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Original Article

Particle Size Matters: A Comparative Study of Transport of Encapsulated Iron through M Cells

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Abstract

Background and Objectives: Bioavailability of iron compounds is inversely related to their size. Decreasing particle size improves iron transport. However, bioavailability through the conventional DMT-1 pathway is hampered by mucosal block caused by hepcidin rise. This makes the microfold cells (M cells) in the intestine attractive targets for delivery of oral iron to systemic circulation. This study aimed to perform a comparative *in vitro* examination of different commercially available oral iron preparations and their transport across intestinal epithelial and M cells.

Method: An *in vitro* model of Caco-2 monoculture and Caco-2/Raji B co-culture was used to study transport across intestinal epithelial and M cells, respectively. The amount of elemental iron (Fe^{3+}) transported across was quantified using ICP-AES.

Results: Of all the iron salts that claim to transport through M cell mechanism, SunActive® Fe showed the highest transport (39.99%) whereas Lipofer® (0.48%) and Sideral® (10.26%) showed poor transport. SunActive® Fe showed the highest transport even through the intestinal endothelial Caco-2 cells and this transport is increased in presence of M cells.

Interpretation and Conclusion: This study paves the way to a greater understanding of therapeutic interventions for the treatment of iron deficiency anemia and identifies the most efficacious iron of those tested.

Key words: Bioavailability, Ferric pyrophosphate, Hepcidin, Iron Deficiency Anemia, M cells

INTRODUCTION

Iron is indispensable for the human body and a vital component of several bodily functions primarily, hemoglobin (Hb) synthesis, and transport of oxygen throughout the body. Proportionally, higher concentrations of iron are found in the basal ganglia of the human brain than in the liver. In breastfeeding infants, parts of the brain, particularly the microglia, continue to develop, and therefore iron is vital for developing cognitive functions at this stage of life.[1]

Anemia is a serious global public health problem that particularly affects young children and pregnant women. The World Health Organization (WHO) estimates that 42% of children <5 years of age and 40% of pregnant women worldwide are anemic.[2]

In spite of advances in healthcare, iron deficiency (ID) remains a foremost public health fear in both developed and developing countries, with adolescent women being mainly susceptible.[3] It affects all age groups including infants, adolescents, reproductive age group women, and elderly people. The prevalence rates for reproductive age group pregnant women and non-pregnant women are 29% and 38%, respectively; however, among different age groups, nearly 468 million women of reproductive age are commonly affected with anemia.[4]

Iron supplementation is the most commonly sought-after solution to prevent and treat iron deficiency and Iron Deficiency Anemia (IDA). Iron is supplemented by various methods such as oral, intravenous (IV) iron therapy, or blood transfusion. Red blood cell transfusion produces a rapid, albeit transient, rise in Hb, thus increasing oxygen-carrying capacity.[5] On the contrary, both IV and

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oral iron therapies restore iron levels and help maintain steady Hb levels. IV iron is administered directly into the bloodstream and therefore bypasses the gastrointestinal (GI) lumen. However, IV iron if not well tolerated can be toxic and may cause anaphylaxis and hypersensitivity reactions.[6] Moreover, IV iron is expensive, and costs over 60 times more than oral iron.[7] Oral iron is the most common treatment for ID and IDA due to its low cost, bioavailability, and effectiveness. While there are many different types of oral iron supplements available, the most commonly prescribed oral iron is ferrous sulfate ($FeSO_4$). However, an important clinical limitation of oral iron therapy is that it often causes significant gastrointestinal (GI) side effects such as constipation, abdominal pain, nausea, and bloating.[8]

The Challenges in Iron Absorption

Non-heme iron is majorly transported through the divalent metal transporter-1 (DMT-1).[9] DMT-1 is a protein expressed in the apical membrane of enterocytes.[10] Iron is taken up by the enterocyte through DMT-1 on the luminal membrane after reduction by a cytochrome Dyctb. Once inside the cell, iron can either be stored in ferritin or absorbed into the body circulation through ferroportin. Hephaestin, a ferroxidase converts the ferrous iron to ferric iron to be bound by transferrin.[11]

