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Research Article

LIPOSOMAL IRON: A NOVEL APPROACH FOR IMPROVED IRON SUPPLEMENTATION, MANUFACTURED BY WEST BENGAL CHEMICAL INDUSTRIES LTD

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ABSTRACT

Iron deficiency remains a prevalent global health concern, necessitating effective supplementation strategies. Traditional iron supplements often pose challenges such as gastrointestinal side effects and poor tolerability. Liposomal iron, utilizing advanced delivery technology, presents a promising solution to enhance iron uptake and mitigate adverse effects. This research article elucidates the distinctive features and advantages of liposomal iron over conventional preparations, highlighting its efficacy, tolerability, and suitability across diverse populations, including pregnant women, children, and the elderly. Furthermore, it emphasizes the superior characteristics of liposomal iron manufactured by West Bengal Chemical Industries Ltd (WBCIL), underscoring its potential as a preferred choice for iron supplementation.

Key words: Iron deficiency, liposomal iron, supplementation, efficacy, tolerability

INTRODUCTION

Liposomal technology used for iron up-take is significantly different from normal intestinal up-take of iron. Liposomal iron absorption involves a sophisticated technology that uses liposome as a carrier, where iron without coming in contact to gastro intestinal mucosa gets directly absorbed in the intestine.[1] In case of normal intestinal iron up-take, gastric acid is required to convert dietary iron into absorbable form, while the iron up-take is largely facilitated by a protein located on the surface of enterocytes, i.e., cell lining of the small intestine; iron is then released into the bloodstream and binds to the transport protein transferrin, which delivers it to various tissues as well as organs. Contrary to this, liposomal iron supplements that are consumed orally are resistant to the acidic environment of the stomach, shielding the encapsulated iron from degradation and oxidation. Liposome encapsulated iron reach the small intestine, precisely the duodenum. In the duodenum, liposome releases iron into the intestinal lumen.[2] The specialty of having liposomal iron supplements includes that liposomal iron is absorbed more efficiently in comparison to traditional iron supplements as it strongly bypasses gastric digestion. The absorbed liposomal iron is then released to the bloodstream and utilized by the body, alike to iron obtained from a normal diet. Although, there are reports existing on the beneficial aspects of liposomal delivery mechanism as well as suitability of ferric pyrophosphate as iron source separately; still, our current product that delivers ferric pyrophosphate iron source through liposomal coating technology provides a

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novel insight in considering this supplement in minimizing the release of iron ions that contribute to significant side effects.

