

Formulations and polymorphic forms of desferrioxamine and the preparation thereof

Summary of the invention

This invention relates to a new polymorphous crystal modification of desferrioxamine-1-decane-sulphonate, and the preparation thereof, as well as pharmaceutical compositions and the use of this crystal modification for therapeutic purposes and the preparation of pharmaceutical compositions; and also to other crystal forms. It generally also relates to new pharmaceutical compositions containing a desferrioxamine-B salt as active ingredient.

Background of the invention

Preparations of desferrioxamine-B and pharmaceutically acceptable addition salts thereof are described in U.S. Patent No. 3247197. The amine and salts thereof such as those described in the above mentioned U.S. patent exhibit a marked ability to form stable complexes with trivalent metal ions, especially Fe^{3+} . Consequently, desferrioxamine-B (as the methanesulphonate salt, Desferal) is of immense importance as a pharmacological iron-chelator in the treatment of iron-overload diseases such as beta-thalassemia. It is one of the very few pharmaceuticals available commercially at the present time for the treatment of thalassemia.

Administration of desferrioxamine-B (as the methane sulphonate salt) via slow (8 to 12 hour) subcutaneous infusion is now widely accepted as the route necessary to control transfusional iron overload in beta-thalassemics. However, such a mode of treatment is laborious, uncomfortable and inconvenient for the patient, and involves high costs. Patient compliance is poor: non-compliance with iron-chelation therapy has been suspected to be the most important cause of death amongst thalassemics. Hence there is a great need for simpler, more convenient and cheaper iron-chelation therapy for iron overload treatment.

This need has been apparent for a long time, and numerous attempts have been made over many years to obtain a form of desferrioxamine-B which is effective in iron-overload therapy when administered by more convenient methods. In WO93/24451 there are described organic sulphonate salts of desferrioxamine-B for oral administration.

The morphology and polymorphy of organo-chemical substances is of immense importance in the chemical and pharmaceutical development thereof. Substances are known which only

appear in a single crystal form, and similarly there are substances with two, three and even a higher number of polymorphous forms. This possible morphological and structural variety and the respective physico-chemical, especially thermodynamic stability relationships cannot be calculated or predicted on a scientific-mathematical basis. The relevant polymorphism of an organo-chemical substance is thus a surprise in respect of the number of forms and the stability thereof.

If two, three or more crystal forms of a substance are known, then in general their absolute and relative physico-chemical stabilities may be determined. The unstable crystal form or unstable crystal forms bring great disadvantages through the entire chemical and pharmaceutical preparation process, since in each step of the process or in each intermediate storage, a partial or total conversion to the stable form may take place. Due to the meta-stability, an unstable crystal form may be maintained for lengthy periods and may possibly transform spontaneously at an indeterminable point in time. This possible outcome of converting to a more stable crystal form evolves for each preparation batch and cannot be foreseen individually. Thus, difficulties may additionally arise in chemical studies and in pharmaceutical-clinical studies. For example, these crystalline conversions may lead to drastic changes in bio-availability of a pharmacon, e.g. through changed solubilities.

The preparation methods of desferrioxamine-B and pharmaceutically acceptable salts thereof are described for example in US Patent No. 3,247,197. The amine and salts thereof, such as those described in the above-mentioned US patent, exhibit a marked ability to form stable complexes with trivalent metal ions, especially Fe^{3+} . Consequently, desferrioxamine-B (in the form of its methanesulphonate salt, Desferal) is of immense importance as a pharmaceutically employable iron chelator, for example in the treatment of diseases associated with iron overload, e.g. thalassemia. It is one of the few pharmaceuticals available commercially at the present time for the treatment of thalassemia.

Administration of desferrioxamine-B (as the methanesulphonate salt) via slow (8 to 12 hours) subcutaneous infusion is now widely accepted as the method of controlling iron overload caused by blood transfusions in thalassemia patients. However, this mode of treatment is laborious, uncomfortable and inconvenient for the patients and involves high

costs. Hence there is a great need for a simpler, more convenient and cheaper iron chelation therapy.

It has now been found, in accordance with the present invention, that certain desferrioxamine-B aliphatic sulphonate salts can be incorporated in a sustained release formulation which can be parenterally administered by convenient injection procedures in comparatively small volumes at convenient intervals, the desferrioxamine-B salt being released gradually over the period between injections. Accordingly, the present invention provides a parenterally injectable composition comprising particles of a desferrioxamine-B salt of an aliphatic sulphonic acid having at least 8 carbon atoms suspended in a parenterally administrable oil.

