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Research paper

Dissimilar ferric derisomaltose formulations – *In vitro* comparisons between an originator and its intended similars

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ABSTRACT

Background: The complex nature of intravenous (IV) iron formulations makes manufacturing and characterising similars challenging. This study examined whether simple *in vitro* tests can distinguish the high-dose IV iron formulation, Monofer® (ferric derisomaltose [FDI]), from the first intended copies of FDI, Rapifer® (FDI intended similar A [FDIIS-A]) and Tosiron® (FDI intended similar B [FDIIS-B]), approved in India and Pakistan, respectively. Neither intended similar is available in Europe or the United States.

Methods: Iron content, pH, density, non-volatile residue, carbohydrate content, molecular weight distribution, complex robustness (measured using acid hydrolysis half-life [$t_{½}$]) and free (dialysable) iron content were examined. Mean results from three batches of FDIIS-A were compared with mean values calculated from three batches of Monofer®. Due to product withdrawal, only one batch of FDIIS-B was available for comparison with Monofer®.

Results: Iron content was similar for all formulations (~100 mg/mL). The chromatograms (obtained using gel permeation chromatography) of FDIIS-A and FDIIS-B differed from that of Monofer®. FDIIS-A was substantially less robust than Monofer® ($t_{½}$: 15 h versus 40.3 h); $t_{½}$ for FDIIS-B was not tested. Free iron content was substantially higher in FDIIS-A (0.091 % w/v) and FDIIS-B (1.0 % w/v) versus Monofer® (<0.003 % w/v). Where tested, remaining parameters varied between the formulations (insufficient sample quantities prevented all tests being conducted for all intended similars). For all tests, greater inter-batch variability was seen for FDIIS-A versus Monofer®.

Conclusions: Simple *in vitro* tests demonstrated that, aside from total iron content, the first intended similars of FDI bear little resemblance to their originator drug. It is clear that the efficacy and safety profile of Monofer® cannot be extrapolated to the two intended similars. The results call for increased regulatory scrutiny of intended IV iron similars.

1. Introduction

Intravenous (IV) iron formulations, used to treat iron deficiency (ID) or iron deficiency anaemia (IDA), are a type of non-biological complex drug that must receive regulatory approval prior to being marketed [1]. Available IV iron formulations consist of nanoparticles made up of iron and carbohydrate – in most IV iron formulations, the nanoparticles consist of an iron-oxyhydroxide (FeOOH) core surrounded by a

Abbreviations: ADE, adverse drug event; CQA, critical quality attribute; DRAP, Drug Regulatory Authority of Pakistan; FCM, ferric carboxymaltose; FDA, Food and Drug Administration; FDI, ferric derisomaltose; FDIIS-A, ferric derisomaltose intended similar A; FDIIS-B, ferric derisomaltose intended similar B; FeOOH, iron-oxyhydroxide; GPC, gel permeation chromatography; HMWID, high molecular weight iron dextran; HSR, hypersensitivity reaction; ID, iron deficiency; IDA, iron deficiency anaemia; IIM, iron isomaltoside 1000; IV, intravenous; LMWID, low molecular weight iron dextran; NVR, non-volatile residue; PK, pharmacokinetic; RCT, randomised controlled trial; SD, standard deviation; $t_{½}$, half-life; US, United States.

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carbohydrate shell; [1–4] these IV iron nanoparticles are difficult to fully characterise with currently available physicochemical analytical techniques alone [2,5–9]. The relevance of certain physicochemical properties with respect to the efficacy and safety profile of IV iron formulations has been explored by various investigators, [5,10,11] and are deemed to be critical quality attributes (CQAs) [5,10] – properties or characteristics that should be within appropriate limits to meet desired quality standards [12]. However, a definite number of properties that affect the clinical profile of an IV iron formulation, and the extent to which they do so, is not known [5,10,11,13,14]. Consequently, the final product should be considered the drug substance, which is largely defined by the manufacturing process [5,8]. Even minor adjustments to the manufacturing process of IV iron formulations can change their properties (e.g., immunogenicity) and affect their clinical performance and safety [5,8,15]. Factors that play a role in the stability of the final product, such as transport, the choice of packaging material, and storage temperature, can also affect the physicochemical properties of the IV iron formulation, impacting on its efficacy and safety [5,8]. Therefore, robust and strictly-controlled procedures in the production of IV iron formulations are key to assure batch-to-batch consistency [5,8].

