optimal pH of 5.5 improving its processing by the reticuloendothelial system for better tissue targeting.[14] This ensures controlled iron delivery and minimizes unintended dissociation or rapid clearance. Deviations from this pH can destabilize the iron carboxymaltose complex, affecting solubility and effectiveness. At neutral pH, carboxyl groups in carboxymaltose provide a stable negative charge, promoting coordination with positively charged ferric ions and preventing precipitation.[29]

The density of FCM formulations is crucial for ensuring product uniformity and long-term stability. Proper density maintains consistent dispersion of the iron-carboxymaltose complex, reducing the risk of phase separation or sedimentation, which is essential for the efficacy and safety of the formulation. Brand H of the FCM formulation demonstrated the highest density among the tested FCM brands, making it an outlier. Therefore, such brands require closer attention to ensure long-term stability.[30]

In injectable formulations, matching osmolality to physiological fluids minimizes pain, swelling and adverse reactions at the injection site. High osmolality can cause irritation, while low osmolality may compromise solubility and stability. Optimal osmolality is crucial for stabilizing iron and ensuring its efficient absorption without degradation.[12]

Similarly, MW significantly impacts the binding affinity of iron in the FCM complex, affecting iron release into the bloodstream. Low MW complexes increase free iron circulation due to weak interactions, while high MW complexes show stronger interactions that enhance stability and reduce iron aggregation.[31] Clinical studies indicate that the low MW formulation (96,000 Da) carries a higher risk of anaphylactic reactions as seen in case of brand D. Formulations with 130,000 and 200,000 Da MW exhibit slower plasma iron clearance and longer half-lives, improving retention and therapeutic effectiveness.[10,14] Additionally, a narrow MW distribution, indicated by a low Mw/Mn ratio, is preferred for consistent performance.

FCM is an iron carbohydrate complex that contains 50 mg of iron/ml and 75 mg of carboxymaltose/ml.[32] The iron core of FCM consists of about 110,000 iron atoms and 180,000 oxygen atoms, contributing to its small and dense structure.[27] This compactness makes the iron core less prone to interactions with chelators or redox processes, resulting in a more stable form of iron upon cellular uptake. The reduced lability of the iron minimizes the release of toxic free ions, enhancing safety and reducing the risk of adverse effects.[14]

Optimal elemental iron is required for rapid repletion of iron stores. However, excess iron content will exceed the binding capacity of transferrin leading to the formation of non- transferrin bound iron, consequently, leading to generate reactive oxygen species, causing oxidative damage. In brand G, the slightly elevated iron content beyond IP limits suggests this risk.[14] The carbohydrate shell in FCM is vital for stabilizing the iron core. Insufficient carbohydrate levels can lead to ferric oxyhydroxide precipitation, compromising formulation integrity and increasing the release of toxic labile iron. Low carbohydrate content in brands E and H raises concerns about their stability and safety. Additionally, smaller particle size increases the surface area of elemental iron, enhancing its solubility in gastric fluid and improving absorption.[33] Understanding the relationship between ζ potential and pH is vital for predicting how pH changes in the body affect nanoparticle surface charge. Additionally, surface charge significantly affects the in vivo clearance and biological distribution of nanoparticles.[21] The formulation must be buffered to a pH that maximizes ζ potential stability in physiological conditions. However, the studies demonstrated poor positive (4.6/ 6.55) or poor negative ζ potential (-4 to -18), indicating potential colloidal instability.

Overall, in summary the studies reveal a clear relationship between MW carbohydrate content and PD. Brand E has low MW and carbohydrate content, suggesting rapid labile iron release and potential tissue toxicity.[27] In contrast, brand B exceeds the acceptable MW range, resulting in a higher PD. Brand F's slightly elevated MW correlates with a marginally increased PD, indicating slower free iron release and potential adverse reactions. Additionally, iron release from polynuclear iron oxyhydroxide carbohydrate complexes is inversely related to MW.[14] Brand D's density and particle size exceed acceptable limits, leading to a high PDI and risk of agglomeration. Brand H also surpasses acceptable density and carbohydrate content, as shown by its elevated PDI, highlighting formulation variability.

CONCLUSION

FCM is widely used to manage CKD, CHF, IDA, cancer and during pregnancy, allowing for rapid iron restoration with fewer doses and economic benefits. Recent research on injectable FCM in India reveals significant quality and safety differences, aiding healthcare professionals in selecting effective treatments. Notably, brand A demonstrates strong physicochemical properties, comparable to the innovator brand and outperforms many other FCM products, making it a reliable choice for intravenous iron supplementation with ensured therapeutic efficacy and patient safety.

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