Iron linked to the mucous cells is carried into the intestinal lumen and thus lost, during the periodic desquamation which occurs within a mean period of 4–5 days. Apoferritin synthesis is inhibited in ID which further hinders iron absorption in the iron-deficient organism. This condition is known as the "mucosal block." Moreover, a number of other factors condition iron absorption, such as the chemical status of iron, presence of reducing agents, cofactors, dissociation from ligands to facilitate uptake by intestinal cells, and pathological processes associated with the GI tract, such as diarrhea, parasitic infestation or infections. With respect to the chemical status of iron, Fe^{2+} iron is readily absorbed by the body. However, excess free iron in the intestinal tract usually produces reactive oxygen species (ROS) triggering oxidative stress. In principle, the easier the dissociation of Fe^{2+} from oral iron supplements, the more serious is the intestinal inflammation.[12] For instance, despite being effective, Fe^{2+} iron has a tendency to trigger the Fenton reaction in the presence of hydrogen peroxide.[13] As a result, Fe^{2+} iron supplements have a high frequency of side effects in comparison to Fe^{3+} iron sources.[14] The reduction in iron concentration after the first pass through the liver greatly reduces its bioavailability.

Recurrent high doses of iron can potentially perturb the composition of the gut microbiome, enable pathogen abundance, and increase inflammation.[15] Hepcidin, a tight regulator of systemic iron levels in mammals, acts in concert with intracellular iron metabolism. High hepcidin levels block intestinal iron absorption and macrophage iron recycling, causing iron-restricted erythropoiesis and anemia. Low hepcidin levels favor bone marrow iron supply for Hb synthesis and red blood cell production.[16] Iron supplementation acutely increases the circulating plasma hepcidin level. Plasma hepcidin negatively correlates with iron bioavailability.[17] In a study by Moretti *et al.,* it was observed that hepcidin levels increased in iron-depleted young women with oral iron supplementation given daily or twice-daily, invariably decreases iron absorption from the subsequent doses.[18]

Other than the above-mentioned regulatory factors, intrinsic factors such as solubility, chemical nature, and particle size also affect iron absorption. The bioavailability of elemental iron powders has been shown to be inversely proportional to particle size. Decreasing particle size to the nanoscale could be a strategy to improve iron bioavailability.[19] Srinivasu *et. al.* showed that decreasing the particle size of FePP to nanoscale levels improved iron absorption leading to high bioavailability in iron-deficient rats. The relative bioavailability of FePP nanoparticles, calculated using Hb regeneration efficiency, was found to be 103.02% with respect to the reference salt, $FeSO_4$. This has been attributed to its reduced size which increased its solubility relative to its larger precursors.[20] It has been reported that $FeSO_4$ supplementation causes significant GI side effects in adults.[21] and may induce organoleptic changes when added to foods. On the contrary, $FePO_4$ is an iron compound that causes no adverse organoleptic changes in food matrices but is poorly absorbed (25%) relative to $FeSO_4$[22], limiting its nutritional value.

To bypass the rate-limited absorption via DMT-1 and to avoid the organoleptic changes caused by active iron, many have now turned to the Microfold cells (M cells) of the Peyer's patches (PPs) as an alternative mediator/target for efficient iron transport.

M Cells: Unconventional Cells with a Distinctive Role

The M cells of the PPs are so-called because they are covered with microfolds. M cells are advanced epithelial cells of the mucosa-associated lymphoid tissues (MALT). They are involved in the transfer of particles and microbes from the luminal side of the intestine to the lamina propria, where they are presented to the immune cells. They have been shown to provide a pathway for delivering orally administered vesicle-like particles to the systemic circulation through the lymphatic system.[23] Thus, they are widely researched as an alternative means of intestinal particle delivery to maximize bioavailability. It is generally agreed that transcytosis of particles increases