As an improvement on the long-used Desferal, EP 643690 discloses *inter alia* the 1-decanesulphonate of desferrioxamine-B as iron chelator. However, it is not written down whether there are further crystal modifications of desferrioxamine-1-decanesulphonate. Now, surprisingly, several new crystal forms of this substance have been found. The present invention therefore also concerns a new stable crystal modification of desferrioxamine-1-decanesulphonate and a process for the production thereof.

Explanation of the Figures

Fig. 1/3 shows an X-ray diagram of crystal modification A₂ of desferrioxamine-decanesulphonate. Abscissa (x-axis): diffraction angle 2θ (range 3° to 30°); Ordinate (y-axis): relative intensity.

Fig 2/3 shows an X-ray diagram of crystal modification A₁ of desferrioxamine-decanesulphonate. Abscissa (x-axis): diffraction angle 2θ (range 3° to 30°); Ordinate (y-axis): relative intensity.

Fig. 3/3 shows an X-ray diagram of crystal modification B (mixture with modifications A₁₁ to A₁₃) of desferrioxamine-decanesulphonate. Abscissa (x-axis): diffraction angle 2θ (range 3° to 30°); Ordinate (y-axis): relative intensity.

Detailed description of the invention

A first preferred embodiment of the invention relates to a parenterally injectable composition comprising particles of a desferrioxamine-B salt of an aliphatic sulphonic acid having at least 8 carbon atoms suspended in a parenterally administrable oil.

The desferrioxamine-B salt may be, in general, a salt of an aliphatic sulphonic acid having 8 to 20 carbon atoms. Such acids include hydrocarbyl sulphonic acids, for example alkanesulphonic, alkenesulphonic and alkynesulphonic acids such as octane-1-sulphonic acid, octane-2-sulphonic acid, nonane-1-sulphonic acid, nonane-2-sulphonic acid, n-decanesulphonic acid, n-dodecanesulphonic acid, tetradecanesulphonic acid, hexadecanesulphonic acid, octadecanesulphonic acid, octene-1-sulphonic acid, decene-1-sulphonic acid, dodecene-1-sulphonic acid, tetradecene-1-sulphonic acid, hexadecene-1-sulphonic acid or decylacetylene sulphonic acid, and such acids substituted in the hydrocarbyl group by, for example, hydroxy, C₁ to C₄ alkoxy, acyloxy, C₁ to C₄ alkoxy carbonyl, halogen or amino. The salt may be prepared as described in WO 93/24451.

Preferably, the desferrioxamine-B salt is a salt of an aliphatic sulphonic acid having 8 to 12, preferably 8 to 10 carbon atoms, especially a salt of n-octanesulphonic acid or n-decanesulphonic acid. A preferred extraordinarily stable form of desferrioxamine-B n-decanesulphonate for use in the present invention is a crystal modification A₂ which is described in more detail below.

Another preferred form of desferrioxamine-B n-decanesulphonate for use in the present invention is a crystal form A₁ having a melting point range of 140 °C to 153 °C determined by DSC and having the following characteristic diffraction lines (2θ in angular degrees ± 0.1 °) in its X-ray diffraction pattern : 4.1 °, 6.3 °, 8.4 °, 10.5 °, 12.6 °, 16.9 °, 18.0 °, 19.8 °, 20.8 °, 22.1 °, 25.0 °, 25.6 ° and 26.4 ° (see below for more details). Crystal form A₁ is less stable than crystal form A₂, especially in the presence of water and polar solvents or mixtures thereof. However, form A₁ is kinetically stable in the parenterally administrable oil of the composition of the invention.

Crystal modification A₂ may be prepared by adding an aqueous solution of an alkali metal salt of n-decanesulphonic acid gradually to an aqueous solution of desferrioxamine-B methanesulphonate at a temperature below room temperature, preferably at 0 to 5 °C. This

mixture is then heated up to elevated temperatures, preferably to a temperature between room temperature and the boiling point of the mixture, more preferably from 30 °C to 80 °C.

Another form of desferrioxamine-B n-decanesulphonate suitable for use in the composition of the invention is a mixture of the crystal form A₁ with crystal form B. Crystal form B has a melting point (determined by DSC) of about 142 °C and has the following characteristic diffraction lines (2 θ in angular degrees $\pm$ 0.1 °) in its X-ray diffraction pattern : 3.5 °, 7.1 °, 8.9 °, 9.9 °, 11.3 °, 12.3 °, 19.0 °, 21.7 °, 22.1 ° and 23.8 °. Crystal form B is less stable than A₁, being transformed, at a temperature increase rate of 10 °C/min, into crystal form A₁. A mixture of the forms A₁ and B can be prepared by reacting decane-1-sulphonic acid with desferrioxamine-B free base as described in Example 1 of WO93/24451 to form the crude salt and recrystallising the latter by dissolving it in aqueous ethanol, filtering the resulting solution, and removing part of the ethanol under reduced pressure until the product is precipitated.

