Drug Development and Industrial Pharmacy, 25(11), 1157–1166 (1999)

RESEARCH PAPER

A Novel Depot Preparation of Desferrioxamine-B: Development of Formulation Principles

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ABSTRACT

This report describes the feasibility of simple oil-based depot formulations of a novel n*-decanesulfonate salt of the iron chelator desferrioxamine-B. After subcutaneous administration in rodents, desferrioxamine-B* n*-decanesulfonate depot induces both (*a*) prolonged release of drug and (*b*) an increase of at least threefold to fourfold in iron excretion efficiency compared with the parent compound Desferal® (desferrioxamine-B mesylate). Optimization experiments probing vehicle composition, surfactant loading, drug loading, and particle size distribution of the depot preparation are described, and the physicochemical stability of an identified pilot formulation is assessed.*

INTRODUCTION

Iron overload continues to be treated with the parenterally effective (but orally inactive) chelator Desferal® (desferrioxamine-B mesylate, DFO). To achieve the necessary treatment of patients with iron overload, it is normally necessary to deliver high doses of DFO via slow subcutaneous infusion, over prolonged periods (8–12 hr), several days a week. This is obviously not an ideal situation for the patient, and compliance can be difficult. Primarily because of this, there is a great need for simpler and more convenient modes of iron chelation therapy. One way of addressing this is to search for new, orally active chelators, although this is proving not to be an easy task (1,2). A significant increase in the compliance of patients with iron overload could also be achieved via development of a long-acting, depot injectable dosage form.

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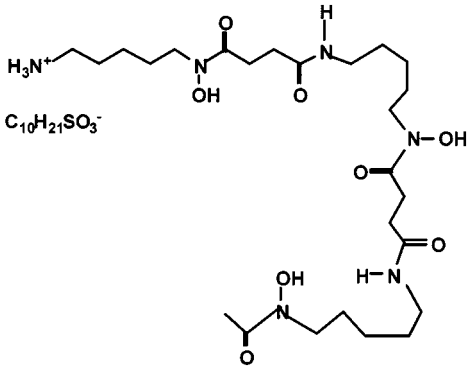

Figure 1. Chemical structure of desferrioxamine-B *n*-decanesulfonate.

This report summarizes activities carried out to develop such a formulation based on a novel *n*-decanesulfonate salt of desferrioxamine-B (3) (Fig. 1) suspended in an oily vehicle. Oil-based sustained-release suspensions for parenteral administration are well established, with the release of drug from such formulations being dependent on dissolution/partitioning into the surrounding aqueous medium (4). Desferrioxamine-B *n*-decanesulfonate has physicochemical properties (solubility, lipophilicity) commensurate with enhancing the long-acting nature of an oil-based suspension preparation (3). The marriage of these factors forms the basis of the desferrioxamine-B depot formulation design.

EXPERIMENTAL

Materials

Desferrioxamine-B *n*-decanesulfonate was supplied by Hans Hirt (Chemical Development, Ciba Pharmaceuticals AG, Basle, Switzerland). Lipoid S 100 (soy lecithin phospholipid) was provided by Peter van Hoogevest (Pharmaceutical Development, Ciba Pharmaceuticals AG). Sesame oil BP came from Brightstern Limited (Stockport, UK), ethyl oleate BP from either Fluka (Buchs, Switzerland) or Croda Oleochemicals (Goole, UK), and Miglyol 812 from Hüls (Marl, Germany). Span 85 was supplied by Sigma (St. Louis, MO) and Tween 80 from either BDH (Poole, UK) or Croda Oleochemicals.

Preparation of Depot Formulations

Mortar and Pestle Technique

Desferrioxamine-B *n*-decanesulfonate was placed in an agate mortar, forming a well in the center. Surfactants and sesame oil (SO) were added to the well and incorporated with an agate pestle using circular motions (when Lipoid S 100 was used, it was necessary to predissolve it in SO by gently heating over a water bath). Mixing continued until a smooth, lump-free, white suspension was generated. This was brought to volume with ethyl oleate (EO).

Depot vehicles formulated using Miglyol 812 were prepared using this technique.

Triple-Roller Milling Technique

Desferrioxamine-B *n*-decanesulfonate was placed into an agate mortar, forming a well in the center. Surfactants and SO were added to the well and incorporated with an agate pestle using circular motions to form a paste. This was then passed through a triple-roller mill (Exakt, gap setting I) until a smooth paste was formed that was free from pockets of dry powder. This was transferred to a clean mortar. The surfactants were added and mixed into the paste before bringing it to volume with EO.

