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Optimization and Characterization of Iron Sucrose Colloidal Formulation with Enhanced Stability and Reduced Labile Iron Content

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ABSTRACT

Background: Iron sucrose is a cornerstone therapy for iron deficiency anemia, particularly in chronic kidney disease. However, marketed formulations can contain labile iron, which catalyzes reactive oxygen species generation, contributing to oxidative stress and infusion reactions. This study aimed to develop an optimized iron sucrose colloidal solution with improved physicochemical stability and a reduced fraction of labile iron.

Methods: A systematic formulation optimization was conducted, investigating critical process parameters: order of addition, pH, sterilization method, and oxygen control via nitrogen sparging. The optimized formulation was characterized for description, pH, particle size (as determined by dynamic light scattering, DLS), zeta potential, iron assay (using FAAS), and labile iron content (via a ferene-SPE assay). Stability was assessed under accelerated (40°C/75% RH) and long-term (25°C/60% RH) conditions for two months.

Results: The optimal process involved adjusting Water for Injection pH to 10.8 before API addition, aseptic filtration, and stringent oxygen control (<2 ppm). The optimized formulation exhibited properties comparable to the reference listed drug (Venofer): particle size (Z-avg: 12 nm, PDI: 0.180), zeta potential (-26.4 mV), and assay (98.9%). Crucially, the labile iron content was significantly reduced to 0.22% compared to 0.35% for Venofer (a 37% reduction). Stability studies confirmed the formulation's robustness, with all critical quality attributes remaining within specification over the study period.

Conclusion: This study successfully developed a stable iron sucrose formulation with a significantly lower labile iron content. The rigorous control of oxygen during manufacturing was identified as a key factor in minimizing oxidative degradation. This optimized product has the potential to offer an improved safety profile for patients requiring intravenous iron therapy.

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1. INTRODUCTION

Iron deficiency anemia (IDA) is a global health concern, especially prevalent in patients with chronic kidney disease (CKD) where inflammation and elevated hepcidin levels often render oral iron therapy ineffective (1, 2). Intravenous (IV) iron-carbohydrate complexes, such as iron sucrose, are essential for managing IDA in this population. These non-biological complex drugs (NBCDs) consist of a polynuclear iron (III)-oxyhydroxide core stabilized by a carbohydrate shell (3, 4).

Despite their efficacy, a significant limitation of existing iron sucrose formulations is the presence of labile iron—a weakly bound, redox-active fraction. Upon infusion, labile iron can catalyze the formation of harmful reactive oxygen species (ROS) via Fenton

chemistry, contributing to acute infusion reactions and systemic oxidative stress (5, 6). The physicochemical stability of these nanocolloids is highly sensitive to manufacturing conditions, including oxygen exposure, pH, and thermal stress, which can influence particle size distribution and labile iron content (7, 8).

This study aimed to formulate, optimize, and characterize a novel iron sucrose colloidal solution with enhanced stability and a reduced labile iron content compared to the reference listed drug (Venofer). A systematic approach was employed to optimize critical process parameters, with a focus on controlling dissolved oxygen to mitigate degradation pathways.

2. Materials and Methods

2.1. Materials

Iron sucrose active pharmaceutical ingredient (API) was sourced from SNJ Labs Pvt. Ltd. Water for Injection (WFI) was generated in-house. Sodium hydroxide pellets (Merck) and nitrogen gas (in-house) were used. All other chemicals and solvents were of analytical grade. The reference product, Venofer (American Regent, Inc.), was used for comparative analysis.

2.2. Pre-formulation Studies

The API was characterized for description, solubility, pH (of a 20 mg/mL solution), and loss on drying (LOD) as per the certificate of analysis (COA) specifications.

2.3. Formulation Optimization

A 100 mL batch of iron sucrose colloidal solution (20 mg Fe/mL) was prepared. The optimization focused on several Critical Process Parameters (CPPs):

1. **Order of Addition:** Three sequences were evaluated: (WFI + API + NaOH), (WFI + NaOH + API), and (Premix NaOH/WFI + API).
2. **pH Variation:** The target pH was tested at 10.5, 10.8, and 11.0.
3. **Sterilization Method:** Terminal sterilization (autoclaving at 121°C/15 min or 100°C/30 min) was compared against aseptic filtration (0.2 µm PES membrane).
4. **Oxygen Control:** The process was performed with and without nitrogen sparging to maintain dissolved oxygen below 2 ppm, as monitored by a Presens optical oxygen meter.

The optimized formulation was filled into 5 mL type-I glass vials, purged with nitrogen (<2 ppm O_2 in headspace), and sealed with bromobutyl rubber stoppers.