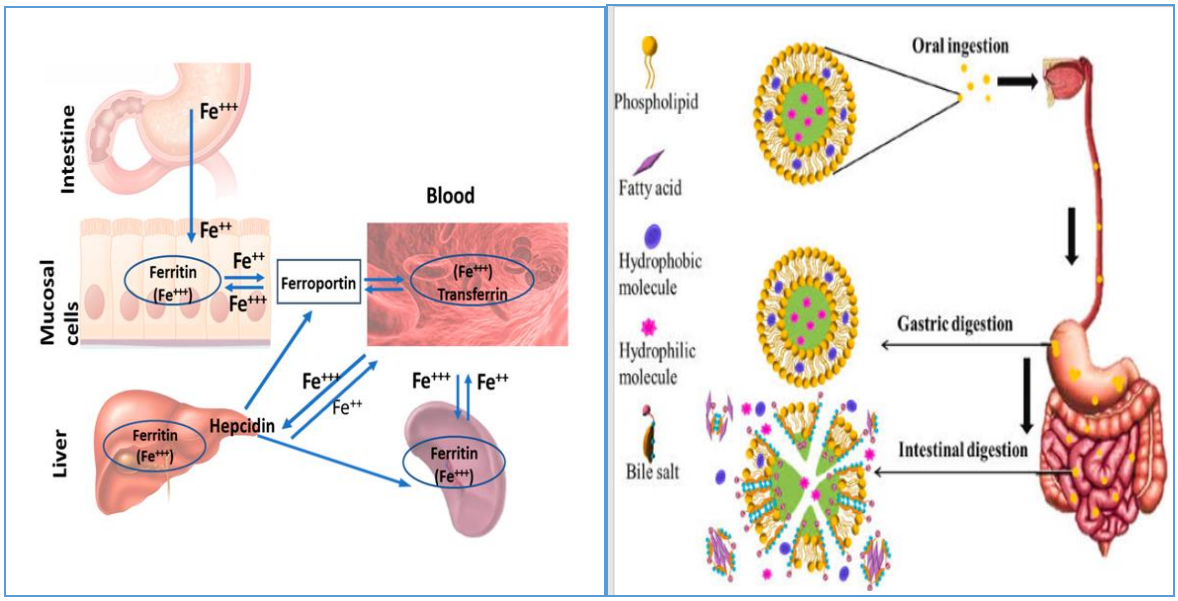

Figure 1: Normal iron absorption versus liposomal iron absorption

2. Beneficial aspects of liposomal iron compared to conventional iron preparations

2.1. Better efficacy:

In liposomal technology, the plasma concentration of liposomal iron reaches the maximum level after 2 hours of supplement consumption which guarantees greater efficacy of the element for all metabolic processes in comparison to traditional iron. Liposomal iron can be given in low quantity as it is 2.7 and 3.5 times more bioavailable than ferrous sulphate and plain ferric pyrophosphate, respectively.2 An experimental study was done to evaluate the efficiency of iron up-take. The group received Liposomal ferric pyrophosphate. Liposomal ferric pyrophosphate has the higher values of iron concentrations at any point of time as compared to other salts, such as Ferrous sulphate or Ferric pyrophosphate.[3]

2.2. Better tolerability:

Since it is Liposomal Iron, it can be given with other nutrients; hence, no interaction is present compared to conventional iron. Liposomal iron is almost devoid of all the common side effects associated with conventional iron, such as gastric irritation, nausea, constipation, etc.[4] While iron supplements potentially interfere with the up-take of other nutrients such as calcium, zinc, and magnesium, liposomal iron has little impact on the efficacy of these nutrients, making it a more versatile option.[2] In a previous study it has been shown that 30 post-menopausal women with iron deficiency (haemoglobin level of < 11.5 g/dL) who were previously been treated with other iron supplements used to experience side effects. They were initiated with the treatment of liposomal iron supplement, i.e., microencapsulated iron pyrophosphate in liposomal form and after 8 weeks of supplementation it was observed that there was a significant improvement in haemoglobin level and the treatment was well tolerated by the women.[4]

