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Original Research Article

Physicochemical characterization of ferric carboxymaltose brands in India: relevance to anemia management in chronic kidney disease

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ABSTRACT

Background: Ferric carboxymaltose (FCM) is widely used in the management of anemia associated with chronic kidney disease. The therapeutic efficacy and long-term safety of FCM related to free iron mediated toxicity can be influenced by its physicochemical properties. This study aimed to compare physicochemical properties across various FCM brands available in India.
Methods: Samples of FCM from 6 different manufacturers were procured including Dr. Reddy's FCM brand injection Irny and subjected to a series of laboratory tests. Key quality attributes like carbohydrate content, molecular weight, etc. were analysed using validated methodologies and compared with USFDA reference-listed drug (RLD) Injectafer.
Results: The carbohydrate content of Dr. Reddy's injection Irny (8.78%) was comparable to USFDA RLD (8.2%), whereas other brands showed variability ranging from 4.38% to 10.56%. Molecular weight of Irny (2.74 lakh) was also in line with USFDA RLD (2.94 lakh), with other brands mostly exhibiting lower molecular weights. Zeta potential of injection Irny (0.17 mV) closely matched that of USFDA RLD (1.25 mV), while other brands showed more negative values ranging from -0.70 mV to -27 mV. Degradation kinetics (T75 value) of injection Irny (19.14 minutes) were similar to USFDA RLD (18.34 minutes), while other brands demonstrated longer degradation times (21 to 52 minutes).
Conclusions: Study highlighted notable variability in physicochemical properties of different FCM brands. Dr. Reddy's injection Irny closely aligns with the USFDA RLD Injectafer quality attributes, suggesting comparable potential clinical outcomes and long-term safety. The observed differences among other brands may influence their bioequivalence and long-term safety.

Keywords: Anemia, Bioequivalence, Chronic kidney disease, Ferric carboxymaltose, Physicochemical properties

INTRODUCTION

Chronic kidney disease (CKD) is a major global public health problem, with an estimated prevalence of 8-16% worldwide.[1] In India, CKD affects approximately 17.2% of the population.[2] Anemia is a frequent complication in CKD, affecting approximately 14-50% of patients in countries like US, India and China.[3-5] A recent cross-sectional, prospective observational study revealed that 82.4% of Indian patients with CKD suffered from anemia.[6] Overall burden of anemia in CKD is substantial, affecting patient's quality of life with increasing risk of

cardiovascular diseases, progression of CKD, hospitalization and mortality.[7,8]

The causes of anemia in CKD are multifactorial and include reduced erythropoietin production by the kidneys, iron deficiency, inflammation, blood loss and shortened red blood cell lifespan.[9,10] Iron deficiency both absolute and functional iron deficiency, is a key factor contributing to anemia in CKD patients and mainly occurs due to factors such as blood loss from dialysis, reduced gastrointestinal absorption and increased hepcidin levels.[10,11]

Current treatment strategies for anemia in CKD involve the use of iron supplementation and erythropoiesis-stimulating agents (ESAs) to replenish iron stores and correct hemoglobin levels.[12] Intravenous (IV) iron therapy is often preferred over oral iron in CKD patients due to poor gastrointestinal absorption and adverse gastrointestinal effects of oral iron.[12] Among the i.v. iron formulations, ferric carboxymaltose (FCM) has emerged as the preferred choice due to its favorable safety profile and ability to deliver high doses of iron in a single administration over a short infusion period, reducing the need for frequent hospital visits.[13]

FCM is a non-dextran strong stable molecule designed to provide stable iron-carbohydrate complexes with controlled release of bioavailable iron for erythropoiesis that allows for rapid and effective replenishment of iron stores in patients with CKD anemia.[13] The clinical benefits of FCM in CKD anemia have been demonstrated in several randomized controlled trials, showing improvements in hemoglobin levels, reduced ESA requirements and better quality of life outcomes.[14-18] The robust clinical data supporting the efficacy and safety of FCM in CKD anemia make it a preferred choice in clinical practice.