when the particle diameter decreases. Accordingly, M cells are capable of taking up particles from 50 nm to 10 μm, although particles in the 0.5–2 μm range are transcytosed most effectively.[24] In studies to determine the subsequent distribution of biodegradable microspheres, it was found that particles <5 μm can be transported through PPs to peripheral lymphoid organs, whereas particles >5 μm remain within PPs.[25] Within a range of 1–10 μm, particles in the 1–2 μm range appear to be preferentially taken up than the larger particles.[26] In a study by Desai *et al.*, the histological examination of the PPs and the non-patch samples showed a higher level of uptake for the 100 nm particles compared to larger size particles.[27] More studies on polystyrene latex revealed that the maximum number of absorbed nanoparticles occurred with particles ranging 50–100 nm in diameter, while particles above 1 μm were trapped in the PPs. Rieux *et al.* investigated the effect of physicochemical properties of nanoparticles on their transport across the human *in vitro* model of FAE. It was seen that the number of 0.2 μm transported nanoparticles was seven times higher ($P < 0.05$) than that of 0.5 μm nanoparticles.[28] Hence, it is generally accepted that particles below 1 μm are taken up by M cells and delivered in the basal medium, while particles larger than 5 μm are taken up by M cells but remain entrapped in PPs. Even if some controversy remains, the optimal size for a particle to be transcytosed by an M cell would be below 1 μm.[29]

Novel Encapsulated Ferric Pyrophosphates that Serve as Targets for M Cell Uptake

Lipid encapsulated FePP offers an easily scalable approach for the delivery of iron to human cells. Lipofer®, Sideral®, and SunActive® Fe are the three well-known examples of encapsulated FePPs used for transport through the M cells.

Lipofer® is ferric pyrophosphate encapsulated in liposomes[30] while Sideral® is a preparation of ferric pyrophosphate within a phospholipid and sucrester matrix.[31] SunActive® Fe is a micronized FePP coated with monoglycerides and diglycerides to minimize particle aggregation.

The purpose of the present study was to make a comparative analysis of M cell and intestinal absorption of the three widely used lipid encapsulated ferric pyrophosphates in an *in vitro* model of Caco-2 monoculture and Caco-2/Raji B coculture.

MATERIALS AND METHODS

An *in vitro* analysis to study the iron transport potential of three different commercial FePP through Caco-2 and Raji B cells using ICP-AES was performed at National Facility for Biopharmaceuticals, Mumbai. The three samples (raw material) tested were; SunActive® Fe, Lipofer®, and Sideral®.

Cell Culture

Caco-2 cells were purchased from National center for cell Sciences (NCCS), Pune, and cultured in growth media; Dulbecco's Modified Eagle Medium (DMEM; Thermo Fisher Scientific -11995065) under a humidified atmosphere (5% CO_2/95% air) at 37°C. The media were supplemented with 10% heat-inactivated FBS (Thermo Fisher Scientific –10437028), 100 units/ml of penicillin, and Primocin – (Biogene India – ant-pm-2).

Cell Culture for Intestinal Epithelial Monolayers

Caco-2 cells (monoculture), representing the intestinal epithelium monolayers of tight junctions, were prepared as follows; after coating Transwell inserts (CC INSERT MD6 3MY DIM 20/25 MM PC SI) with Matrigel matrix (Geltrex™ LDEV-Free Reduced Growth Factor Basement Membrane Matrix) for 1 h, supernatants were removed, and inserts washed with DMEM. Caco-2 cells (4.5×10^5 cells/well) were seeded on upper insert sides with 1.5 mL of growth media and cultured for 21 days. Media were replaced twice a week. After 21 days of incubation (37°C at 5% CO_2) of the cells, the medium was replaced from both apical as well as the basal layer of the cells and treated with the given samples (1500ppm of available Fe ion) on the apical side of the insert and incubated (37°C at 5% CO_2) for 6 h. The concentrations of transported Fe in basolateral solutions were determined by ICP-AES (Avio 500 ICP-OES, PerkinElmer**).**

Cell Culture for FAE Model

Caco-2 cells (4.5×10^5 cells/well) were grown on upper sides of the inserts in the same manner as described in the Caco-2 monoculture system and incubated (37°C at 5% CO_2) for 14 days. Raji B cells (4.5×10^5 cells/well) in DMEM were then added to basolateral insert compartments, and these co-cultures were maintained for 5 days. The apical side of the insert was replaced with fresh medium. Given samples (1500 ppm of available Fe ion) were added on the apical side of the insert and incubated for 6 h. Samples collected from the basolateral side of the insert, post-incubation, were centrifuged at 1500 rpm (REMI C20BL) for 10 min and the supernatant was used to determine the transported Fe by ICP-AES (Avio 500 ICP-OES, PerkinElmer). ICP-AES analysis was performed at Laxmi Analytical Laboratories, Mumbai.