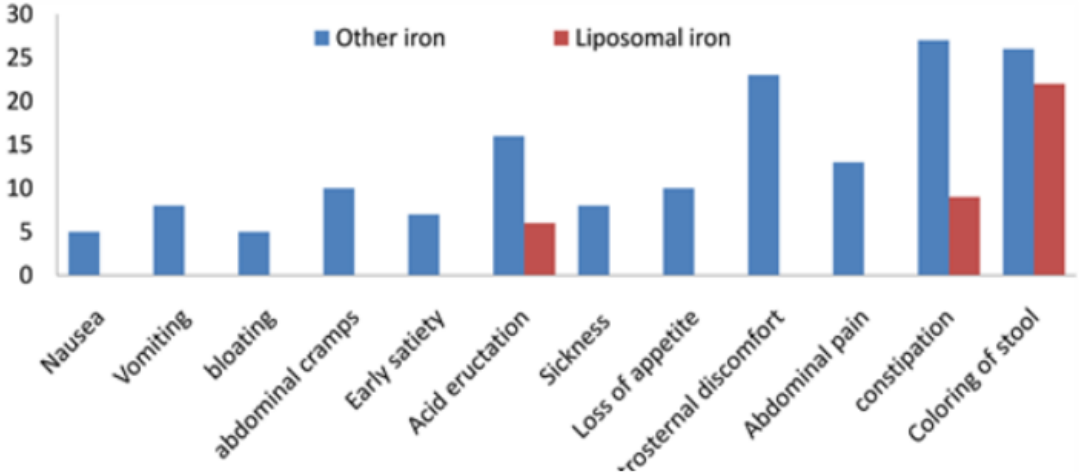

Figure 2: Side effect total score from iron and liposomal iron treatment2

2.3. No oxidative adverse effects:

Iron can induce oxidative stress in the body that can be harmful. Liposomal delivery might help mitigate this risk by minimising the release of iron ions contributory to oxidative damage. The conventional iron is known to increase the oxidative damage by altering the levels of malondialdehyde (MDA) as well as super-oxide dismutase (SOD). Studies have verified that liposomal iron is related to decreased levels of MDA and increased levels of SOD. This can help in decreasing the oxidative damage otherwise found with conventional iron supplements.5

2.4. No Interaction with Dietary Inhibitors:

The uptake of traditional non-haem iron might be prevented by several factors, such as dietary inhibitors. Phytic acid is one of such inhibitors. Phytic acid present in cereals and legumes-based diet has been shown to inhibit iron uptake in-vivo as well as in cell culture models. However, in case of liposomal iron delivery it provides a better delivery system for iron in the sense that iron uptake occurs without getting affected by dietary inhibitors.6 A recent study has shown remarkable report accentuating the fact that oral liposomal iron can be considered as a safe and efficacious alternative to IV iron gluconate for correcting iron deficiency in non-dialysis-chronic kidney disease individuals.[5] This report strongly highlights the potentiality of the product liposomal iron as supplements in cases of iron deficiency.

3. Beneficial aspects of liposomal iron in special population

3.1. Liposomal iron in Pregnancy and lactating mothers:

As per the study conducted by Parisi et al. a comparison report was obtained on liposomal iron versus ferrous sulphate in 80 pregnant women. They were recruited in the study at 11 to 13 weeks of gestation. The women were randomised to control and treatment groups. Controls and treatment groups were supplemented with ferrous iron 30 mg, liposomal iron 14 mg and liposomal iron 28 mg per day up to 6 weeks post-partum. Women who received liposomal iron 28 mg and liposomal iron 14 mg presented significantly higher improvements compared to those who received ferrous sulphate and control group. Birth weight of foetus revealed a tendency to increase with supplementation, resulting in higher birth weight in the liposomal iron 28 mg group compared with controls.[7,8] The study of Vitale et al. aimed to determine the effects of liposomal iron pyrophosphate on clinical and psychological outcomes in pregnant women. Women with iron deficiency who were at the 11th to 13th weeks of gestation were recruited in the study. Haemato-chemical, neonatal, obstetric, and psychological outcomes were measured at the time of enrolment to the study, at 21 to 23 weeks of gestation, at 30 to 32 weeks of gestation, and after 6 weeks from childbirth. Results showed significant positive impacts compared to baseline data. Significant improvements were observed for anxiety and depression levels. With respect to the quality of life, all the parameters were significantly improved, especially the Physical Role domain.[9] Depending on the information provided from the studies conducted by Parisi et al. and Vitale et al., it appears that liposomal iron supplementation, specifically liposomal ferric pyrophosphate, have positive effects on various health outcomes during pregnancy.[10]