Particle Size Analysis

A Mastersizer X (Malvern Instruments, Malvern, UK) equipped with a small-volume liquid dispersion unit (MSX1) and with an active beam length of 2.4 mm, was used to assess the particle size distribution of desferrioxamine-B *n*-decanesulfonate in the depot preparation. SO was used as the dispersion medium. Unless otherwise stated, 300-mm and 100-mm lenses were used, covering the range 0.5–600 μm.

Rheological Assessment

A Controlled Stress Rheometer (Carrimed, Dorking, UK) equipped with a 2 cm, 1° ss cone measuring system was employed. Samples were subjected to linear shear stress ramps (0 to 300 and back to 0 dyne · cm^{-2}) over a period of 4 min at 25°C. Analysis was in duplicate; mean data are presented in this report.

Sedimentation/Redistribution Properties of the Depot Suspension

Depot formulations were sedimented by centrifugation (2000 *g*, 25°C). Ease of redispersion was assessed by shaking the sedimented depots under controlled conditions (MM2000 high-speed mixer mill, shaking amplitude 10, Glen Creston, Stanmore, UK) and assessing the time necessary to produce a dispersed suspension. A rating system was then applied to characterize the depot formulation as follows:

* Suspension easily redispersed (≤1 min) following sedimentation,

** Suspension required more time (several minutes) and effort to redisperse sedimented drug following centrifugation, and

*** Suspension very difficult or virtually impossible to redisperse (>10 min) and thus was considered unacceptable.

In Vitro Release Methodology

Intrinsic Release

An adaptation of the method of Wood et al. as described by Wells (5) was adopted. Desferrioxamine-B *n*-decanesulfonate or DFO (200 mg, each containing 2% magnesium stearate) was compressed into a tablet using a 13-mm IR punch and die set (surface area 1.33 cm^2) to 3 tons at a dwell time of 5 sec. The tablet was fixed to the holder of a USP rotating basket apparatus with low-melting paraffin wax BP (Fisons, Loughborough, UK) and successively dipped so that the tablet was coated with wax, with only the lower face cleared using a scalpel.

Dissolution was performed under sink conditions (DT6R USP dissolution bath, Erweka, Heusenstamm, Germany). Tablets of drug were rotated at 100 rpm in 1 L of degassed deionized water at 37°C. Drug released was monitored spectrophotometrically at 215 nm (CE5501 spectrophotometer, Cecil Instruments, Cambridge, UK).

Release from the Depot Preparation

A method for the in vitro release of desferrioxamine-B *n*-decanesulfonate from the depot formulation was developed using a Langenbucher flow-cell (Erweka) procedure. Depot formulation was injected into a size 00 clear/clear gelatin capsule (Capsugel), ensuring total omission of air from the capsule. This was placed inside the sample chamber of a 13 mm i.d. dissolution cell (Sotax, Basel, Switzerland) maintained at 37°C. Freshly prepared and degassed USP simulated intestinal fluid (SIF, pH 7.5) was passed though the cell for several hours at a flow rate of 12 $ml \cdot min^{-1}$ maintained by two pumps, a six-cylinder piston pump (Sotax) and an eight-channel peristaltic pump (Ismatec, Zurich, Switzerland). Testing was carried out under turbulent flow. Dissolution fluid was analyzed spectrophotometrically at 215 nm (Uvikon 810 spectrophotometer, Kontron, Zurich, Switzerland) after dilution as necessary.

Solubility of Compound A in the Depot Vehicle

The depot formulation was centrifuged (2000 *g*) for several minutes. The supernatant was separated, filtered, and analyzed by high-performance liquid chromatography (HPLC) using procedures described in the following section.

Physicochemical Stability of Identified Depot Preparation

The chosen formulation (1.0 g desferrioxamine-B *n*-decanesulfonate in a vehicle containing 2.5 ml SO, 2.5 ml EO, and 0.043 ml Tween 80) was prepared using the triple-roller milling technique, packaged in type I glass vials, and stored at 4°C, 25°C, and 37°C. The physical stability of the depot preparation was assessed over a 24-week period using procedures described above. The chemical stability of desferrioxamine-B *n*-decanesulfonate was assessed using an extraction procedure and assay by HPLC. To an aliquot of depot preparation (ca. 300 mg) was added dichloromethane/methanol (3.75 ml of a 1:2 v/v mixture), and the whole mixture was vortex mixed and allowed to stand for 20 min. Dichloromethane (1.25 ml) and water (7.5 ml) were added, followed by further vortex mixing and standing for 20 min. An aliquot of the supernatant (ca. 8 ml) was weighed accurately into a volumetric flask and brought to volume (100 ml) with water. This was analyzed by HPLC, under isocratic conditions, using a Nucleosil $10C_{18}$ 250 mm × 4.6 mm stainless steel column. The mobile phase comprised 95:5 (v/v) phosphate buffer (pH 2.8) containing 0.04% (w/v) sodium edetate:tetrahydrofuran. The flow rate was 2.0 $ml \cdot min^{-1}$, and the injection volume was 20 µl. Analysis was by ultraviolet (UV) radiation at 220 nm. The linearity of response was verified, and the limit of detection was 0.0001% (w/v).