In general, a new medicinal product can acquire the same non-proprietary name as an existing drug if it is classed as a generic, meaning that it is considered identical to the existing (reference or originator) drug by regulatory authorities [16,17]. However, because IV iron formulations are not fully characterisable, the terms ‘similars’ or ‘nanosimilars’ have also been used in the literature to describe intended copies of IV iron formulations. Many of these so-called ‘similars’ were approved via a regulated pathway for generics but later demonstrated non-equivalence to their originator, reflecting the concern that it is difficult to ascertain the sameness of complex drugs that are not fully characterisable using currently available *in vitro* techniques [7,15]. The term ‘similars’ is the nomenclature used in this paper; for the two products investigated in this study (which intend to copy an IV iron originator but are not approved in highly regulated markets – namely, Europe and the United States [US]), the term ‘intended similars’ is used. It is evident that producing an IV iron similar that is therapeutically equivalent to the reference drug, and demonstrating the pharmaceutical equivalence and bioequivalence of the similar to its reference drug, is challenging [1,5]. Indeed, there is a growing awareness that many currently approved IV iron similars are concerningly different to their corresponding reference drug [1,7,18–22].

In the EU and the US, similars must follow specific pathways to gain approval; for complex drugs, the amount of evidence required by the regulator is determined on a case-by-case basis [1,7]. Guidelines have been issued to recommend a broad battery of *in vitro*, non-clinical, and clinical testing to establish sameness of an IV iron similar and its reference drug [4,23–25]. Recommended *in vitro* tests include assessments of parameters proposed as CQAs for IV iron products: nanoparticle properties (e.g., stoichiometric ratios of relevant components, molecular weight distribution, labile iron content), FeOOH properties (e.g., size and morphology, crystallinity, ferrous iron content, magnetic properties), and carbohydrate properties (e.g., carbohydrate composition, interactions with the iron, zeta potential) [4,25–31]. Various *in vitro* techniques to assess physicochemical properties that may be critical to the efficacy and safety profile of IV iron formulations have been reported in the literature, [11,25,32] and include tests to assess parameters indicative of the risk of labile iron toxicity, such as half-life ($t_{½}$; also referred to as complex robustness, a surrogate for the rate of physiological iron release), free (dialysable) iron content, and other measures for labile iron content [11,25]. While early parenteral iron formulations were associated with serious toxic effects related to immediate iron release, [33,34] the nanoparticles in modern IV iron formulations contain a carbohydrate that stabilises the FeOOH, slowing the release of iron during an infusion [3]. Therefore, measures of labile iron toxicity are particularly relevant when developing and testing similar versions of the newest IV iron formulations, ferric carboxymaltose (FCM), ferric derisomaltose (FDI), and ferumoxytol, each of which can be infused as a high single dose over a relatively short time [35–39]. In addition to recommended *in vitro* and non-clinical testing, guidelines recommend human pharmacokinetic (PK) studies, [4,23] and therapeutic equivalence studies [24].

Given the above, there is a pressing need to change the current paradigm for approval of IV iron similars – the focus should be expanded beyond molecular identity to include a requirement for documented clinical efficacy and safety. Two prime examples that demonstrate this need are noted. The first example is that of high molecular weight iron dextran (HMWID; Dexferrum®, Vifor), [40] which was approved in the US in 1996 as a less expensive alternative to the existing and widely used low molecular weight iron dextran (LMWID; INFeD® in the US, Allergan; CosmoFer® in Europe, Pharmacosmos A/S) [41–43]. Within months of the release of Dexferrum®, and during a period when INFeD® was temporarily unavailable, there was an 11-fold increase in serious adverse events reported to the US Food and Drug Administration (FDA) [42]. A chart review conducted at The Children’s Hospital of Pennsylvania found that, between 1994 and 2000, when both INFeD® and Dexferrum® were used, substantially more side effects were reported in patients who had received Dexferrum® than in those who received INFeD®, [44] suggesting that the two IV iron formulations have different safety profiles. Subsequently, Dexferrum® was proscribed by the National Comprehensive Cancer Network and American Society of Nephrology, removed from formularies, and is no longer available [42]. In a second example from 2021, a similar of Feraheme® (ferumoxytol; branded formulation manufactured by AMAG Pharmaceuticals, Inc.) [35] was approved by the FDA as bioequivalent and therapeutically equivalent to Feraheme®, for marketing by Sandoz Inc [45,46]. The only clinical data in Sandoz’ filing with the FDA was a 60-patient cohort, in which the incidence of adverse events was double that reported with Feraheme® [47]. One death has been reported and, following review of the National Drug Code of the formulation used, was attributed to the similar [47]. Of further concern is that current regulations in the US and many other countries allow or mandate – or even incentivise – pharmacists to substitute a branded formulation with cheaper similars, unless the ordering practitioner specifically requests that the branded formulation is to be dispensed [48,49].

