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Diluting ferric carboxymaltose in sodium chloride infusion solution (0.9% w/v) in polypropylene bottles and bags: effects on chemical stability

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ABSTRACT

Objectives This study was designed to assess the physicochemical stability of colloidal ferric carboxymaltose solution (Ferinject) when diluted and stored in polypropylene (PP) bottles and bags for infusion.

Methods Two batches of ferric carboxymaltose solution (Ferinject) were diluted (500 mg, 200 mg and 100 mg iron in 100 mL saline) in PP bottles or bags under aseptic conditions. The diluted solutions were stored at 30°C and 75%±5% relative humidity (rH) for 72 h, and samples were withdrawn aseptically at preparation and after 24 h, 48 h and 72 h. Multiple parameters were used to test stability-related measures (pH, total iron and iron (II) content, molecular weight range determination, microbial contamination and particles count ≥10 µm).

Results Overall, Ferinject diluted in 0.9% (w/v) NaCl solution and stored in PP bottles and bags was stable within the specifications for the complex and the acceptability limits set for all assays. In both containers, total iron content remained stable, within 10% of the theoretical iron content, and levels of iron (II) remained far below the threshold of acceptability. All preparations were free from sediments, particle numbers were acceptable and there was no microbial contamination. The molecular weight distribution and polydispersity index were also acceptable.

Conclusions Under the tested experimental conditions, colloidal ferric carboxymaltose solution (Ferinject) diluted in saline in PP infusion bottles or bags demonstrated physical and chemical stability for up to 72 h at 30°C and 75% rH. Because of the lack of additional clinical data, when using ferric carboxymaltose, physicians/pharmacists should refer to the dilution and storing recommendations given in the product's summary of product characteristics.

INTRODUCTION

Iron is essential for living organisms and their well-being. However, iron deficiency (ID) has a high prevalence worldwide.^{1–3} Its role in anaemia, which affects more than 30% of the population, is well established, with at least 50% of anaemia cases due to ID.³ Iron is essential for growth and the development of cognitive and motor functions during pregnancy and childhood.^{4–8}

Causes of ID can be described as reduced or depleted iron stores (eg, bleeding disorders leading to a loss of iron (absolute ID)), and as impaired mobilisation of the body's iron stores to meet erythropoiesis needs (functional ID due to intense stimulation of erythropoiesis by endogenous erythropoietin or secondary to erythropoiesis-stimulating agent treatment).^{9–11} The main signs

and symptoms of ID include fatigue, lethargy, reduced exercise tolerance, malaise, depressed mood and epithelial problems such as ulceration and slow wound healing.^{12–14}

Treatment of ID and ID anaemia with either oral or intravenous iron formulations can compensate for insufficient iron supply and help to reduce fatigue, increase exercise capacity and normalise haemoglobin levels.^{15–17} Iron treatment is also associated with improved outcomes in specific conditions. These include pregnancy (prevention of low birth weight, reduced risk of maternal ID anaemia),¹⁷ chronic heart failure (reduced symptom severity, better quality of life, increased 6-min walk test distance)^{15 18–20} and inflammatory bowel disease (prevention of disease-related anaemia).¹⁶

Colloidal ferric carboxymaltose solution (Ferinject, Vifor Pharma, Switzerland) is a latest-generation iron product that comprises a polynuclear iron (III)-oxyhydroxide core stabilised by a carbohydrate shell. This structure allows for controlled delivery of iron to target tissues.²¹ Preclinical testing has shown the carboxymaltose complex to be stable and robust at physiological pH, with a good toxicity profile in animal models.²² Ferric carboxymaltose solution (Ferinject) is indicated in Europe and the USA for the treatment of ID when oral iron preparations are ineffective or cannot be used. Ferric carboxymaltose complex is representative of nanoparticulate, non-biological complex drugs (NBCDs), which are defined as synthetic, large molecular, complex medicinal products (MPs) consisting of non-homomolecular structures that cannot be fully characterised physicochemically. This new class of complex MPs represents a challenge for regulatory evaluation, in particular to assess comparability when it comes to follow-ons and nanomedicines in general.^{23–25} In addition, they pose challenges to the evaluation of stability after admixing to injection or infusion solutions because of their highly complex character and composition, such that well selected tests have to be applied. This is in contrast to classical small molecule active pharmaceutical ingredients, which can be fully characterised by physicochemical tests demonstrating full pharmaceutical identity.