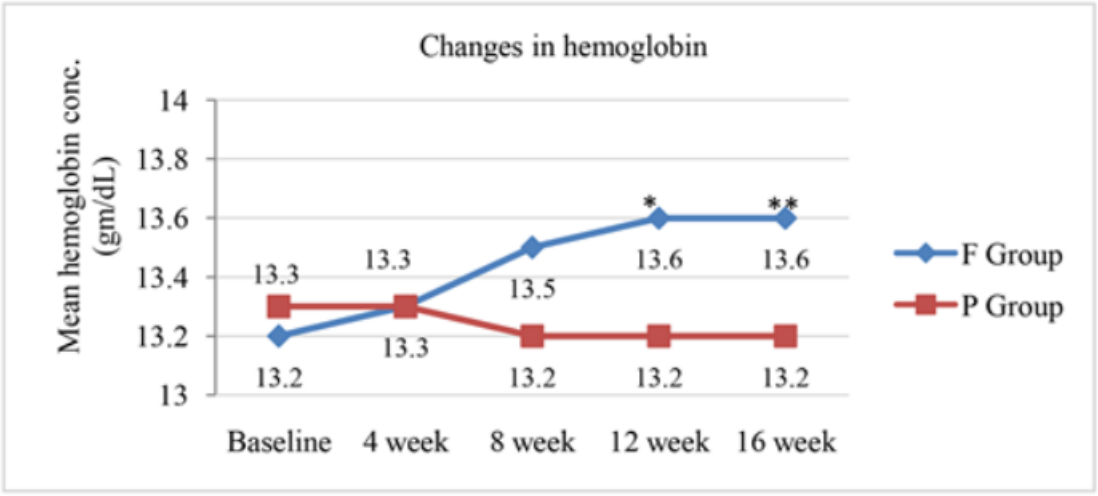

Figure 3: Changes in haemoglobin level in liposomal iron (F) group and placebo (P) group[2]

3.2. Liposomal iron in Children:

The study of Moscheo et al. showed benefits of using liposomal iron in children. The benefits include no adverse effects, outstanding palatability, and availability of supplement in drop formulation. As a matter of fact, liposomal supplements maintain a satisfactory efficacy profile with significantly lower adverse effects, in comparison to the conventional elemental iron salts. This is usually considered as a second-choice therapy and should be reserved for selected paediatric cases.[11] Capra et al. (2017) showed that liposomal iron supplementation in paediatric patients with iron-deficiency causes stable improvement in haemoglobin level at long-term.12 While oral ferrous salts are considered as standard treatment for children with iron deficiency, previous studies have conducted to screen oral iron therapy with liposomal iron supplementation in children aged 3 months to 12 years. It showed an increase in reticulocyte level at 3 days, and haemoglobin increase occurred at 2 weeks with no gastrointestinal side effects.[13] These studies provide evidence on safety and efficacious profile of liposomal iron in children.

3.3. Liposomal iron in Elderly Population:

Iron deficiency can affect a considerable proportion of the elderly population.[14] Iron deficiency is considered to be the second most common cause of anaemia in the elderly. Lullo et al. has been safely utilised Ferric liposomal formulation in the study for oral iron supplementation of secondary anaemia in elderly individuals within the age group of 68.4 ± 1.724 years.[15]

4. Superior features of liposomal ferric pyrophosphate manufactured by West Bengal Chemical Industries Ltd (WBCIL).

4.1. Effect of Lecithin Coating on Particle Size and Morphology:

Cell membranes are built from fatty molecules called phospholipids, one type being lecithin. Liquid state scanning electron microscopy (SEM) analysis at 7500x magnification (Fig-4) revealed significant differences between uncoated and lecithin-coated ferric pyrophosphate particles. Uncoated particles appeared with non-uniform crystals (4-7 microns). As the lecithin coating increased (2-10%), particles became more spherical and uniform, growing in size. The particle size increased from 12-13 micron (2% Soy Lecithin coated) to 15-16 micron (10% Soy Lecithin Coating) This suggests successful encapsulation of the cargo within the lecithin-coated liposomes, potentially influencing stability as well.