FDI – widely marketed as Monofer® and previously known by the non-proprietary name iron isomaltoside 1000 (IIM) [50] – is a high-dose IV iron formulation (manufactured by Pharmacosmos A/S, Holbæk, Denmark) [38,39]. FDI has been approved in more than 40 countries; [51] no similar versions are currently available in Europe or the US. The efficacy and safety profile of Monofer® has been demonstrated in a comprehensive portfolio of clinical trials and observational studies involving >8,900 patients with ID or IDA of various aetiologies (Appendix A, supplementary material), and in a real-world UK study involving a diverse population of >7,000 patients treated with the IV iron formulation [52]. Regarding safety aspects, randomised controlled trials (RCTs) and analyses have shown that Monofer® is associated with a low incidence of serious hypersensitivity reactions (HSRs), [53–56] and with a significantly lower incidence of hypophosphataemia, compared with FCM, another high-dose IV iron formulation [50,57]. Long-term safety has also been demonstrated in the IRONMAN trial in a population with heart failure – the median length of follow-up was 2.7 years [58].

Monofer® consists of nanoparticles that have a matrix structure composed of interchanging layers of iron atoms and short linear derisomaltose carbohydrates (Fig. 1) [11,13,38]. This structure is unique to Monofer® – the nanoparticles of other IV iron formulations are different, and have been described as consisting of a pure iron core surrounded by a carbohydrate shell (Fig. 1) [11,42,59]. Consequently, given the close relationship between the inherent structure and characteristics of an IV iron formulation and its efficacy and safety profile, Pharmacosmos A/S follows specific protocols to ensure the consistent production of the high-dose IV iron formulation [60].

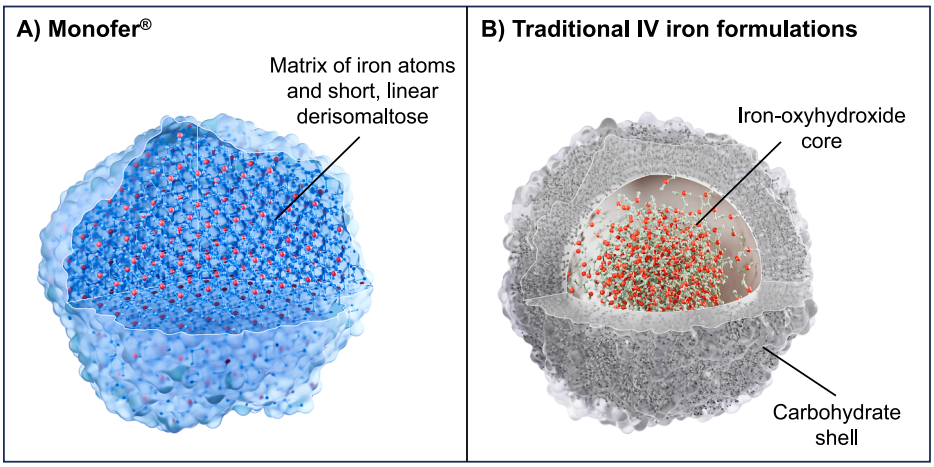

Fig. 1. Structure of (A) Monofer® versus (B) traditional IV iron formulations. IV=intravenous.

As mentioned, no similar versions of Monofer® are currently available in Western markets. However, Rapifer® (an IV iron formulation marketed by Corona Remedies Pvt. Ltd.; referred to as FDI intended similar A [FDIIS-A] from hereon) is available on the Indian market with the non-proprietary name of IIM [61] – the non-proprietary name by which Monofer® was previously known [50]. Another intended similar of the IV iron reference product, Tosiron® (manufactured by Bio-Labs (Pvt) Ltd.; referred to as FDI intended similar B [FDIIS-B] from hereon) was made available on the Pakistani market with the non-proprietary name of IIM, [62] but has since been deregistered by the Drug Regulatory Authority of Pakistan (DRAP). As described earlier, fully characterising IV iron formulations using instrumental analytical methods only is not possible; [4] therefore, it is not sufficient to use *in vitro* tests alone to prove the sameness of an intended IV iron similar and its reference drug. Instead, in order to demonstrate sameness of an intended similar to its reference drug, a full battery of *in vitro*, non-clinical, and clinical testing is required. In this respect, a single *in vitro* test that identifies a material difference between formulations is sufficient to prove dissimilarity. Accordingly, this study was conducted to test the hypothesis that simple *in vitro* tests can be used to discriminate between intended copies (FDIIS-A and FDIIS-B) and the reference drug, Monofer®.