2.4. Characterization of Optimized Formulation

The final optimized batch and Venofer were characterized for:

- **Description:** Visual inspection for color and appearance.
- **pH:** Measured using a calibrated pH meter.
- **Particle Size, PDI, and Zeta Potential:** Analyzed by dynamic light scattering (DLS) using a Malvern Zetasizer Nano ZS after 1:100 dilution with nitrogen-purged WFI (pH 10.8).
- **Assay (Total Iron Content):** Quantified using Flame Atomic Absorption Spectrophotometry (FAAS) at 248.3 nm.
- **Labile Iron Content:** Determined using an in-house ferene-based solid-phase extraction (SPE) method. Briefly, the formulation was spiked into serum, and transferrin-bound iron was isolated using an NH_2-SPE cartridge. The iron was complexed with ferene reagent, and absorbance was measured at 604 nm.

2.5. Stability Studies

The optimized formulation was stored under accelerated (40°C ± 2°C / 75% RH ± 5%) and long-term (25°C ± 2°C / 60% RH ± 5%) conditions as per ICH guidelines (9). Samples were analyzed at 0, 1, and 2 months for the above quality attributes.

3. Results and Discussion

3.1. Pre-formulation and Optimization

The API complied with all COA specifications: dark brown powder, freely soluble in water (insoluble in ethanol), pH (20 mg/mL) of 11.03, and LOD of 0.51% w/w.

Systematic optimization revealed that the sequence WFI + NaOH (pH adjusted to 10.8) + API (Trial 2) yielded the most stable dispersion, preventing local pH shifts and API precipitation. Aseptic filtration was selected over autoclaving, which induced particle aggregation and a drop in pH. Crucially, maintaining dissolved oxygen below 2 ppm via nitrogen sparging was paramount; formulations prepared under ambient oxygen (~7.5 ppm) showed visible darkening, increased PDI, and higher labile iron.

3.2. Comparative Characterization

The optimized formulation demonstrated physicochemical properties equivalent to the RLD, Venofer (Table 1). The particle size distribution (D50: 13 nm, PDI: 0.180) and zeta potential (-26.4 mV) confirmed a stable, monodisperse colloidal system with strong electrostatic repulsion, mirroring the reference product.

Table 1: Comparative analysis of the optimized formulation and Venofer (RLD)

Parameter	Specification	Optimized Formulation	Venofer (RLD)
Description	Brown, colloidal dispersion	Complies	Complies
pH	10.5 - 11.10	10.71	10.98
Z-Ave (d. nm)	NA	12	12
PDI	NA	0.180	0.154
Assay (% of label)	95.0 - 105.0	98.9%	98.4%
Zeta Potential (mV)	NA	-26.4	-26.5
Labile Iron (%)	NMT 0.4 %	0.22%	0.35%

The most significant finding was the 37% reduction in labile iron content (0.22% vs. 0.35%) in the optimized formulation. This underscores the success of the oxygen-controlled process in preserving the integrity of the sucrose shell and minimizing the generation of free, redox-active iron, which is linked to adverse reactions.

3.3. Stability Studies

The optimized formulation exhibited excellent stability over two months (Table 2). Under long-term conditions (25°C/60% RH), all parameters remained well within acceptable limits. Under accelerated stress (40°C/75% RH), a slight increase in particle size (D50: 16 nm) and labile iron (0.33%) was observed after two months, indicating mild stress-induced degradation. Nevertheless, the labile iron content remained below that of the fresh RLD, confirming the superior stability of the developed formulation.

Table 2: Stability data of the optimized formulation

Parameter	Initial	1M (25°C)	1M (40°C)	2M (25°C)	2M (40°C)
Description	Brown, colloidal dispersion	Brown, colloidal dispersion	Brown, colloidal dispersion	Brown, colloidal dispersion	Brown, colloidal dispersion, Slight Haze
pH	10.71	10.68	10.55	10.65	10.50
Z-Ave (d. nm)	12	12.5	13.8	13.0	15.2
PDI	0.180	0.195	0.230	0.200	0.265
Assay (%)	98.9	98.5	97.8	98.2	96.5
Labile Iron (%)	0.22	0.24	0.29	0.25	0.33

4. Conclusion

This study successfully developed an optimized iron sucrose colloidal formulation through meticulous control of critical process parameters, especially oxygen concentration. The resulting product is physicochemically equivalent to the reference standard but possesses a key advantage: a significantly reduced labile iron content. This reduction is anticipated to translate into a lower potential for oxidative stress and improved tolerability in patients. The findings highlight the critical importance of manufacturing process control for the quality, efficacy, and safety of complex nano colloidal drugs like iron sucrose. This optimized formulation presents a promising alternative for the safer management of iron deficiency anemia.

Author Contributions

Nitin Suthar: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing - Original Draft, Visualization. **Narendra Singh Solanki:** Supervision, Project administration, Writing - Review & Editing. **Deepak Singodia:** Resources, Supervision. **Jayesh Gadhiya:** Supervision, Resources.

All authors have read and agreed to the published version of the manuscript.

Conflict of Interest

The authors declare no conflict of interest.

Ethical Approval

This article does not contain any studies with human participants or animals performed by any of the authors.

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