Ease of Dispensing

The ''syringeability'' of the depot was assessed by passing through a 1-ml composite syringe (Beckton and Dickinson, Franklin Lanes, NJ) equipped with a small 26-gauge needle.

Iron Excretion in Rat

Primary in vivo efficacy of desferrioxamine-B *n*-decanesulfonate was carried out in the bile duct cannulated,

non-iron-overloaded rat model based on that described by Bergeron et al. (6).

Oil-based depot preparations of desferrioxamine-B *n*-decanesulfonate were tested in comparison with a standard aqueous solution of DFO.

After compound administration (150 μmol · kg^{-1} desferrioxamine-B) via subcutaneous injection (Hamilton gas-tight syringe) into the sides of the animals, the excretion of both biliary and urinary iron was monitored for at least 24 (normally 48) hr. Iron concentration in bile and urine was measured colorimetrically using the bathophenanthroline method (7).

RESULTS AND DISCUSSION

Choice of Excipients

SO and EO are well established as bulk vehicles in pharmaceutical parenteral formulations (8). The ratio of SO:EO may be varied, allowing some flexibility with the rheological properties of the depot suspension. A 50:50 (%v/v) mixture of the two was chosen as the starting point.

Surface-acting agents are normally necessary in suspension preparations to act as wetting aids and to control the degree of flocculation in the depot, thus enabling satisfactory redispersion properties. Tweens, Spans, and lecithins are well-known surfactants used in parenteral products (9). A combination of Tween 80/Span 65 was used in the ''research'' formulation, which comprised desferrioxamine-B *n*-decanesulfonate (1.0 g) in a vehicle containing SO (2.5 ml), EO (2.5 ml), Span 85 (57 μl), and Tween 80 (43 μl). This preparation was easily syringeable. The solubility of desferrioxamine-B *n*-decanesulfonate in this vehicle was found to be undetectable (<0.0001% w/v).

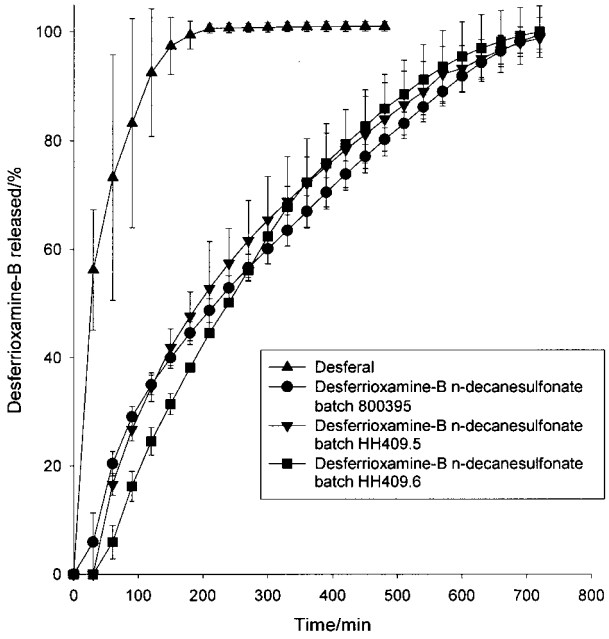

Figure 2. In vitro release of desferrioxamine-B (±SD, n = 3) from a depot formulation with a composition of 1.0 g desferrioxamine-B *n*-decanesulfonate (or an equivalent amount of DFO), 0.02 ml Tween 80, 2.5 ml SO, and 2.5 ml EO.