2. Materials and methods

Three batches of FDIIS-A (Rapifer®; batch IIM00419, referred to as FDIIS-A_1, batch IIM102721, referred to as FDIIS-A_2, and batch IIM100223, referred to as FDIIS-A_3) and one batch of FDIIS-B (Tosiron®; batch A-413) were tested using validated or published analytical procedures. The intended similars were sourced from local pharmacies, were stored locally at room temperature, and shipped via air freight to Pharmacosmos in Denmark, where they were stored at room temperature until analyses were conducted. No further batches of FDIIS-B were available for testing due to product withdrawal. The same validated or published analytical procedures were performed on three batches of Monofer® produced between 2019 and 2021 (batches 158358, 158903, and 159630).

2.1. Total iron content

The total iron (both free and bound iron) content of each sample was determined using complexometric titration with Titriplex® III, a titration reagent that contains ethylenediaminetetraacetic acid, which forms a strong complex with many metal ions [63,64]. For this titration procedure, sulfosalicylic acid was used as an indicator to determine the equivalence point (i.e., when all ferric iron [Fe^{3+}] has reacted) [63,64]. The equivalence point was then used to calculate the total iron content of each sample.

2.2. pH

pH was measured directly in the sample according to the European Pharmacopoeia method 2.2.3 [65].

2.3. Density

Density was measured directly in the sample according to the European Pharmacopoeia method 2.2.5 [66].

2.4. Carbohydrate content

The carbohydrate content of each sample was determined using an anthrone–sulfuric acid assay. This method is described in detail in the 2017 British Pharmacopoeia monograph for iron dextran injection [67].

2.5. Non-volatile residue

Non-volatile residue (NVR) was measured using the method described in detail in the US Pharmacopeia monograph for iron dextran injection [68].

2.6. Free (dialysable) iron content

The free iron content was estimated using a dialysis technique described in detail by Jahn et al. (2011) [11].

2.7. Complex robustness (half-life in acid hydrolysis test)

Sample half-life, $t_{½}$ (defined as the time at which the absorption was equivalent to half of the baseline value), was determined by acid hydrolysis, according to the method described in detail by Jahn et al. (2011) [11].

2.8. Molecular weight distribution

The elution profile of each sample was determined using a gel permeation chromatography (GPC) system, using the method described in detail by Jahn et al. (2011) [11]. The apparent peak molecular weight of each iron–carbohydrate complex was also calculated. To check for intra-batch variability in chromatographic profiles, GPC was conducted on three samples of each batch of intended similar (FDIIS-A_1, FDIIS-A_2, FDIIS-A_3, FDIIS-B) and Monofer® (batches 158903 and 159630; only

two chromatograms could be generated for batch 158358 due to batch expiry). There was little batch-to-batch variation between the chromatographic profiles of Monofer®, so a representative batch (159630) was selected for comparisons to chromatograms of the intended similars.

2.9. Statistical analysis

All analytical procedures on FDIIS-A_1, FDIIS-A_2, FDIIS-A_3, and FDIIS-B were performed in duplicate, except GPC, which was performed in triplicate. Mean values were determined for each batch and means were used to calculate an inter-batch mean for comparison with inter-batch means for Monofer®; for FDIIS-B, as only one batch was available for testing, the batch means were compared to the inter-batch means for Monofer®. The inter-batch means for Monofer® were calculated from results of the same analytical tests performed in duplicate on the three batches of Monofer®.

3. Results

The results of the analytical tests are presented in Table 1. Of the selected *in vitro* tests, those examining pH, complex robustness, and NVR could not be conducted with FDIIS-B, as it was not possible to obtain sufficient quantities of sample due to withdrawal of the product by health authorities. Sample quantities of FDIIS-A were also limited. Therefore, pH of FDIIS-A_1 and FDIIS-A_3 and complex robustness of FDIIS-A_2 could not be tested.

3.1. Total iron content

Total iron content was similar for all three formulations (~100 mg/mL), though it was inconsistent between the three FDIIS-A batches (FDIIS-A_1, 100 mg/mL; FDIIS-A_2, 104 mg/mL; FDIIS-A_3, 102 mg/mL).

3.2. pH

The pH of FDIIS-A_2 was 7.0 and the pH of Monofer® was 5.8.

3.3. Density

Density varied between the formulations (FDIIS-A_1, 1.24 g/mL; FDIIS-A_2, 1.22 g/mL; FDIIS-A_3, 1.21 g/mL; FDIIS-B, 1.19 g/mL; Monofer®, 1.22 g/mL).