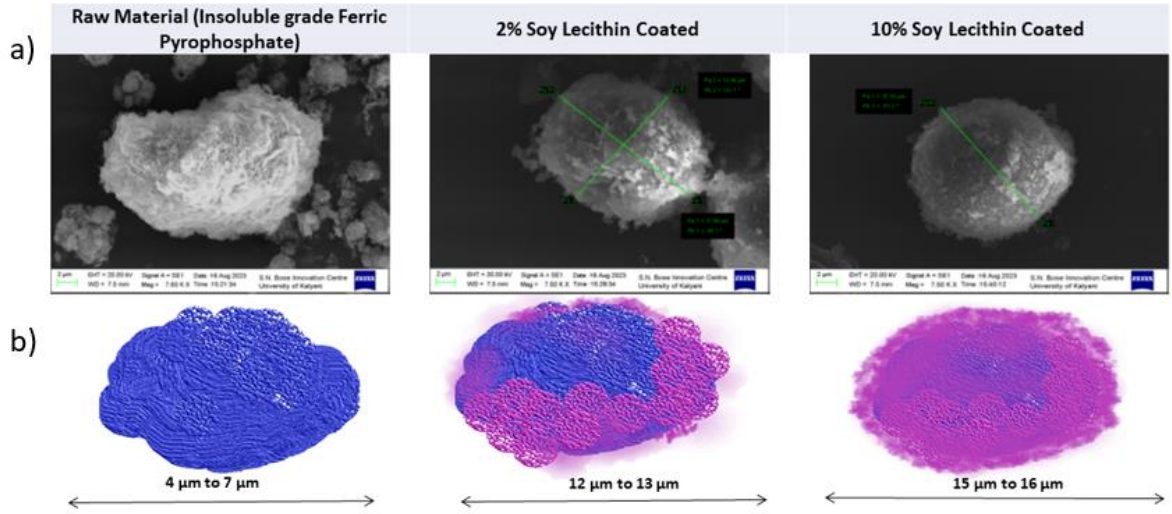

Figure 4: SEM Magnification View (7500X) (a) Single Particle view (b) 2-D representation

4.2. Morphology and Surface Characterization (ICH Q1):

The shape and surface features of iron-containing liposomes (Insoluble grade) were examined to see how they affect stability. We have used energy-dispersive X-ray spectroscopy (EDX) to analyse the elements in two samples: one stored under accelerated stability conditions for 3 months and another under real-time conditions for 3 months. EDX found carbon, nitrogen, and oxygen as the main elements in both samples, likely due to lecithin, a key component of the liposome membrane. Iron was also present, but at much lower levels (Table 1). Liposomes are comprised mainly of phospholipids, rich in these detected elements. Secondly, the iron payload is encapsulated within the liposome structure, resulting in a lower overall abundance compared to the bulk membrane components. Which ultimately assures the higher EE. This suggests successful iron encapsulation within the liposomes. Interestingly, no major differences were found between the two storage conditions. This finding suggests that the storage conditions do not markedly influence the stability of the liposomes, potentially indicating their robustness across varying storage scenarios. The successful encapsulation of iron within the liposomes, coupled with their uniform spherical morphology and minimal impact from storage conditions, suggests a well-designed and stable drug delivery system (Fig-5).