Considering various brands of FCM available in the market, bioequivalence between different brands along with high similarity to the innovator FCM brand is critical to ensure consistent therapeutic outcomes with long term safety in clinical practice. Clinicians often rely on bioequivalent brands to the innovator product that are expected to have similar clinical efficacy and safety profile, especially long-term safety; however, subtle differences in formulation characteristics can impact the clinical performance of these different brands. Key parameters such as carbohydrate content, molecular weight, surface charge, degradation kinetics by alpha-amylase play crucial roles in the pharmacokinetics (PK) and pharmacodynamics (PD) of FCM.[19,20] These physicochemical properties influence the stability, bioavailability and safety, especially long-term, of FCM, potentially affecting patient long term outcomes.[19]

Given the growing use of various FCM brands in clinical practice and the critical role of these parameters, it is essential to evaluate the critical bioequivalence parameters of different available brands of FCM and their closeness to the innovator FCM brand to ensure optimal patient outcomes. This study aimed to compare the physicochemical characteristics including surface charge (zeta potential) and in-vitro behaviour of Dr Reddy's indigenously manufactured FCM, injection Irny (Dr Reddy's Laboratories Limited, Srikakulam District, Andhra Pradesh, India) with various other commercialized FCM brands available in the Indian market, including the USFDA reference-listed drug (RLD), Injectafer (American, Regent, Inc., Shirley, NY 11967, United States). By comprehensively analyzing these parameters, this study sought to provide valuable insights into the importance of formulation quality in the therapeutic effectiveness and long-term safety of FCM products, ultimately aiding clinicians in making informed decisions when selecting i.v. iron therapies for their patients.

Hence, this study was carried to evaluate the critical quality attributes of various commercially available FCM brands such as carbohydrate content, molecular weight, surface charge, degradation kinetics by alpha-amylase and compare them with Dr. Reddy's indigenously manufactured FCM brand injection Irny at USFDA authorized manufacturing plant and the USFDA RLD Injectafer.

METHODS

Study design

This study was an in-vitro, laboratory-based comparative analysis carried out in Analytical laboratory of Integrated Product Development Organization (IPDO), Bachupally, Hyderabad in August 2023. Samples of FCM manufactured by major pharmaceutical companies were subjected to a series of validated laboratory tests.

Sample collection and preparation

FCM samples of 5 different brands were procured from the market along with Dr Reddy's FCM brand injection Irny. Each sample was carefully inspected to ensure that the packaging was intact and there was no evidence of tampering or damage. The samples were stored according to the manufacturer's instructions until the time of testing. The USFDA Prescribing Information of Injectafer, revised on May 2023 was used to compare results of laboratory analysis of all FCM brands with USFDA RLD.

Laboratory analysis

All laboratory analyses were performed in the analytical laboratory of IPDO, Bachupally, Hyderabad, using validated analytical methods and various attributes were assessed. To confirm the presence of FCM, an iron identification test was conducted. The test was considered positive if the solution turned pink upon the addition of amyl alcohol or diethyl ether and the red color was discharged upon the addition of mercuric chloride. This

qualitative test confirmed the presence of ferric ions in the FCM molecule.

The molecular weight of the FCM product was determined using gel permeation chromatography (GPC). The molecular weight distribution is a key attribute that affects the PK and PD of the iron complex. The carbohydrate content, specifically dextrin, in the FCM products was estimated using high-performance liquid chromatography (HPLC).

Degradation kinetics by alpha amylase was evaluated using Dynamic light scattering to monitor specifically the T75 value. The release profile provides insight into the controlled release characteristics of the FCM complex. The zeta potential of each FCM sample was measured using a Malvern Zetasizer instrument. Zeta potential is an indicator of the stability of colloidal dispersions and can influence the aggregation and clearance of iron nanoparticles in the bloodstream.