3.4. Carbohydrate content

The carbohydrate content was lower in FDIIS-A (14.4 % w/v) compared with Monofer® (19.0 % w/v). Furthermore, carbohydrate content was inconsistent across the three FDIIS-A batches (FDIIS-A_1, 18.2 % w/v; FDIIS-A_2, 12.7 % w/v; FDIIS-A_3, 12.4 % w/v); for two of the three batches, carbohydrate content was up to 1.5-fold lower compared with Monofer® (19.0 % w/v). The carbohydrate content was more than 3-fold lower in FDIIS-B (5.4 % w/v) compared with Monofer® (19.0 % w/v).

Table 1
Analytical test results for FDIIS-A and FDIIS-B versus Monofer®.

Parameter	FDIIS-A				FDIIS-B	Monofer®			
	FDIIS-A_1 (batch IIM00419)	FDIIS-A_2 (batch IIM102721)	FDIIS-A_3 (batch IIM100223)	Inter-batch mean (SD)	Batch A-413	Batch 158358	Batch 158903	Batch 159630	Inter-batch mean (SD)
Total iron content (mg/mL)	100	104	102	102 (2)	97	100	100	102	101 (0.1)
pH	Not enough sample	7.0	Not enough sample	NA	Not enough sample	5.9	5.7	5.9	5.8 (0.1)
Density (g/mL)	1.24	1.22	1.21	1.22 (0.0)	1.19	1.22	1.22	1.22	1.22 (0.0)
Carbohydrate content (% w/v)	18.2	12.7	12.4	14.4 (3.3)	5.4	19.0	19.0	19.0	19.0 (0.0)
Non-volatile residue (% w/v)	44.0	37.3	36.0	39.1 (4.3)	Not enough sample	40.9	40.7	41.7	41.1 (0.5)
Free (dialysable) iron content (% w/v)	0.033	0.123	0.118	0.091 (0.05)	1.0	<0.003[a]	<0.003[a]	<0.003[a]	<0.003[a] (NA)
Complex robustness ($t_{½}$) (h)	3	Not enough sample	27	15 (17)	Not enough sample	42	37	42	40.3 (2.9)
Peak molecular weight (kDa)[b]	192 (0.7)	197 (0.9)	208 (0.9)	199 (7.1)	191 (0.9)	151	157 (0.7)	152 (3.9)	153 (3.9)
Chromatographic profile[c]	Dissimilar to Monofer®; consists of a higher molecular weight fraction and a peak of unknown identity	Dissimilar to Monofer®; consists of a higher molecular weight fraction and a peak of unknown identity	Dissimilar to Monofer®; consists of a higher molecular weight fraction and a peak of unknown identity	NA	Dissimilar to Monofer®; consists of a higher molecular weight fraction and a peak of unknown identity	Gaussian distribution	Gaussian distribution	Gaussian distribution	NA

Data are presented as mean values, calculated using duplicate results obtained from testing on each batch of FDIIS-A (batches IIM00419, IIM102721, and IIM100223), FDIIS-B (batch A-413), and Monofer® (batches 158358, 158903, and 159630, produced between 2019 and 2021). Where three batches of product were tested, mean (SD) values have been calculated to determine inter-batch variation.
FDIIS-A=Rapifer®; FDIIS-B=Tosiron®; LOQ=limit of quantification; NA=not applicable; SD=standard deviation; $t_{½}$=half-life; w/v = weight by volume.
[a] The LOQ for the analysis was 0.003% w/v;
[b] data for each batch are presented as mean (SD), calculated using triplicate results obtained from testing on each batch, except for batch 158358, which is a mean based on duplicate results;
[c] data obtained from three samples of each batch, except for batch 158358, for which only two chromatograms were produced (it was not possible to produce a third chromatogram due to batch expiry).

3.5. Non-volatile residue

A comparison of mean results showed that the NVR of FDIIS-A (39.1 % w/v) differed from the NVR of Monofer® (41.1 % w/v). Additionally, NVR was inconsistent across the three FDIIS-A batches (FDIIS-A_1, 44.0 % w/v; FDIIS-A_2, 37.3 % w/v, FDIIS-A_3, 36.0 % w/v), with greater intra-batch variation (standard deviation [SD]: 4.3) than was evident for the Monofer® batches (SD: 0.5).

3.6. Free (dialysable) iron content

Free iron content was substantially higher with FDIIS-A (0.091 % w/v) compared with Monofer® (<0.003 % w/v). Additionally, free iron content was inconsistent across the three FDIIS-A batches (FDIIS-A_1, 0.033 % w/v; FDIIS-A_2, 0.123 % w/v; FDIIS-A_3, 0.118 % w/v). Free iron content was also substantially higher in FDIIS-B (1.0 % w/v) compared with Monofer® (<0.003 % w/v).