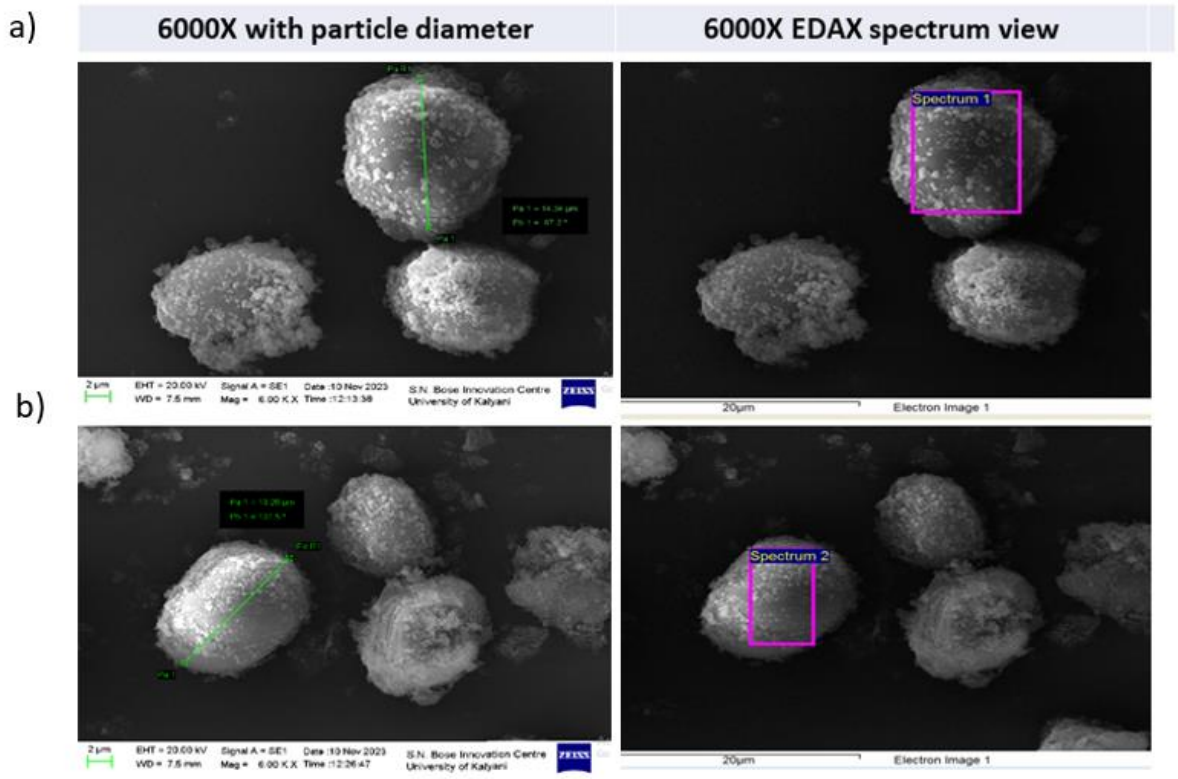

Figure 5: Ferric Pyrophosphate in (a) 3 months accelerated solubility, (b) Real time stability

Table 1: Elemental composition 3 months accelerated solubility, Real time stability

	ACCELERATED STABILITY		REAL TIME STABILITY	
Element	**Weight %**	**Atomic %**	**Weight %**	**Atomic %**
C K	31.28	36.83	32.51	38.49
N K	21.28	22.09	15.75	15.99
O K	46.28	40.91	50.78	45.13
P K	0.10	0.04	0.69	0.32
Fe K	0.47	0.12	0.27	0.07
Total	100.00		100.00	

4.3. Encapsulation Efficiency and Elemental Iron Content

The results indicate successful production of Liposomal Ferric Pyrophosphate that meets quality standards. Encapsulation efficiency reached 89.01%, exceeding the minimum acceptable level of 85%. An elemental iron assay confirmed 8.12% iron in the final product, which falls within the acceptable range of 7.8% to 9.0% (Ref: USP Food Chemical Codex). The high encapsulation efficiency suggests most iron particles are trapped within the liposomes, potentially leading to better absorption and fewer digestive issues compared to traditional iron supplements.

4.4. Zeta Potential and Colloidal Stability

The electrical charge (zeta potential) on the surface of liposomal iron particles were measured to assess their stability in suspension. Established guidelines suggest higher absolute zeta potential (positive or negative) indicates greater stability, with values exceeding +/- 30 mV considered ideal.16 The liposomal formulation was dispersed in a neutral (pH 7.0) solution. This increased the surface charge from -18.05 mV to a more stable -39.47 mV (Table 2), exceeding the recommended threshold. This successful formulation with a zeta potential of

-39.47 mV indicates sufficient surface charge for stability in suspension. This improved stability is essential for maintaining product quality during storage and potentially improving its effectiveness within the body.