Statistics

In this study, we chose not to apply formal statistical analyses due to the nature of the data and the objectives of the research. The data presented were derived from a series of laboratory tests conducted using validated methodologies, and our intent was to provide a descriptive overview of the characteristics of each brand. The results were presented as absolute values obtained from these laboratory tests for parameters such as carbohydrate content, molecular weight, surface charge (zeta potential), and degradation kinetics by alpha amylase. This approach was chosen to highlight the observed differences in physicochemical properties directly and to facilitate a better understanding of how these properties may influence the clinical performance and long-term safety of the FCM preparations.

RESULTS

The study evaluated and compared the critical quality attributes of 5 FCM brands available in the market with Dr. Reddy's indigenously manufactured FCM brand injection Irny and the USFDA RLD Injectafer. The results of these analyses are presented below.

Carbohydrate content (dextrin)

The carbohydrate content, specifically dextrin content of the different FCM brands was determined using HPLC. There was notable difference in carbohydrate content among the brands. As shown in Figure 1, Dr. Reddy's FCM brand had a carbohydrate content (8.78%) similar to the USFDA RLD (8.2%, p>0.05), while brands 1, 2 and 4 had lower carbohydrate contents and brands 3 and 5 had higher contents compared to the USFDA RLD.

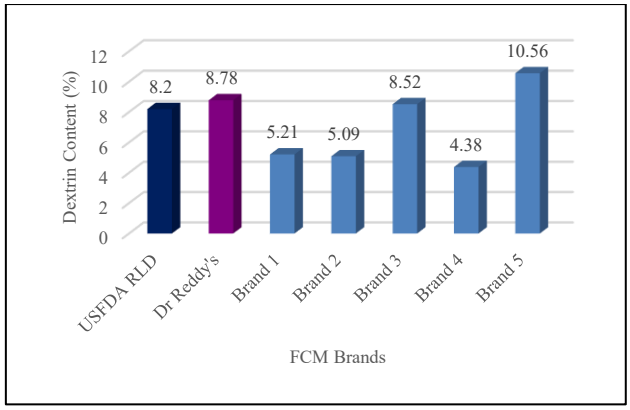

Figure 1: Carbohydrate content (%) of different ferric carboxymaltose (FCM) brands compared to the USFDA reference listed drug (RLD).

FCM- ferric carboxymaltose, USFDA RLD- USFDA reference listed drug.

Molecular weight

The molecular weight of the FCM complexes was measured using GPC. The molecular weight of Dr. Reddy's FCM brand (2.74 lakh) was in line with the USFDA RLD (2.94 lakh). Brands 1, 4 and 5 had lower molecular weights. Brands 2 and 3 had molecular weights closer to the USFDA RLD, suggesting similar molecular weight (Figure 2).

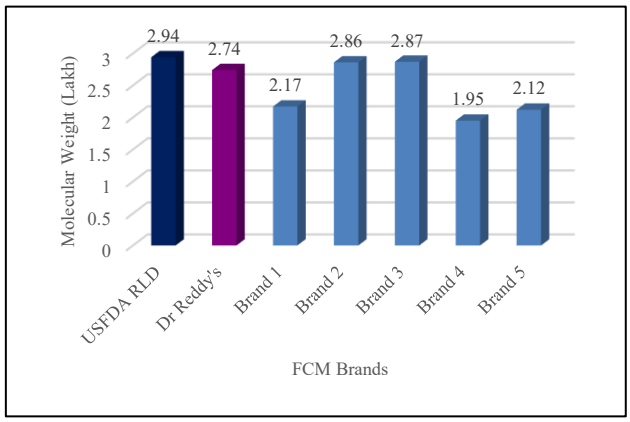

Figure 2: Molecular weight of different ferric carboxymaltose (FCM) brands compared to the USFDA reference listed drug (RLD).