3.7. Complex robustness (half-life in acid hydrolysis test)

Following the observation that the absorbance of FDIIS-A, which was used to quantify the acidic hydrolysis of the sample, decreased to less than half of its baseline value at 24 h, the procedure was adjusted to take spectrometer readings at 2-hour intervals up to 6 h for FDIIS-A. FDIIS-A was substantially less robust than Monofer® (acid hydrolysis $t_{½}$: 15 h versus 40.3 h). A large difference was seen in complex robustness between the two FDIIS-A batches tested (FDIIS-A_1, 3 h; FDIIS-A_3, 27 h), while the acid hydrolysis half-life of all three Monofer® batches was closer to ~40 h.

3.8. Molecular weight distribution

The chromatograms produced by GPC for each batch of product tested showed no or limited intra-batch variability (standard deviations for peak molecular weight data for each batch are shown in Table 1). Therefore, one of the three chromatograms generated for each intended similar was overlaid with one of the chromatograms for a representative batch of Monofer®. The chromatograms differed for FDIIS-A_1, FDIIS-A_2, FDIIS-A_3, and FDIIS-B compared with Monofer®, with variation visible between the three FDIIS-A batches (Fig. 2). The chromatogram for Monofer® showed a narrow gaussian distribution of the complex, dissimilar to the chromatograms for each batch of FDIIS-A and for FDIIS-B. The chromatograms for each batch of FDIIS-A and for FDIIS-B showed altered iron–carbohydrate peaks, with a fraction at a substantially higher molecular weight than for the iron–carbohydrate peak for Monofer® (indicated by box I on Fig. 2A and B). Additionally, the peak molecular weights of FDIIS-A (FDIIS-A_1, 192 kDa; FDIIS-A_2, 197 kDa; FDIIS-A_3, 208 kDa) and FDIIS-B (191 kDa) were much higher than that of Monofer® (representative batch 159630, 152 kDa; mean for all three Monofer® batches, 153 kDa). The chromatograms for each batch of FDIIS-A and for FDIIS-B also had peaks at a relatively low molecular weight (indicated by box II on Fig. 2A and B), representing distinct structures or possible impurities that were absent on the chromatogram for Monofer®.

4. Discussion

IV iron formulations are complex drugs with large molecular weights (34–750 kDa), [1,69] whose known properties are critical to their safety and efficacy profile, and are highly affected by the manufacturing process [5]. Consequently, it is difficult to produce IV iron similars that are essentially identical to their reference drug [5]. Evidence from preclinical and clinical studies comparing reference and currently available similar versions of other IV iron formulations, namely iron sucrose and FCM, [18–22] suggests that some similar IV iron formulations may be less efficacious than their reference formulation, [18–20] and can have deleterious haemodynamic and oxidative effects [18,20–22]. Furthermore, it is noteworthy that the HMWID formulation DexFerrum® (withdrawn from the market in 2009) [70] has been associated with a higher rate of adverse drug events (ADEs), including life-threatening ADEs, than the LMWID formulation, INFeD® [71]. This suggests that molecular weight differences, as seen with the formulations in this study, may affect immunogenicity, although it has never been clearly established that the higher event rate for Dexferrum® versus INFeD® was caused by greater molecular weight.

In the US, an analysis of physicochemical properties of a sodium ferric gluconate similar and the originator drug, Ferrlecit®, revealed that the two IV iron formulations are different, despite some of the tests demonstrating similar properties between them [72]. In the current study, based on the simple *in vitro* tests conducted, it is clear that aside from the total iron content, FDIIS-A and FDIIS-B bear little resemblance to Monofer®. Substantial differences were seen on the chromatographic profiles of the two intended similars versus Monofer®. The peak molecular weight of the iron–carbohydrate complex in FDIIS-A and FDIIS-B was larger than in Monofer®. Additionally, the molecular weight distributions of the intended IV iron similars differed from Monofer®, and included additional peaks of unknown identity. Based on the results of the iron and carbohydrate content tests, the stoichiometric relationship between iron and derisomaltose in the iron–carbohydrate complexes was approximately 1:1.9 for Monofer® (roughly similar for the individual batches) versus 1:1.4 for FDIIS-A (with greater variation between batches: FDIIS-A_1, 1:1.8; FDIIS-A_2, 1:1.2; FDIIS-A_3, 1:1.2) and 1:0.6 for FDIIS-B. In addition to differences in carbohydrate content and chromatographic profiles, the tests related to labile iron toxicity (i.e., the tests for complex robustness and dialysable iron) further highlighted marked differences between the intended similars and Monofer®. The acid hydrolysis $t_{½}$ (a measurement of complex robustness [11] that is recognised as a surrogate for the rate of physiological iron release) of FDIIS-A was 15 h – less than half the $t_{½}$ of Monofer® (40.3 h). There was also a concerningly large difference in $t_{½}$ between the FDIIS-A batches tested (FDIIS-A_1, 3 h; FDIIS-A_3, 27 h) – for FDIIS-A_1, $t_{½}$ was more than 12-fold shorter than the $t_{½}$ of Monofer® (40.3 h). The proportion of dialysable free iron was more than 10-fold higher in FDIIS-A_1 (0.033 % w/v), more than 40-fold higher with FDIIS-A_2 (0.123 % w/v), and more than 39-fold higher with FDIIS-A_3 (0.118 % w/v) than in Monofer® (<0.003 % w/v). In FDIIS-B, the proportion of free iron (1.0 % w/v) was more than 100-fold higher than in Monofer® (<0.003 % w/v).