Table 2: Characteristic features of the coated and non-coated materials.

	pH 7.0 (Zeta Potential in mV)	Particle size in Liquid particulate (nm)	Polydispersity in liquid state
Ferric Pyrophosphate API	-18.05	3896	0.3517
10% coating	-39.47	1296	0.4465
Limit	± 30	500-2000	Less than 1

4.5. Particle Size Distribution and Polydispersity:

Liposomal iron formulation size and distribution were characterized using Dynamic Light Scattering (DLS). DLS measures scattered light fluctuations to determine particle size. The analysis revealed a mean hydrodynamic diameter of 1296 nm, consistent with the predefined acceptable range for this application (Table 2). Polydispersity Index (PDI), a measure of size distribution, was also assessed. Ideally, PDI values closer to 1 indicate a more uniform population.[17] The formulation exhibited a PDI of 0.4465 (Table 2), suggesting moderate polydispersity.

4.6. Particle Size and Encapsulation Efficiency Relationship (ICH 06):

This study investigated the relationship between particle size and encapsulation efficiency (EE) of iron microspheres. EE, expressed as a percentage, reflects the amount of iron successfully encapsulated. Particle size was categorized by mesh size, with lower numbers indicating larger particles. A decreasing trend in EE was observed with decreasing particle size within the #18 to #200 mesh range (approximately 1000 µm to 75 µm sieve size). EE dropped from 93.91% (mesh#18) to 86.27% (mesh#200), but remained above 85% across this range. This suggests efficient encapsulation for these sizes. However, a significant decrease to 74.35% EE was observed for the smallest particles (#325 mesh) (Table 3). Two factors might explain this trend. Firstly, smaller particles offer limited internal volume to house iron molecules, potentially restricting encapsulation capacity. Secondly, their increased surface area to volume ratio exposes encapsulated iron to the external environment, possibly leading to leakage. These findings suggest a trade-off between particle size and EE for iron microspheres. In this study, a particle size between 18 and 200 mesh seems optimal for high EE.

Table 3: Particle Size study (ICH 06)

Serial No	Mesh Size	Assay Elemental Iron	Assay of free Iron	Encapsulation efficiency
1	Mesh#18	9.42	0.57	93.91
2	Mesh#35	9.52	0.64	93.30
3	Mesh#40	8.93	0.89	90.00
4	Mesh#60	9.63	1.15	88.08
5	Mesh#80	9.19	1.34	85.41
6	Mesh#140	9.75	1.53	85.01
7	Mesh#200	9.30	1.28	86.27

4.7. Leakage Rate and Shelf-Life Stability

A stability study assessed iron leakage from liposomes over a simulated 6-month shelf life under accelerated conditions (Table-4). Two key measures were assessed: encapsulation efficiency and elemental iron content. Encapsulation efficiency refers to the percentage of medication protected within the spheres. The acceptable level was at least 85%, and throughout the study, the medication remained above 87%. Elemental iron content refers to the amount of iron within the medication. The acceptable range was 7.8% to 9.0%, and the medication stayed within this range throughout the entire study. In conclusion, based on the findings from this investigation, liposomal ferric pyrophosphate appears to be stable even when stored at 40°C for 6 months. This suggests it's likely to remain stable at room temperature for an extended period of time.

Table 4: Leakage rate of drug from the liposomes (shelf-life period)

Period completed in month	Encapsulation efficiency	Elemental Iron Assay
Initial (0 month)	89.5%	8.12%
1 month	88.0%	8.02%
2 months	87.5%	7.95%
3 month	87.5%	7.90%
6 months	87.0%	7.91%

4.8. Phase Transition Behavior via Differential Scanning Calorimetry (DSC)

Differential scanning calorimetry (DSC) was used to investigate the phase transition behaviour of liposomal iron [18]. In liposomes, this refers to the temperature-dependent transformation from a gel-like to a more fluid state, impacting stability and drug delivery[19]. The lecithin thermogram displayed multiple endothermic peaks, consistent with its known phase transitions [18]. The "Liposomal Ferric Pyrophosphate" curve, reflecting the entire formulation, exhibited a more complex profile with several peaks at distinct temperatures (Fig-6). This suggests potential multi-step phase transitions within the liposomal iron. API is breaking at 2 different segments in 2 different product temperature 112 and 177, but this pattern is missing in 10% formulation. 1st stage breakage at 112 degrees and 2nd stage breakage at 177 degrees. These two fragments breakage is absent in 10% coating, which is indicative of Coating is happening (Table 4).