Ferric carboxymaltose solution (Ferinject) is supplied as a sterile colloidal solution of 50 mg iron per mL that can be administered intravenously according to the summary of product characteristics (SmPC) as a slow bolus injection (for doses up to 200 mg iron: no prescribed minimal administration time; for doses greater than 200 mg iron and up to

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500 mg iron: administration rate should be of up to 100 mg iron/min; for doses greater than 500 mg and up to 1000 mg iron: administration time should be at least of 15 min) using undiluted solution (up to 1000 mg iron for a maximum of 15 mg iron/kg body weight) or appropriately diluted in sterile 0.9% mass per volume (m/v) sodium chloride solution for up to 1000 mg iron (for a maximum of 20 mg iron/kg body weight) infused through an intravenous catheter over 15 min. The product meets the criteria for nanomedicines due to its particle characteristics. Recent expert opinions clearly highlight the need to demonstrate physicochemical stability as thoroughly as possible to eliminate clinically meaningful differences between products.^{25 26} The iron complex and the solution composition, and the container material for infusion has to be considered when handling the medicinal product. In contrast to molecular, dispersed solutions, in such colloidal solutions the complex may be destabilised upon too high dilution, which might negatively affect tolerance due to an increased amount of labile iron. For regulatory submission glass and polyethylene containers have been tested for stability with appropriately diluted ferric carboxymaltose solutions (Ferinject).²⁷ Polypropylene (PP) bags are heavily used in hospitals for intravenous infusions. However, to date no stability data for ferric carboxymaltose solutions (Ferinject) diluted and stored in PP infusion containers are available and therefore, such use cannot be considered from a regulatory perspective.

To evaluate the physicochemical stability of ferric carboxymaltose solution (Ferinject) in PP containers, this investigation was made under dilution and storage conditions similar to those of daily clinical practice. A panel of physicochemical assays was applied to assess the colloidal solutions in PP bags and bottles for up to 72 h to determine whether these processes had any effect on the integrity of the drug.

MATERIAL AND METHODS

In 2012 two different batches of ferric carboxymaltose solution (Ferinject), 50 mg/mL iron colloidal solution, were analysed: batch 166101 (expiry June 2014) and batch 169001 (expiry May 2014). Both batches conformed to physicochemical and microbial requirements regarding pH, iron content, chemical purity, clarity and bacterial endotoxins.

Ferric carboxymaltose solution (Ferinject; 2 mL, 100 mg iron equivalent per vial) was diluted in saline under aseptic conditions (laminar air flow class 100). PP bags (Laboratorium und Grosse Apotheke Dr G Bichsel AG, Interlaken—batch 8150612; expiry June 2014) and PP bottles (Laboratorium und Grosse Apotheke

Dr G Bichsel AG, Interlaken—batch 1150612; expiry June 2015), both with a volume of 100 mL saline, were used in this study. Sampling of the solutions for analysis was done via a 175 cm infusion line (CODAN Medizinische Geräte GmbH & Co KG; di (2-ethylhexyl) phthalate free polyvinyl chloride tubing, batch K867 91-1; expiry February 2017). Three Ferinject dilutions were prepared and analysed in duplicate, using 0.9% (m/v) NaCl solution for infusion as diluent and control: 500 mg iron (5 vials, 10 mL) in 100 mL NaCl solution (nominal iron content of 4.5 mg/mL); 200 mg iron (2 vials, 4 mL) in 100 mL NaCl solution (nominal iron content of 1.9 mg/mL); 100 mg iron (1 vial, 2 mL) in 100 mL NaCl (nominal iron content of 1.0 mg/mL, not recommended in the Ferinject label as no clinical data are available with this dilution).