The results of the tests related to labile iron toxicity have important implications for the safety profiles of FDIIS-A and FDIIS-B, as free iron has been associated with infusion reactions during IV iron administration [11,73,74]. Given the high free iron content of FDIIS-A and FDIIS-B, and the lower complex robustness of FDIIS-A, there is a potentially increased risk of labile iron toxicity and infusion reactions compared with Monofer®. Based on the differences between FDIIS-A and Monofer®, it is particularly concerning for patient safety that FDIIS-A is marketed as a similar version of Monofer® and approved for use at a high dose.

As a difference between an intended IV iron similar and its reference drug can be demonstrated using any one of several relatively simple *in vitro* tests, there is no immediate limitation in the approach of this study. With respect to the hypothesis, the results clearly demonstrated large differences between the two intended copies of Monofer® and the originator drug. However, for intended similars with less apparent and more subtle differences, a broader range of *in vitro* tests are needed to establish dissimilarity. Certainly, in order to claim similarity, manufacturers of intended IV iron similars should be required to perform more complex tests and clinical trials, prior to approval of the formulation. Examples of additional parameters that were not assessed in this study include: morphology; particle size, size distribution, charge, and surface properties of the iron–carbohydrate complexes; physical and chemical degradation; characterisation of carbohydrate raw materials; [4] the detailed empirical chemical formula for each formulation;