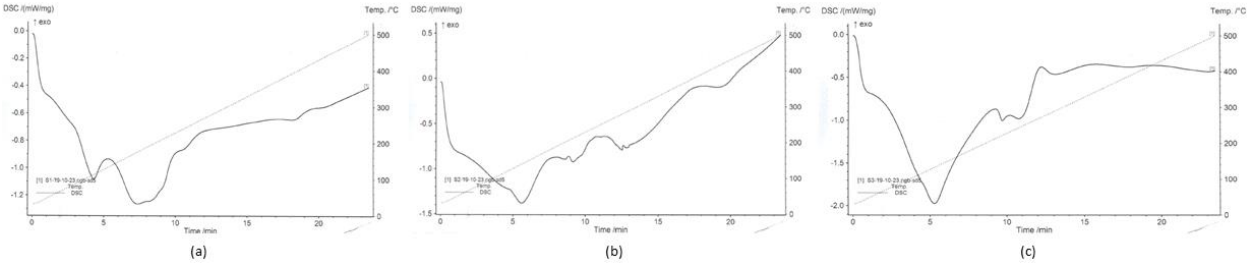

Figure 6: DSC diagram of (a) Ferric Pyrophosphate API, (b) Lecithin, (c) Liposomal Ferric Pyrophosphate.

Table 4: Phase Transition Temperature (ICH 07)

	Temp (°C)	Time (min)	DSC (mW/mg)
Ferric Pyrophosphate API	112.23	4.25	-1.07886
	177.67	7.5	-1.26281
Lecithin	136.85	5.5	-1.37756
	212.78	9.25	-0.92002
	278.42	12.5	-0.78655
Liposomal Ferric Pyrophosphate	132.30	5.25	-1.97411
	223.04	9.75	-1.00296
	288.63	13	-0.46391

4.9. Temperature Exposure and Stability of Liposomal Iron (Insoluble Grade):

An accelerated stability test exposed the liposomal iron to 105°C for 10 minutes (commercial batch FPPLI092306A), simulating harsher storage conditions to predict long-term stability.[20] Iron content (assay % w/w) remained stable, with values of 7.87% at room temperature and 8.05% after heat exposure. This slight increase falls within expected variability, suggesting minimal impact. Encapsulation efficiency (%) even showed a potential benefit. The initial value of 89.75% increased to 91.27% after treatment, warranting further

investigation into the underlying mechanism. Observed changes in iron content and encapsulation efficiency were minimal. This suggests potential resistance to thermal degradation within the tested parameters.

5. Conclusion

Liposomal iron represents a promising advancement in iron supplementation, offering improved efficacy, tolerability, and suitability across diverse populations. The key factor to treat anaemia is adherence to therapy and it can be achieved by greater tolerance and fewer side effects. Conventional therapy hampers compliance whereas liposomal iron is proved to be an efficient supplement with greater efficacy and tolerance. For long Liposomal Iron has been used as a carrier supplement. The unique characteristics of liposomal iron, particularly those manufactured by West Bengal Chemical Industries Ltd (WBCIL)9, underscore its potential as a preferred choice for addressing iron deficiency and promoting overall health. Our research at WBCIL successfully produced a lecithin-coated liposomal ferric pyrophosphate formulation. This coating significantly improved particle shape, yielding uniform spheres compared to uncoated particles. Importantly, the coating-maintained stability across various storage conditions. The formulation achieved a high encapsulation efficiency (89.01%), exceeding requirements and indicating successful iron entrapment. A trade-off between particle size and encapsulation efficiency was observed, highlighting the need for further optimization. Encouragingly, the formulation exhibited minimal leakage throughout a simulated shelf-life study. While the complex phase transition profile warrants further investigation, minimal impact from high-temperature exposure suggests promising stability under broader conditions. Overall, these findings demonstrate the potential of our WBCIL-developed lecithin-coated liposomal iron delivery system for improved iron delivery.

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