The desferrioxamine-B salt particles when suspended in the oil generally have a mean diameter of from 1 to 1000 microns, preferably from 3 to 500 microns, especially from 5 to 100 microns, most preferably from 5 to 10 microns.

The parenterally administrable oil may be any pharmaceutically acceptable oil or mixture of pharmaceutically acceptable oils having a viscosity suitable for delivery by injection. Such oils include mineral oils, vegetable oils and animal oils and esters of fatty acids obtained from such oils, preferably vegetable oils or esters of fatty acids obtained from them, such as refined paraffin oil, castor oil, sesame oil, cottonseed oil, sunflower oil, coconut oil, palmkernel oil, peanut oil, wheat germ oil, ethyl oleate, isopropyl myristate, esters of coconut and palmkernel fatty acids, i.e. caprylic and capric acids, with glycerol or propylene glycol, and mixtures of two or more thereof. Preferably, the parenterally administrable oil comprises ethyl oleate, a mixture of ethyl oleate with sesame oil or a triglyceride of a mixture of caprylic and capric acids. In especially preferred embodiments, the parenterally administrable oil comprises 25 to 100% by weight of ethyl oleate and 0 to 75% by weight of sesame oil, or the parenterally administrable oil comprises a triglyceride of a mixture of caprylic and capric acids, the weight ratio of caprylic acid to capric acid being from 10:9 to 13:6. Such triglyceride is commercially available as Miglyol 812 from Hüls AG, Germany.

In a composition of the invention, the desferrioxamine-B salt may be present generally in a therapeutically effective amount, usually in an amount of 0.05g to 0.4g per ml of the parenterally administrable oil, preferably in an amount of 0.1g to 0.3g per ml of the oil. The composition is conveniently in the form of a parenteral injection dosage unit, usually having a volume of 0.5 to 10ml, preferably 3 to 7ml, which may be in a conventional container such as a glass or plastic syringe or vial or polyethylene container. The composition is preferably supplied in, and administered from, a prefilled syringe or a bottlepack polyethylene container.

In some instances, it may be desirable that a composition of the invention also contains a surfactant (emulsifying agent). The inclusion of the latter, preferably in an amount of 0.1 to 3% by volume of the composition, inhibits a tendency of solid desferrioxamine-B salt particles to aggregate and facilitates a more uniform dispersion of the salt particles in the oil. Suitable surfactants include pharmaceutically acceptable non-ionic surfactants, preferably lipophilic surfactants such as sorbitan fatty acid esters, particularly sorbitan monolaurate, sorbitan monooleate and sorbitan trioleate, polysorbates such as polyoxyethylene (20) sorbitan monolaurate, polyoxyethylene (20)sorbitan monostearate, polyoxyethylene (20) sorbitan monooleate and polyoxyethylene (20) sorbitan trioleate, C₁₀ to C₂₀ alkyl ethers of polyoxyethylene glycols such as polyoxyethylene (4) lauryl ether, and phospholipid surfactants such as soy lecithin.

Compositions of the invention may also contain other excipients such as those used in conventional compositions to be administered by parenteral injection, for example tonicity agents such as dextrose and sodium chloride, preservatives such as benzyl alcohol, benzyl benzoate and methyl and propyl esters of p-hydroxy benzoic acids and antioxidants such as butylated cresols and tocopherols.

The present invention also provides a method of preparing a composition of the invention as hereinbefore defined which comprises mixing particles of the desferrioxamine-B salt with the parenterally administrable oil and, where present, the surfactant. In one convenient embodiment the mixing is carried out in two stages in which (a) the salt is milled with part of the oil and (b) the remainder of the oil is added to the milled mixture, the surfactant, where present, being added in stage (a) and/or stage (b). Where the oil comprises a mixture of oils of