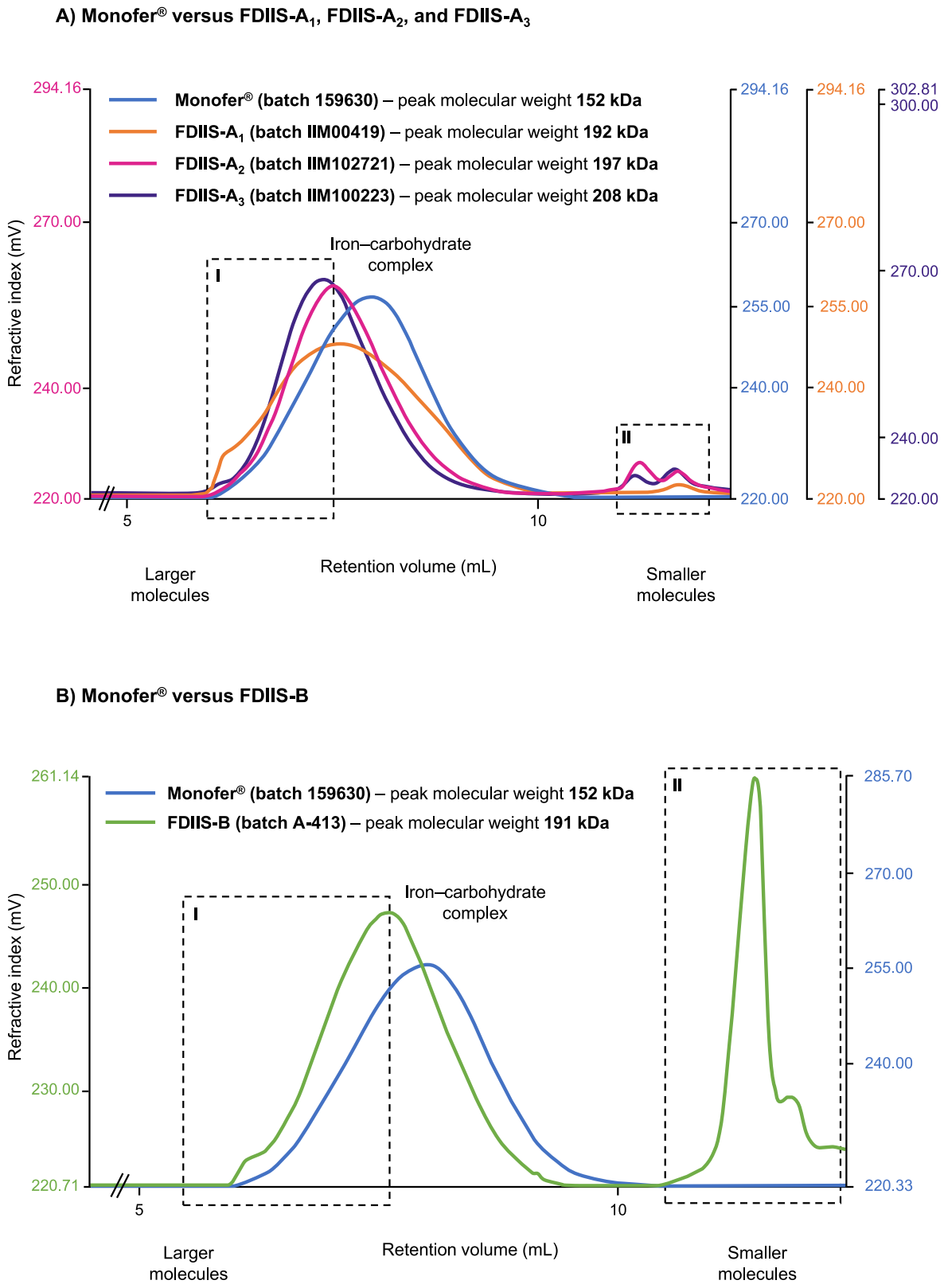

Fig. 2. Overlaid size-exclusion chromatograms for (A) Monofer®, FDIIS-A_1, FDIIS-A_2, and FDIIS-A_3, and (B) Monofer® and FDIIS-B. The dashed boxes indicate the position of I) distinct structures or high molecular weight impurities in FDIIS-A_1, FDIIS-A_2, FDIIS-A_3, and FDIIS-B, and II) unidentified structures or impurities in FDIIS-A_1, FDIIS-A_2, FDIIS-A_3, and FDIIS-B. For Monofer®, a representative chromatogram is shown, from batch 159630. The peak molecular weights shown for FDIIS-A_1, FDIIS-A_2, FDIIS-A_3, FDIIS-B, and Monofer® (batch 159630) are mean values calculated from triplicate results obtained from testing on each batch. FDIIS-A=Rapifer®; FDIIS-B=Tosiron®.

chemical bond energies in the iron core; magnetic properties of the iron core; heavy metal content of each formulation. However, it is acknowledged that there are limitations to currently available physicochemical techniques, and that IV iron formulations remain difficult to fully characterise using only these tools [2,4–8,25]. Additionally, there are concerns as to the translational value of available PK preclinical models with regard to the *in vivo* performance of iron–carbohydrate complexes [4,75]. Adding suitable *in vivo* bioequivalence studies in humans [23,24] to the investigations may shed light on the similarities and differences in the fate of a similar and its reference drug in the body. For formulations claiming to be similars, head-to-head RCTs of the intended similars versus their originators should be conducted to address key efficacy and safety aspects, such as hypersensitivity and hypophosphataemia, that cannot be elucidated by other methods. This is important as immediate infusion reactions can occur with any IV iron, and hypophosphataemia has been increasingly recognised as a side-effect of certain IV iron formulations [13].

In conclusion, this study found that a small selection of simple *in vitro* tests was sufficient to demonstrate that FDIIS-A and FDIIS-B do not show a high degree of sameness to Monofer®. Therefore, the efficacy and safety profile of Monofer® cannot be extrapolated to the two intended similars. In the specific case of FDIIS-B, action has been taken in Pakistan, resulting in the local regulatory authority deregistering the product. The findings of this study add to the concerning conclusions of previous studies that have compared intended IV iron similars to reference formulations and found that they are, in fact, different [18–22,72]. Collectively, the evidence calls for regulators to reassess and strengthen the regulatory approval process of intended IV iron similars, in order to ensure that only formulations that are proven to be well tolerated and efficacious are approved and marketed.

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CRediT authorship contribution statement

Peter Langguth: Writing – review & editing. **Reetesh Sharma:** Writing – review & editing. **Sameer Tulpule:** Writing – review & editing. **Martin Hansen:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. **Michael Auerbach:** Writing – review & editing.

Declaration of Competing Interest

Peter Langguth, Reetesh Sharma, and Sameer Tulpule have no competing interests to declare. Martin Hansen is employed by Pharmacosmos A/S. Michael Auerbach has received research funding for data management from Covis Pharma and for educational, non-promotional programs for Pharmacosmos.

Data availability

The data that has been used is confidential.

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Appendix A. Supplementary data

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