Diluted samples were stored at 30°C and 75%±5% relative humidity (rH) for 72 h (climate cabinet). Samples for analysis were withdrawn aseptically from the test intravenous infusions immediately (t=0) and at 24 h, 48 h and 72 h after dilution using the infusion line as stated above.

As described below, multiple parameters were used to test stability-related measures including pH, iron quantifications and molecular range determination and the presence of particles ≥10 µm. Each batch was analysed separately with parameters measured in duplicate to calculate a mean per sample and subsequently for data per time point.

Total iron content was assessed using a complexometric titration with EDTA.²⁸ The acceptance criterion was the nominal value ±10%. Iron (II) content was assessed using a redox titration with cerium (IV) sulphate.²⁹

Sedimentation was assessed visually. Failure was defined as the presence of visible sediments in the solution.

The pH of the solutions was measured using potentiometry.³⁰ The acceptable pH range was 4.5–7.0, according to the specification of the saline solution. The acceptable change in pH from the initial value should be not more than 0.6 as observed in long-term stability studies with Ferinject finished product.²⁷

Molecular weight distribution of the ferric carboxymaltose solution was assessed using gel permeation chromatography as described by Geisser *et al.*³¹ Results were reported as relative molecular weights M_w and M_n , using the polydispersity index (P) according to the following equation:

$$P = \frac{\text{weight - average molecular weight}(M_w)}{\text{average molecular weight}(M_n)}$$

Figure 1 The effect of dilution as described in the Material and methods section and after storage for 72 h on the pH of the iron solutions (dotted lines represent the predefined upper and lower limits of acceptability).

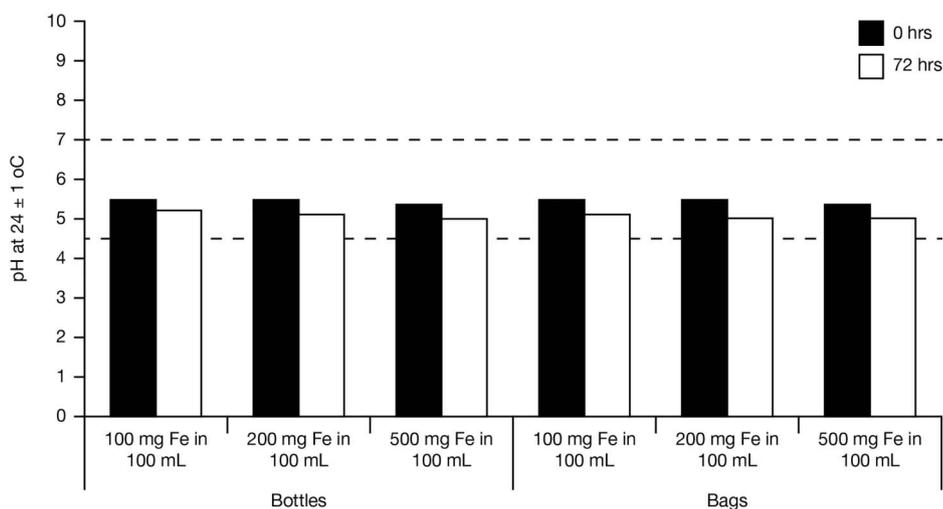


Table 1 Total iron content, sedimentation, microbial count and aggregation immediately after dilution in 0.9% NaCl as described in the Material and methods section and after storage for 72 h in polypropylene bottles

Variable	Units	Acceptability limit	100 mg iron in 100 mL		200 mg iron in 100 mL		500 mg iron in 100 mL	
			0 h	72 h	0 h	72 h	0 h	72 h
Total iron content	% mg/mL	±10%	0.9	0.9	1.8	1.8	4.3	4.4
Visual control	NA	Free from sediments	Complied	Complied	Complied	Complied	Complied	Complied
Total viable aerobic microbes	Counts per mL	<1	<1	<1	<1	<1	<1	<1
Particulate matter ≥10 µm	Counts per container	≤6000	177	170	221	195	265	215
Particulate matter ≥25 µm	Count per container	≤600	1	0	0	1	1	0

NA, not applicable.