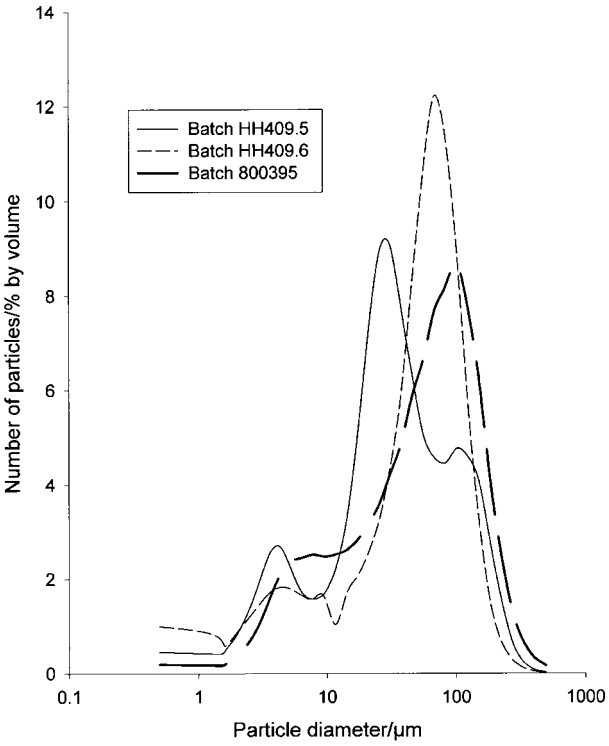

Figure 3. Particle size distribution of desferrioxamine-B *n*-decanesulfonate in the three batches used for in vitro release studies displayed in Fig. 1 (D[4,3] ranging from 40.0 to 93.8 μm).

In vitro release profiles of depots prepared using three representative batches of desferrioxamine-B *n*-decanesulfonate appear in Fig. 2. The data show sustained release of active moiety over at least a 12-hr period, with excellent batch-to-batch consistency. Perhaps surprisingly, the in vitro release characteristics appear to be relatively insensitive to particle size distribution as some batch-to-batch variation in the particle size distribution was extant (volume mean particle diameters D[4,3] ranged from 40.0 to 93.8 μm; Fig. 3). For comparison purposes, a formulation of identical vehicle composition

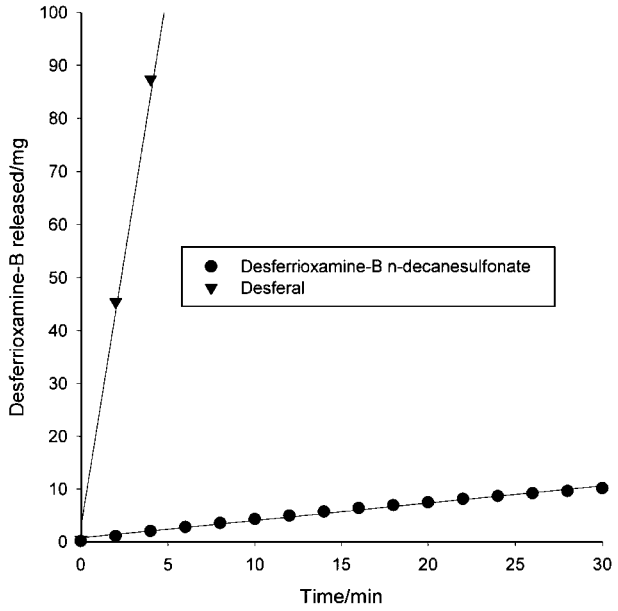

Figure 4. Aqueous intrinsic release profiles of desferrioxamine-B *n*-decanesulfonate and DFO in water at 37°C.

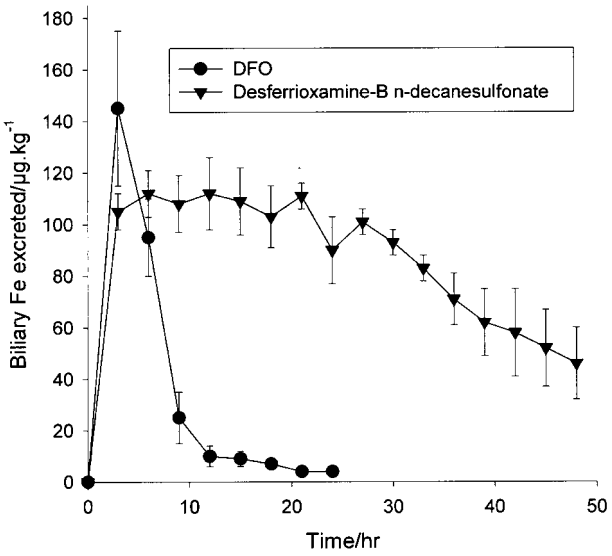

Figure 5. In vivo biliary iron excretion induced by desferrioxamine-B *n*-decanesulfonate depot versus DFO at equivalent doses (150 μmol · kg^{-1}) in the rat (±SD, $n = 3$).

containing DFO in place of desferrioxamine-B *n*-decanesulfonate is appended to Fig. 2. DFO is clearly much more rapidly released from the vehicle than desferrioxamine-B *n*-decanesulfonate, as might be anticipated from the respective aqueous intrinsic dissolution rates of the two salts of desferrioxamine-B (0.18 mg · cm^{-2} · min^{-1} for desferrioxamine-B *n*-decanesulfonate and 16.3 mg · cm^{-2} · min^{-1} for DFO; Fig. 4).