FCM- ferric carboxymaltose, USFDA RLD- USFDA reference listed drug.

Surface charge (zeta potential)

The surface charge (zeta potential) of the FCM brands was measured using a Malvern Zetasizer. There were notable differences in zeta potential among the brands. Dr. Reddy's FCM brand had a zeta potential (0.17 mV) similar to the USFDA RLD (1.25 mV). Brands 1, 4 and 5 showed more negative zeta potential values compared to the USFDA RLD. Brands 2 and 3 also showed slightly negative zeta potentials, but closer to neutral (Figure 3).

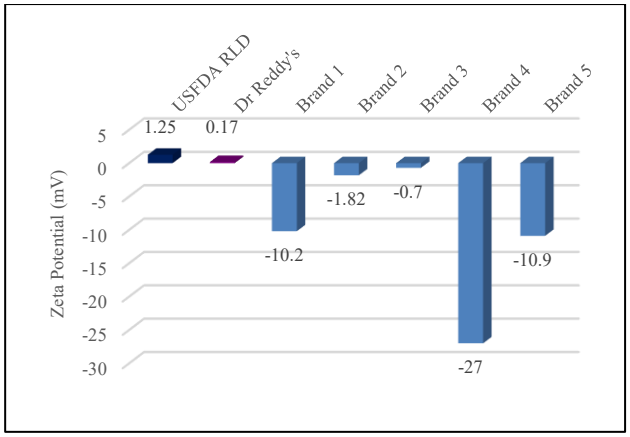

Figure 3: Surface charge (zeta potential) of different ferric carboxymaltose (FCM) brands compared to the USFDA reference listed drug (RLD).

FCM- ferric carboxymaltose, USFDA RLD- USFDA reference listed drug.

Degradation kinetics by alpha amylase (T75 value)

We also observed notable differences in T75 values among the brands. The T75 value of Dr. Reddy's FCM brand (19.14 min) was not different from the USFDA RLD (18.34 min). Brands 1, 2, 4 and 5 exhibited longer T75 values. Brand 3 had a T75 value (21 min) closer to the USFDA RLD, indicating a degradation rate more aligned with the reference product (Figure 4).

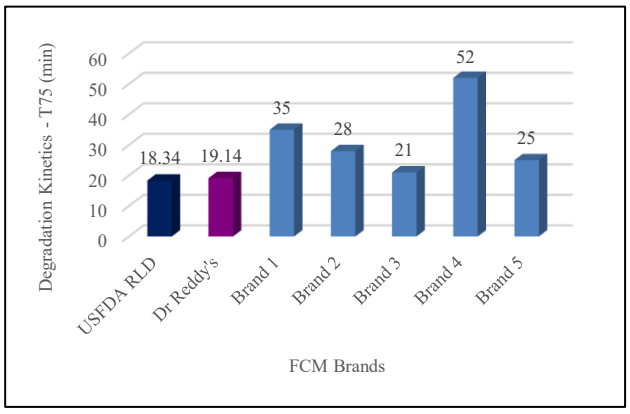

Figure 4: Degradation kinetics (T75 values) of different ferric carboxymaltose (FCM) brands by alpha amylase compared to the USFDA reference listed drug (RLD).

FCM- ferric carboxymaltose, USFDA RLD- USFDA reference listed drug.

DISCUSSION

This study provides a comprehensive analysis of the physicochemical properties of various FCM brands, including Dr. Reddy's brand injection Irny and the USFDA RLD Injectafer. Study indicates significant variability in carbohydrate content, molecular weight, surface charge (zeta potential) and degradation kinetics by alpha amylase among the different brands. Dr. Reddy's FCM brand demonstrated similar characteristics to the USFDA RLD across all measured parameters, suggesting comparable stability, efficacy and safety profiles. In contrast, other brands showed notable differences in these critical attributes, which could potentially impact their clinical effectiveness and long-term safety in the management of anemia in CKD. These findings underscore the importance of considering these physicochemical properties when selecting FCM brand for clinical use, as even small differences may significantly affect long-term safety.