RESULTS

Caco-2 cells transform into FAE-like cells in the presence of Raji B cells, and this model is an established *in vitro* model of intestinal enterocytes (Caco-2) and M cells (Raji B). To

determine the transport of micronized FePP through M cells, an *in vitro* analysis with three different commercially available FePPs was performed using Caco-2 and Raji B cells. The amount of iron transported was determined using ICP-AES.

In the monoculture model, the percentage of iron transported with SunActive® Fe was 27.51% (412.58 ppm of 1500 ppm loaded) followed by Lipofer® and Sideral® with 16.34% (245.03 ppm) and 15.14% (227.06 ppm) iron transport, respectively (Figure 1).

In the co-culture model, the percentage of iron transported from SunActive® Fe was significantly higher at 39.99% (599.84 ppm) as compared to Lipofer® and Sideral® with 0.48% (7.18 ppm) and 10.26% (153.91 ppm), respectively (Figure 2).

The percentage of iron transported SunActive® Fe was significantly higher in the co-culture system, indicating SunActive® Fe's selective uptake through the M cells.

Of note is that the percentage of iron transported through not only M cells but also through Caco-2 cells dropped in the case of Lipofer® and Sideral® in the co-culture.

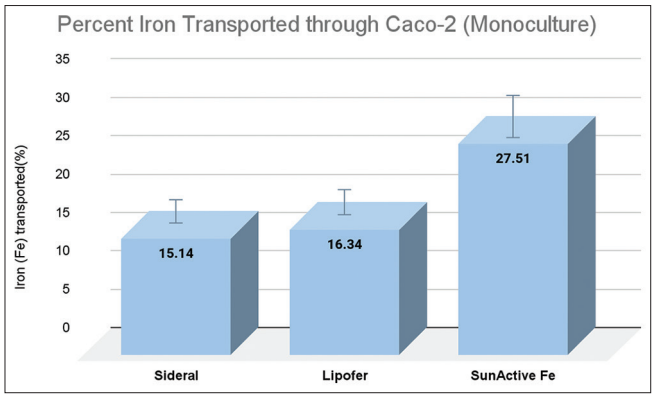

Figure 1: Comparison of percentage of iron transported in monoculture model

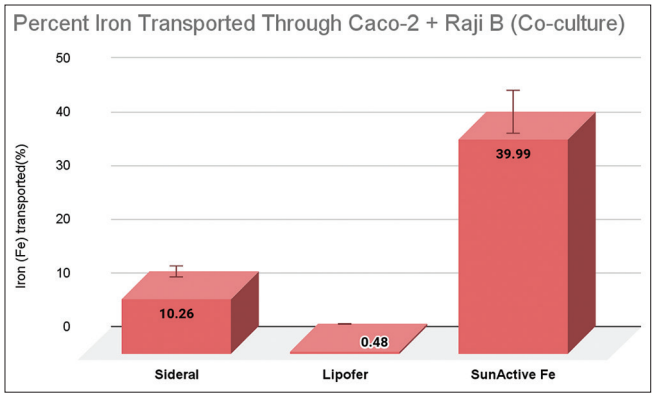

Figure 2: Comparison of percentage of iron transported in a co-culture model

DISCUSSION

Iron is an essential micronutrient and plays an important role in numerous physiological processes such as hematopoiesis, oxygen metabolism, energy production, brain health, and human well-being in general. IDA is still regarded as one of the major health concerns worldwide.

Conventional oral iron salts are poorly absorbed; consequently, the unabsorbed iron leads to several GI adverse effects and in turn reduces the patient's compliance. This undermines the long-term efficacy of oral iron supplements.

With an intent to improve iron bioavailability and effectively reduce the side effects of oral therapy, innovative approaches to novel dietary supplements such as microencapsulation, microsomes, liposomes, and sucrosomes have emerged and are being marketed.

The advantages of such alterations ensure the iron are protected through the digestive process, the release of unabsorbed iron is limited, resulting in enhanced bioavailability by utilizing contemporary intestinal routes of absorption which are not iron-dependent.