Biliary iron excretion data from the rat confirm the extended-release properties of desferrioxamine-B *n*-decanesulfonate in vivo (Fig. 5). Significant iron excretion is still observed 42 hr after administration of desferrioxamine-B *n*-decanesulfonate. By comparison, the duration of action of DFO is much shorter. In addition, and importantly, the total (biliary + urinary) iron excreted by the desferrioxamine-B *n*-decanesulfonate depot is at least four times greater than that elicited by DFO at an equivalent dose (Fig. 6).

Formulation Composition

Surfactants

Formulations with various surfactants and loadings were prepared using the pestle-and-mortar technique. Compositions of each preparation, together with associated ease of redistribution, particle size distribution, and rheological data, appear in Table 1. All formulations tested were easily dispensed by syringe. Each formulation exhibited similar particle size distributions regardless of surfactant and loading.

At Tween 80 loadings of 0.043 ml/5 ml depot and above, a deleterious effect on ease of resuspension was detected, suggesting potential knock-on effects, such as caking, on prolonged storage. At Tween 80 loadings of ≤0.02 ml/5 ml depot, there were no detectable differences in ease of resuspension of the sedimented depot; each preparation resuspended easily and rapidly (comparing very favorably with the lead formulation containing a combination of Tween 80 and Span 85). Inclusion of Lipoid S 100 in the vehicle yielded no detectable galenical advantage.

Each preparation exhibits a combination of plastic and pseudoplastic (shear thinning) rheological properties characteristic of disperse systems. The formulation containing 0.5 ml Tween 80/5 ml vehicle demonstrated slightly higher viscosity than the others (Fig. 7).

Composition of the Oil Phase

As expected, the rheological characteristics of the depot preparation were modified as the EO:SO loading changed. Although the shear thinning characteristics remained throughout, preparations with increasing SO content became significantly more viscous (236 cP at 100 sec^{-1} at 25:75 EO:SO, 76 cP at 100 sec^{-1} at 100:0 EO:

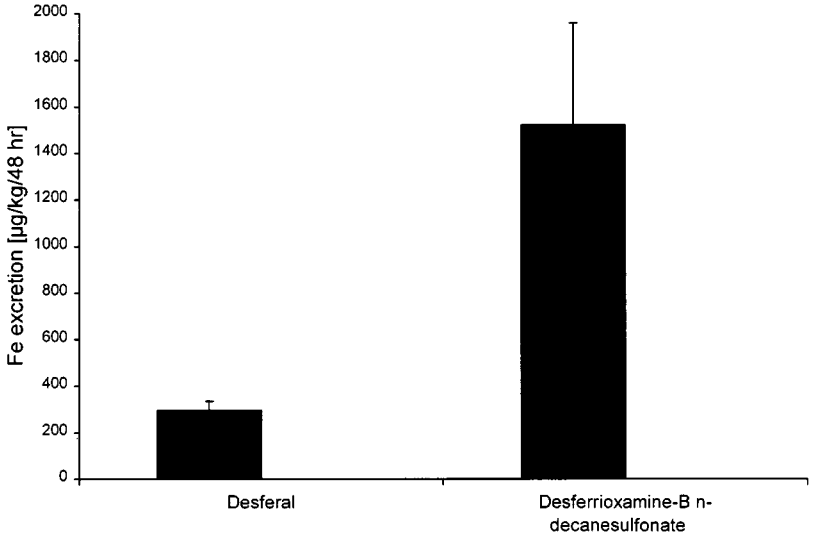

Figure 6. Total (biliary + urinary) iron excretion (±SD, $n = 3$) induced in rats by desferrioxamine-B *n*-decanesulfonate depot versus DFO at equivalent doses (150 µmol · kg^{-1}) over a 48-hr period (DFO data measured only up to 24 hr; negligible chelation assumed after this period due to short duration of action; see Fig. 5).

SO loading). This undoubtedly accounts for the observed increased difficulty in resuspension of formulations containing a high SO content.

Despite the influence of the vehicle composition on the rheological properties of the formulation, in vitro dissolution profiles suggest that the rate of release of drug was not significantly affected (Fig. 8). In addition, pharmacodynamic evaluation revealed no detectable difference in the rate of iron excretion in rats challenged with formulations containing different EO : SO vehicle compositions (Fig. 9). Small differences in the absolute extent of biliary iron excreted are apparent, with the 50 : 50 (v/v)

Table 1

Composition, Ease of Redistribution, Particle Size Distributions, and Viscosity of Depot Preparations Formulated Using Various Loadings of Surfactant and Prepared by the Pestle and Mortar Technique