FCM is a non-dextran parenteral iron formulation approved for the rapid and high-dose replenishment of depleted iron stores. FCM is composed of an iron complex featuring a ferric oxyhydroxide core surrounded by a carbohydrate shell. This macromolecular structure enables controlled iron delivery to the reticuloendothelial (RES) system's cells and facilitates the subsequent transfer to iron-binding proteins, such as ferritin and transferrin, while minimizing the risk of excessive release of free or labile iron into the bloodstream.[13]

The safety and effectiveness of iron colloid drug products can be influenced by their physicochemical properties, which are grouped into three main categories: properties of the entire nanoparticle, such as molecular weight and particle size; characteristics of the iron core; and attributes of the carbohydrate shell, including surface charge. These properties are likely associated with the PK and tissue distribution of iron colloids and they may also affect the in-vivo stability and kinetics of iron release.[19]

The carbohydrate shell in FCM preparations plays a pivotal role in the stability and functionality of the iron-carbohydrate complex. The carbohydrate content, primarily dextrin, is integral to form a protective shell around the iron core.[21] This shell stabilizes the iron complex, slows the release of bioactive iron, affects uptake by mononuclear phagocyte system and protects the particles from further aggregation and sustaining the particles in a colloidal suspension.[19,22,23]

Our results showed that the carbohydrate content of Dr. Reddy's FCM brand (7.68%) was similar to the USFDA RLD (7.47%), while other brands exhibited notable variability, ranging from 4.38% to 10.56%. The lower carbohydrate content observed in brands 1, 2 and 4 may lead to reduced stability and faster release of iron, potentially increasing the risk of adverse reactions such as oxidative stress, iron overload and organ toxicities. Conversely, brands with higher carbohydrate content, such as brands 3 and 5, may have a slower iron release profile, potentially reducing bioavailability and therapeutic efficacy. Therefore, maintaining an optimal carbohydrate content is critical for balancing the stability and bioavailability of iron in FCM preparations.

Carefully engineered carbohydrate ligands are complexed with polynuclear iron cores to achieve pharmacological

activity in a safe and effective manner. These iron-carbohydrate complexes are designed to facilitate the clearance from the serum by macrophages and then transported to the liver and spleen, where they supply iron to the physiological iron storage and transport systems. Even minor alterations in carbohydrate content, alkali content or the pH at the precipitation point can significantly impact the safety profile of the final drug product.[20] Data suggest that manipulating the concentration of the carbohydrate ligand or modifying the manufacturing process can result in varied safety outcomes for iron-carbohydrate complexes.[24,25] Thus, carbohydrate ligand is a key factor influencing the PK and PD properties of these nanoparticles, as well as in-vivo bioavailability of iron.[20,21,26]

The molecular weight of the FCM complex is another critical factor influencing the rate of iron release and the safety profile of the product. The rate at which iron is released from polynuclear iron hydroxide-carbohydrate complexes in inversely proportional to the molecular weight of the complex.[27] Higher molecular weight complexes typically have a slower rate of iron release, which can provide a more sustained delivery of iron and minimize the risk of rapid iron overload and associated toxicity. Conversely, lower molecular weight complexes may release iron more rapidly, potentially leading to a higher risk of acute toxicity and long-term adverse events.[28]

In our study, the molecular weight of Dr. Reddy's FCM brand (2.74 lakh) was comparable to the USFDA RLD (2.94 lakh), suggesting a similar rate of iron release and safety profile. Brands 1, 4 and 5 exhibited significantly lower molecular weights, which could result in a faster release of iron and increased risk of adverse reactions.[28] In contrast, brands 2 and 3 had molecular weights closer to the RLD, indicating a potentially safer profile with a controlled release of iron. These findings underscore the importance of molecular weight in determining the safety and efficacy of FCM preparations.