M cells serve a critical role in immune surveillance. Being morphologically distinct from the canonical enterocytes, M cells confer a new functional capability. Unique cellular mechanics of the M cells, capture the molecule at the apical membrane and transport them to the basolateral side from where the molecule is delivered to the dendritic cells.[32]

Due to its non-invasive nature, oral drug delivery is the route of choice, avoiding pain and discomfort, and enabling excellent patient compliance. However, some bioactive molecules remain poorly bioavailable if administered orally because of their lack of stability in the hostile GI environment, which results in degradation prior to absorption or a significantly reduced absorption.

The objective of this study was to determine the intestinal absorption mechanism of three encapsulated iron preparations SunActive® Fe, Lipofer® and Sideral®, employing the *in vitro* models of Caco-2 monolayer and human FAE, representing the intestinal endothelial and M cells in PPs, respectively.

This study was essential to independently understand the underlying mechanism and validate the claims about the three major FePP formulations being transported by M cells.

From the results, it can be seen that iron from SunActive® Fe was primarily transported by M cells, although transport

through Caco-2 monolayer was also seen. Our study was in accordance with the study carried out by Kim *et.al*.,[33] where the intestinal transport mechanism of SunActive® Fe was observed. The result demonstrated that SunActive® Fe was transported fundamentally through M cells. In the present study, percent of iron transported was greater from SunActive® Fe at 39.99 % when compared to the percent of iron transported by Lipofer® and Sideral®, which was 0.48% and 10.26%, respectively (Figures 1 and 2).

The results of the present study are in line with the previous findings on M cells that the particle size of the iron holds essence where M cells are utilized for transport of iron. The optimal size of a particle to be taken up by the M cells and trancytosed from the basolateral side is below 1 μm. In contrast, particles that are larger than 5 μm are absorbed by M cells but remain entrapped in the PPs for up to 35 days.[34] A reported particle size of 0.3–0.5 microns would be best suited for transport through M cells in line with our results.[33] Lipofer® with a particle size of 7 μm[35] and Sideral® with approximately 11–13 μm[36] may pass through M cells but will remain entrapped in the PPs and thus, may not display the desired results whereas the above will not be the case for SunActive® Fe with a particle size below 1 micron. This would be possible since the M cell would be able to endocytose the iron, but it would thereafter be trapped within the M cell or at the PPs due to its size. As per previously reported literature on particle size and M cell transport, as well as results from this study, only an iron with a particle size smaller than 1 μm would pass through the M cells.

Co-culture mimics the model of human intestinal FAE consisting of M cells. A reduction in iron transport observed with Lipofer® and Sideral® in the co-culture model could be attributed to the reduced surface area in the presence of Raji B cells along with Caco-2 cells as well as to the iron that gets trapped within the M cells with nowhere to go.

In the case of SunActive® Fe, a high oral absorption efficacy can be ascribed to its increased intestinal transport primarily through M cells and partly through Caco-2 monolayers, taking advantage of both the models studied.

The above data reiterates the importance of particle size in the absorption of molecules; in our case iron, through M cells, and validates SunActive® Fe as the most bioavailable iron compared to Lipofer® and Sideral®.

CONCLUSION

Recent advances in the use of M cells suggest their practical applications for optimal stimulation of immunological or physiological responses following oral administration. M cells are a unique mode of delivery for particulate drugs or bioactive, due to their ability to capture particles at the apical membrane and transport them to the basolateral end. Of the 3 encapsulated Ferric Pyrophosphate preparations, SunActive® Fe efficaciously makes use of this unique mechanism exhibited by M cells to bypass the conventional DMT-1 channels and directly reach the lymphatics, which may eventually result in superior absorption, bioavailability, and excellent patient compliance. Particle size plays a cardinal role in this unconventional delivery route; not all iron molecules absorbed through M cells can pass through PPs. As seen in the present study SunActive® Fe, the smallest available encapsulated FePP with a particle size below 0.5 microns, is predominantly transported through the M cells. This innovative approach can serve as a potent therapy for IDA, both prophylactically and therapeutically.

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ETHICS

Ethical permission not applicable as our study is *in vitro* and no human participants/animals were involved.

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