	Loading								
Component									
Desferrioxamine-B *n*-decanesulfonate/g	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Sesame oil/mL	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Ethyl oleate/mL	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Tween 80/ml	—	0.004	0.02	0.043	0.1	0.5	0.043	—	—
Span 85/ml	—	—	—	—	—	—	0.057	—	—
Lipoid S 100/mg	—	—	—	—	—	—	—	0.056	0.134
Ease of redistribution	*	*	*	**	***	***	**	*	*
Particle size									
D[4,3]/µm	43.75	43.60	41.48	30.60	42.28	43.21	40.36	43.13	42.07
<90%/µm	104.8	104.1	99.19	73.40	100.6	106.2	109.3	93.62	117.6
<50%/µm	25.32	26.63	26.31	17.18	27.06	23.26	28.94	34.26	39.98
<10%/µm	5.36	5.22	5.24	5.22	5.46	6.17	5.12	4.98	5.99
Viscosity at 100 sec^{-1}/cP	115	119	131	123	169	219	114	89	96

See Experimental section in text for key.

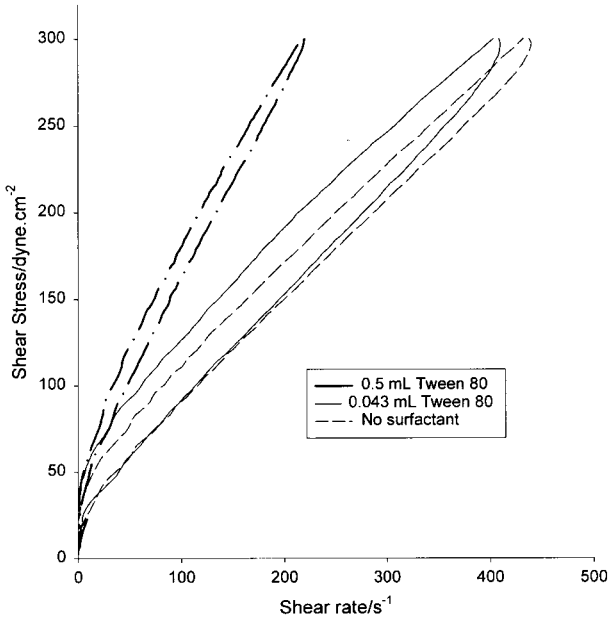

Figure 7. Shear stress versus shear rate rheological profiles of desferrioxamine-B *n*-decanesulfonate depot suspensions prepared with various surfactant loadings.

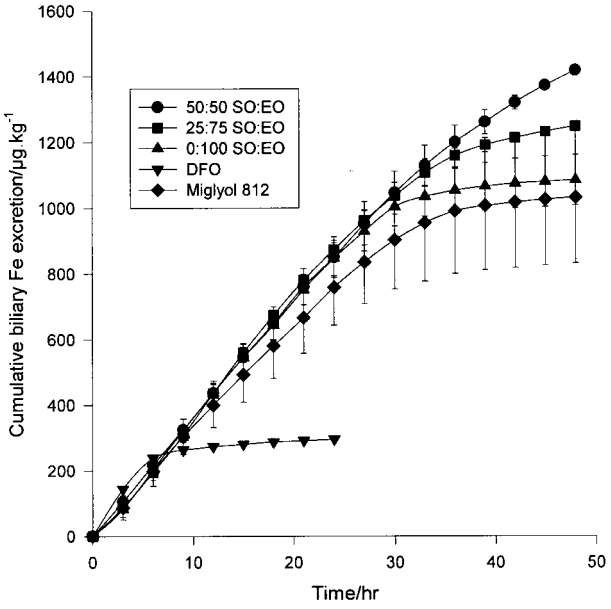

Figure 9. Cumulative biliary iron excretion (±SD, $n = 3$) in rats treated subcutaneously with desferrioxamine-B *n*-decanesulfonate depots of varying vehicle compositions.

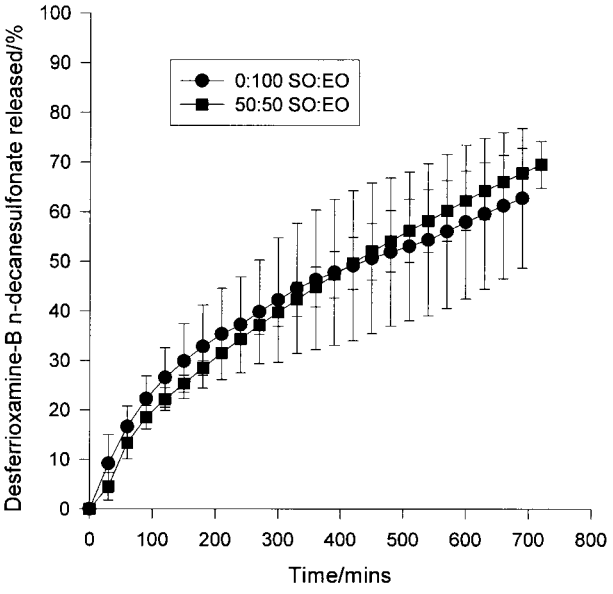

Figure 8. In vitro release profiles (±SD, $n = 3$) of desferrioxamine-B *n*-decanesulfonate depot formulated using 0:100 and 50:50 SO:EO vehicle compositions (*D*[4,3] 35.44 µm and 39.50 µm, respectively).