Total particle count was assessed as the light obscuration particle count.³⁰ Each sample underwent individual testing using seven repetitions of 10 mL; first measurements were disregarded for the calculation of the mean number of particles. Failure was defined as counts exceeding published total counts exceeding 6000 particles ≥10 µm and 600 particles ≥25 µm.³⁰

Sterility was tested by assessing the total viable aerobic microbial count per mL solution. Failure was defined as at least 1 colony forming unit (CFU) per mL.³¹

RESULTS

This study was designed to assess the physicochemical stability of the iron carbohydrate complex, ferric carboxymaltose after dilution. The parameters were measured to determine stability up to 72 h after dilution to detect trends in the nature of the solutions, according to the emerging requirements for the assessment of nanomedicines and NBCDs.^{25 26}

Overall, Ferinject diluted in 0.9% NaCl solution, and stored in PP bottles and bags for up to 72 h at 30°C and 75% rH was stable within the specifications and the acceptability limits set for all assays. The results shown here are mean values for the two batches of ferric carboxymaltose solution (Ferinject) and the multiple measurements for each parameter at each time point. Data from each batch individually were also within acceptability limits. Data are shown immediately after dilution and after 72 h. All parameters were also within the limits of acceptability at 24 h and 48 h (data not shown).

As shown in figure 1, the pH decreased slightly, by 0.3–0.5 units, in PP bags and bottles. However, these changes did not exceed the predefined limits of acceptability. For the control solutions (0.9% NaCl solution without iron), the starting pH was already 1.7 units lower in the bags than in the bottles.

Over the course of the study, the total iron content remained stable, within 10% of the theoretical iron content in PP bottles

(table 1) and bags (table 2). Likewise, all preparations were free from sediments on visual inspection and particle numbers were within the limits of acceptability (tables 1 and 2).

The physicochemical stability of the colloidal ferric carboxymaltose solution (Ferinject) was also assessed by measuring its molecular weight distribution. M_w and M_n were within limits (table 3), as was the polydispersity index (P). Additionally, the iron (II) content did not change significantly (figure 2). In addition, microbial contamination testing revealed that sterility was maintained throughout the study (<1 CFU/mL in all samples).

DISCUSSION

We set out to investigate the physical and chemical stability of colloidal ferric carboxymaltose solution (Ferinject) stored in PP bottles and bags for up to 72 h at 30°C and 75% rH. The temperature of 30°C allowed us to evaluate stability under a moderately elevated, ‘stress’ temperature, which also reflects realistic conditions often encountered during the hot season in a hospital. This is the first demonstration of the stability of Ferinject with these widely used containers under conditions of daily practice.

Iron complexes for intravenous administration represent NBCDs that cannot be fully characterised physicochemically. Changes in concentration upon dilution could destabilise the complex because there is equilibrium between ligand molecules bound to the iron core and unbound in solution. If concentration of ligand molecules decreases upon dilution, the number of ligand molecules bound to the iron core will also decrease and may cause further polymerisation of the polynuclear iron core. This can finally result in precipitation of ferric hydroxide. Also, changes in pH could destabilise the complex. This has been shown for iron sucrose which is only stable in alkaline solution with sufficient amount of sucrose.³²

We used a range of analyses, per emerging requirements for quality evaluation of NBCDs.^{25 26} The data showed a high

Table 2 Total iron content, sedimentation, microbial count and aggregation immediately after dilution in 0.9% NaCl as described in the Material and methods section and after storage for 72 h in polypropylene bags

Variable	Units	Acceptability limits	100 mg iron in 100 mL		200 mg iron in 100 mL		500 mg iron in 100 mL	
			0 h	72 h	0 h	72 h	0 h	72 h
Total iron content	% mg/mL	±10%	0.9	0.9	1.8	1.8	4.3	4.3
Visual control	NA	Free from sediments	Complied	Complied	Complied	Complied	Complied	Complied
Total viable aerobic microbes	Counts per mL	<1	<1	<1	<1	<1	<1	<1
Particulate matter ≥10 µm	Counts per container	≤6000	95	112	158	115	257	256
Particulate matter ≥25 µm	Count per container	≤600	1	1	1	0	0	0

NA, not applicable.