The net charge on the surface of a particle, known as the zeta potential, is a significant physical property that affects PK and biodistribution (BD).[29] In the absence of pH adjustment, all iron formulations exhibit a negative charge, except for iron carboxymaltose.[30] The zeta potential, or surface charge, of FCM complexes plays a crucial role in their colloidal stability and interactions with biological systems. It influences the uptake by the mononuclear phagocyte system, as well as the tissue distribution and PK of the complexes.[19] A positive zeta potential is generally associated with better colloidal stability and reduced aggregation of nanoparticles whereas negative zeta potential of particles is associated with more rapid uptake by RES.[31] However, a highly positive or highly negative zeta potential can also influence the uptake of particles by the RES, potentially affecting their BD and clearance from the body.

Our findings showed that Dr. Reddy's FCM brand had a positive zeta potential (0.11 mV) similar to the USFDA RLD (1.25 mV), indicating comparable colloidal stability and uptake by RES. Brands 1, 4 and 5 exhibited significantly more negative zeta potentials, which could lead to increased uptake by the RES and potentially faster clearance from the body, reducing bioavailability and therapeutic efficacy.[31,32] Brands 2 and 3, with zeta potentials closer to neutral may have a more balanced profile, reducing the likelihood of rapid clearance while maintaining stability. This highlights the importance of zeta potential in influencing the PK and therapeutic effectiveness of FCM brands.

After intravenous administration of FCM, the carbohydrate shell is only partially degraded in the bloodstream by alpha amylase.[33] The degradation kinetics of FCM complexes, especially their partial breakdown by alpha-amylase, are critical in determining their stability and iron release profile.[33] The T75 value, which represents the time required for alpha amylase to partially degrade 75% of the FCM complex, is an important indicator of the stability of the iron-carbohydrate complex. A shorter T75 value indicates faster degradation and potentially faster release of bioactive iron, which may enhance the efficacy but also increase the risk of adverse effects.

In this study, the T75 value for Dr. Reddy's FCM brand (19.14 min) was comparable to the USFDA RLD (18.34 min), suggesting a similar release profile. Brands 1, 2, 4 and 5 had significantly longer T75 values, indicating a slower degradation rate and potentially reduced bioavailability due to the delayed release of iron. This delayed release could be beneficial in minimizing toxicity but may compromise the therapeutic efficacy in patients requiring rapid iron replenishment. Brand 3 with a T75 value closer to the RLD, may offer a balanced profile, providing both safety and efficacy. These findings suggest that the degradation kinetics of FCM complexes are critical determinants of their clinical performance and should be carefully considered when selecting a brand for clinical use.

There are certain limitations to this study that must be taken into account while interpreting the results. The analysis conducted in this study was based on in-vitro laboratory tests. While these tests provide valuable insights into the physicochemical properties of different FCM brands, they may not fully replicate the complex in-vivo conditions. The clinical relevance of the differences observed may vary in actual clinical settings. Future prospective clinical studies are necessary to confirm these in-vitro findings and determine their impact on clinical outcomes in patients with CKD anemia. Secondly, the study compared a select number of FCM brands. Although these brands represent a range of available products, there may be additional FCM brands in the market with different formulations or manufacturing processes. As a result, the findings may not be generalizable to all FCM brands.

CONCLUSION

The findings of this study highlight notable differences in the physicochemical properties of various FCM brands, which could have important implications for their clinical use. Dr. Reddy's FCM brand injection Irny demonstrated critical quality attributes comparable to the USFDA RLD Injectafer, suggesting it may provide similar clinical benefits. However, other brands showed considerable variability in these attributes, which could impact their bioequivalence, therapeutic effectiveness and long-term safety. Clinicians should consider these factors when selecting FCM brands to ensure optimal patient outcomes in the management of anemia in CKD.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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