EO:SO preparation apparently being best in this respect, although the effects may well be methodological. What is important to note is that all of these formulations showed an increase of at least threefold to fourfold in chelation efficiency versus DFO.

All formulations referred to in this section were administrable by syringe, although as expected, as the relative SO:EO loadings increased, there was a concomitant increase in difficulty.

Further studies have identified medium-chain triglycerides (Miglyol 812) as an interesting vehicle alternative to EO/SO. Miglyol 812 is used in a variety of emulsions, solutions, or suspensions for parenteral administration (10). A possible advantage of Miglyol 812 over EO is that there is no need for the manufacturer to include ''stabilizers'' in the former, whereas addition of trace quantities of antioxidants, such as butylated hydroxyanisole (BHA) and/or butylated hydroxytoluene (BHT), are needed to preserve the stability of EO. The solubility of desferrioxamine-B *n*-decanesulfonate in Miglyol 812 is negligible (<0.001% w/v). The viscosity of Miglyol 812 lies between that of EO and SO such that a preparation of 202.5 mg desferrioxamine-B *n*-decanesulfonate/1 ml Miglyol 812 yields a viscosity similar to that exhibited by a formulation of equivalent drug loading in a vehicle comprised of 50:50 EO:SO. Biliary iron excretion data

Table 2

Effect of Drug Loading and Vehicle Composition on Ease of Redistribution After Sedimentation

EO:SO (%v/v) Vehicle Composition	Desferrioxamine-B *n*-Decanesulfonate Loading per 5 ml Depot Vehicle					
	1.0 g	1.3 g	1.5 g	1.6 g	1.8 g	2.0 g
25:75	**	[a]	[a]	[a]	[a]	[a]
50:50	*	[a]	***	[a]	***	***
75:25	*	[a]	[a]	***	[a]	[a]
80:20	*	*	[a]	***	***	[a]
100:0	*	*	**	**	***	***

See Experimental section in text for key.
[a] Not measured.

from the rat demonstrate the in vivo effectiveness of desferrioxamine-B *n*-decanesulfonate depot formulated using Miglyol 812 (Fig. 9).

Drug Loading

As anticipated, the difficulty in resuspension of sedimented drug increases with drug loading (Table 2). This correlates with the respective rheological characteristics (Table 3). As drug loading increased, all formulations maintained their plastic characteristics, but there was a concomitant increase in viscosity, yield point, and extent of hysteresis. This suggests a higher degree of ''structure'' in the preparations with increased drug loading, which may indicate a decreased propensity of the higher loaded formulations to sediment on prolonged storage.

All of the formulations described in Table 3 were syringeable except those rated ***, for which the degree of difficulty became unacceptable.

Clearly, if elevated drug loadings are a requirement of the final formulation, then due consideration of a lower viscosity vehicle should be the aim.

Over the range 1.0–1.4 g/5 ml vehicle, no significant effect of drug loading on in vitro release of drug from the depot preparation was found.

Particle Size

Triple-roller milling imparts increased shear compared to the standard pestle-and-mortar laboratory technique used for preparation of the depot. This results in formulations of different particle size distribution since desferrioxamine-B *n*-decanesulfonate (unprocessed) is largely agglomerated. In typical formulations, for example, mean particle volume diameters $D[4,3]$ are 57 μm (prepared by pestle and mortar) and 16 μm (prepared by triple-roller mill). As stated above, in vitro release pro-

Table 3

Effect of Vehicle Composition and Drug Loading on the Rheological Properties of the Depot Formulation

SO:EO Composition in Vehicle (%v/v)	Drug Loading in 5 ml Vehicle (g)	Yield Point (dyne · cm^{-2})	Viscosity at 100 sec^{-1} (cP)
50:50	1.0	29.53	123
	1.5	67.50	289
	2.0	115.13	590
0:100	1.0	14.24	73
	2.0	87.01	269
	3.0	253.3	1510