Table 3 Molecular weight distribution immediately after dilution in 0.9% NaCl as described in the Material and methods section and after storage for 72 h

	100 mg iron in 100 mL		200 mg iron in 100 mL		500 mg iron in 100 mL	
	0 h	72 h	0 h	72 h	0 h	72 h
Bottles						
M _w , Da*	144 000	141 000	144 000	141 000	143 000	141 000
M _n , Da*	92 800	90 300	92 700	90 600	92 700	90 700
Polydispersity index P [†]	1.6	1.6	1.6	1.6	1.5	1.6
Bags						
M _w , Da*	144 000	140 000	144 000	141 000	143 000	141 000
M _n , Da*	92 300	90 100	92 500	90 500	92 000	90 600
Polydispersity index	1.6	1.6	1.6	1.6	1.6	1.6

*The accuracy of molecular weight determination by gel permeation chromatography is $\pm 5\%$, the precision of Mw values is $\pm 0.6\%$.

[†] $P = M_w/M_n$, where M_n: number-average molecular weight; M_w: weight-average molecular weight; P: polydispersity index.

degree of stability at three dilutions, strongly suggesting that once diluted, ferric carboxymaltose solution (Ferinject) can be stored for up to 72 h, although the potential impact on clinical effectiveness and safety require demonstration. This also gives important indications about the stability of the infusion after dilution when appropriately admixed, for example, when considering a pharmacy-based intravenous admixing service.

Our results were obtained reproducibly for two batches, with acceptance criteria being met for all parameters measured. We observed that the pH of the solutions in PP containers decreased slightly with an increasing iron concentration and with longer duration of storage. However, these changes were well within the set specifications. We noted that for the control saline solution the starting pH of the solution in the bags was 1.7 units lower than that in the bottles. The low air permeability of the stiff PP bottles compared with the higher permeability of soft PP bags and the absence of any buffering ingredient in saline are the most likely causes of this difference.

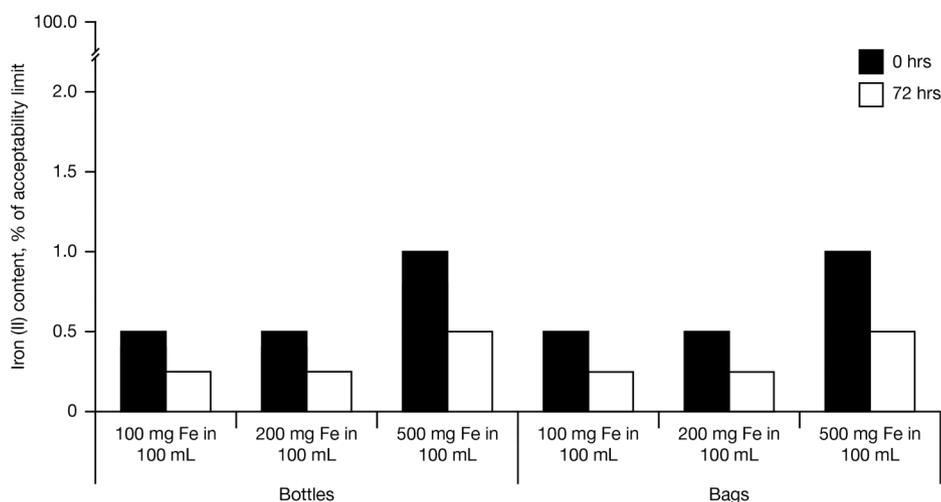
As stated earlier, a variety of assessments is necessary to get as complete a picture as possible of the stability of a diluted complex acting as a prodrug to deliver iron. Overall, the total iron content varied less than 5% (acceptance criterion: 10%) from the theoretical iron content for all concentrations at each time point and in both types of containers, that is, in accordance with the specifications. This observation shows that there is no measurable absorption of iron at the surface of the containers.