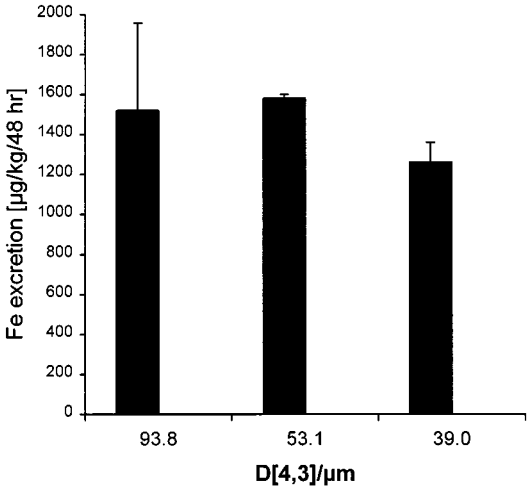

Figure 10. Total (biliary + urinary) iron excretion (±SD, $n = 3$) after subcutaneous delivery of desferrioxamine-B *n*-decanesulfonate depot formulated with drug of various particle sizes.

files are relatively insensitive to particle size over the range tested (D[4,3] 40.0–93.8 µm). This would suggest little influence of particle size on in vivo performance of the depot suspension over this range. Biliary iron excretion data from the rat largely substantiate this (Fig. 10).

Preliminary Stability Data

Chemical Stability

No significant chemical degradation of desferrioxamine-B *n*-decanesulfonate in the identified depot formulation was detected by HPLC over a 24-week storage period at the temperatures indicated. No degradation products were observed. Supporting data appear in Table 4.

Physical Stability

Samples settled slightly during storage; all were readily resuspended. No significant changes in particle size distribution or rheological characteristics were detectable after storage under the conditions tested. The data suggest no particle growth (Ostwald ripening) on storage, consistent with the known lack of solubility of desferrioxamine-B *n*-decanesulfonate in the vehicle.

CONCLUSIONS

A simple preparation of desferrioxamine-B *n*-decanesulfonate suspended in SO/EO (no surfactant necessary) was identified as a suitable vehicle for the sustained delivery of drug via subcutaneous administration in an animal model. Significant iron excretion was found up to 48 hr after delivery of desferrioxamine-B *n*-decanesulfonate depot in rat. Good in vitro/in vivo correlation was demonstrated in terms of drug release. The prolonged release and an increase of at least threefold to fourfold in iron excretion efficiency of desferrioxamine-B *n*-decanesulfonate over DFO promise significant potential benefits in chelation therapy with knock-on effects in improved patient compliance.

Changes in particle size distribution within the depot preparation over the mean diameter range 40 to 93 µm do not appear to have a significant effect on either in vitro release or in vivo iron excretion efficiency.

Changes in EO:SO vehicle composition, giving rise to depot viscosities ranging between 76 and 236 cP (at 100 sec^{-1}), yielded no significant difference in either in vitro release or in vivo iron excretion.

For formulations containing similar particle size distributions of desferrioxamine-B *n*-decanesulfonate, changes in drug loading over the range 1.0–1.4 g/5 ml

Table 4

Chemical Stability of Desferrioxamine-B n-*Decanesulfonate Pilot Depot Formulation*

	Desferrioxamine-B *n*-Decanesulfonate (% by HPLC Peak Area ±SD, $n = 3$)				
Condition	2 weeks	6 weeks	8 weeks	12 weeks	24 weeks
Initial	98.6 ± 0.7	—	—	—	—
4°C	99.1 ± 0.1	99.3 ± 0.1	98.6 ± 0.1	98.6 ± 0.1	99.2 ± 0.2
25°C	99.2 ± 0.2	98.7 ± 0.1	98.5 ± 0.2	98.4 ± 0.1	99.2 ± 0.1
37°C	99.0 ± 0.1	99.2 ± 0.1	98.4 ± 0.1	98.6 ± 0.1	99.2 ± 0.2

vehicle gave rise to no significant difference in the in vitro release profile.

The composition of the vehicle may be modified according to the desired drug loading. At 1 g/5 ml, either SO, EO, or EO/SO combinations gave acceptable galenical performance (over the particle size ranges tested). However, if higher drug loadings are required, the viscosity of the vehicle should be reduced, and either EO or an EO/SO combination with the former dominating is necessary to maintain acceptable properties.

In addition to EO and SO, medium-chain triglycerides (Miglyol 812) offer the formulator an alternative vehicle that may prove advantageous in terms of pharmaceutical acceptability.

ACKNOWLEDGMENTS

The authors thank Jean Marie Glantzmann (Pharmaceutical Development, Ciba Pharmaceuticals AG, Basle, Switzerland) for expert assistance in dissolution method development and Terry Madigan (Drug Preformulation and Delivery, Ciba Pharmaceuticals, Horsham, UK) for technical assistance in developing the extraction procedure for quantifying desferrioxamine-B in the oily vehicle. Thanks are also due to Bertrand Sutter (Pharmaceutical Development, Ciba Pharmaceuticals AG, Basle) for measuring the solubility of desferrioxamine-B *n*-decanesulfonate in Miglyol 812.

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