The small deviations measured could be explained by losses during the transfer of samples using polyvinyl chloride tubes showing high absorption properties. Likewise, there was no evidence of visually identifiable sediment (precipitation) or changes in total particle count, indicating physical stability under test conditions.

The molecular weight distribution is a very sensitive parameter concerning stability, indicating whether or not there is degradation or aggregation of the individual complex components. This is reflected in the polydispersity index (P), a measure of the heterogeneity/homogeneity of non-homomolecular structures in a solution. In our tests, considering the accuracy of the instrument for this type of relative molecular weight determination, we found essentially no changes.

It must be stressed that data such as we have shown here must be provided for each individual NBCD from a specific manufacturer. Additionally, data for the originator cannot be extrapolated from follow-on versions (ie, nanosimilars²⁶) due to their structural complexity. This is to be expected given the regulatory challenges for comparing originators and intended follow-on versions, for which stability-related issues have previously been demonstrated, for example, the originator iron sucrose (Venofer) and its similars.^{33 34}

Safety of IV iron MP has recently become of particular interest due to possible hypersensitivity reactions. Although investigation of safety was not in the scope in this study, it is worth

Figure 2 The effect of dilution as described in the Material and methods section and after storage for 72 h on iron (II) content.

remarking that (A) the impact of the dilution/material on the likelihood of inducing hypersensitivity reactions cannot be tested in vitro and (B) recently, the European Medicines Agency, working with the manufacturers of iron products, undertook a detailed assessment of safety reported in preclinical and clinical trials, as well as data collected via postmarketing and pharmacoepidemiology programmes and other published literature.³⁵ The agency concluded that the benefit–risk profile for intravenous iron products remained “favourable as the benefits continue to outweigh the risks in the treatment of ID when the oral route is insufficient or poorly tolerated.”³⁵ Monitoring of patients for 30 min after administration was included in the SmPC of all intravenous iron compounds.³⁵

In conclusion, our results demonstrate that colloidal ferric carboxymaltose solution (Ferinject) under the considered experimental condition shows no major loss of physical or chemical

stability. Because of the lack of additional clinical data, when using ferric carboxymaltose, physicians/pharmacists should refer to the dilution and storing recommendations given in the product’s SmPC.

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Competing interests EP, MB, SM are Vifor Pharma employees. TB is a Laboratorium Dr G Bichsel AG Employee.

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Key messages

What is already known on this subject

- ▶ Ferric carboxymaltose solution for injection (Ferinject) is a colloidal solution. The exact physicochemical characterisation of such a nanoparticulate non-biological complex drug is not possible.
- ▶ Physical and chemical stability of intravenous iron carbohydrate solutions is associated with their pharmacokinetic, safety and efficacy profiles. The stability of the complex, that is, of the interaction between the polynuclear iron (III)-oxyhydroxide core and the carbohydrate shell, is dependent on the dilution of the solution for infusion.
- ▶ Changes in pH and concentration upon dilution could destabilise the complex, potentially leading to an increased amount of labile iron, which ultimately affects the tolerability of the product, especially for high, rapidly administered intravenous doses.
- ▶ Last-generation, innovative parenteral iron products such as ferric carboxymaltose solution (Ferinject) have been designed to have increased stability under physiological conditions and consequently limited labile iron, thereby allowing administration of high intravenous doses over short injection times.

What this study adds

- ▶ Iron in the form of ferric carboxymaltose solution (Ferinject), when diluted in saline according to the experimental conditions described in this report, remains stable in polypropylene bags and in polypropylene bottles for at least 72 h at elevated room temperature (30°C) and 75% relative humidity, without physical or chemical degradation, aggregation or adsorption to the container surface.
- ▶ In particular, there was no increase in the amount of iron (II) beyond acceptable limits.
- ▶ These results show that colloidal ferric carboxymaltose solution (Ferinject) can be diluted according to study conditions and, when diluted under aseptic conditions, the solution can be stored for up to 3 days with no apparent risk of physicochemical instability. However, because of the lack of additional clinical data, when using ferric carboxymaltose, physicians/pharmacists should refer to the dilution and storing recommendations given in the product’s summary of product characteristics.

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