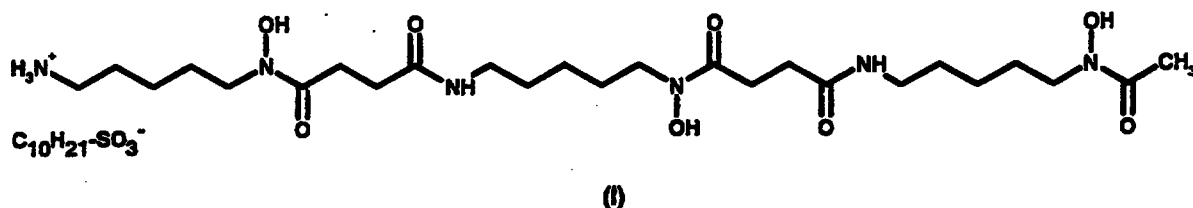
different viscosities, for example a mixture of sesame oil and ethyl oleate, the salt may conveniently be mixed with the more viscous oil before addition of less viscous oil. In a preferred embodiment, the desferrioxamine-B salt is added to the oil, or to a mixture of oil and surfactant, and the resulting mixture is homogenised by a pharmaceutically acceptable acceptable milling process, preferably in a colloid mill or the like, until the desired particle size of the salt is obtained. Alternatively, the desferrioxamine salt may be micronised using an air jet mill, resuspended in the oil phase using an ultraturrax mixer, followed by filling the desired container and sterilisation of the container and drug product by means of gamma or beta irradiation (10-100 kGy dose) or heat treatment.

The preparation of a sterile composition of the invention can be ensured by purifying the desferrioxamine-B salt under aseptic conditions, sterilizing the oil using conventional procedures, for example by filtration through a filter having a pore size of 0.22 μm or by heating it at 170 °C for at least 2 hours, and mixing the sterilised oil with the purified desferrioxamine-B salt under aseptic conditions.

Parenteral administration of compositions of this invention may be carried out, for example, by intramuscular or subcutaneous injection. After parenteral administration of the compositions, sustained release of desferrioxamine-B can occur over 48 hours. The dosage of desferrioxamine-B salt administered to a patient may be up to about 4g per day, for example 500mg to 4g per day. This dosage is conveniently delivered by bolus injection once a day or once every two days. The invention includes a method of treating iron-overload disease, aluminium overload, Alzheimer's disease, malaria, reperfusion injury or cancer which comprises parenterally injecting a composition of the invention as hereinbefore defined into a warm-blooded mammal, particularly a human, in need of such treatment.

The present invention also concerns a new stable crystal modification of desferrioxamine-1-decanesulphonate (that is preferably used in the compositions mentioned above and for their preparation) and a process for the production thereof.

It relates to a crystal modification of desferrioxamine-1-decanesulphonate (N-[5-{3-[(5-aminopentyl)-hydroxycarbonyl]-propionamido}-pentyl]-3-[(5-(N-hydroxyacetamidopentyl)-carbonyl]-propionohydroxamic acid-1-decanesulphonate) of formula I



which in Differential Scanning Calorimetry under nitrogen has a melting point range of 154°C to 158°C inclusive, at a heating rate of 10°C/min and possesses the following characteristic diffraction lines (2θ in angular degrees $\pm 0.1^\circ$) in its X-ray pattern: 3.1°, 7.3°, 9.4°, 13.7° and 23.7°.

In particular, the invention relates to a crystal modification of desferrioxamine-1-decanesulphonate, which in DSC under nitrogen has a melting point range of 154°C to 158°C inclusive at a heating rate of 10°C/min and possesses the following characteristic diffraction lines (2θ in angular degrees $\pm 0.1^\circ$) in its X-ray pattern: 3.1°, 4.2°, 7.3°, 8.4°, 9.4°, 10.5°, 13.7°, 16.8°, 17.4°, 18.0°, 18.4°, 19.6°, 20.1°, 20.9°, 22.3°, 23.7°, 25.1° and 25.6°.

This new specific crystal form (referred to here as "crystal modification A₂") has properties superior to all other known crystal modifications of desferrioxamine-1-decanesulphonate. Crystal modification A₂ is physico-chemically and thermodynamically more stable than the other known modifications in the customary temperature range, and for this reason is more suitable for production of the chemical substance in solid form, as well as the development and production of pharmaceutical formulations, and also for therapeutic application thereof. In more precise terms, all known crystal forms are metastable, when compared to crystal modification A₂. Therefore only crystal modification A₂ will not show solid state transformation, independent of the dispersion phase in production, storage and during therapeutic application e.g. after depot injections. In addition, crystal form A₂ is better to mill than crystal form A₁.

The crystal modification A₂ is very stable with good thermal stability up to the melting range. It melts at a heating rate of 10°C/min in a range of 148°C to 162°C with a melting point range of 154°C to 158°C inclusive.

Very preferred is the crystal modification A_2 displaying the x-ray diagram according to FIG. 1/3.

As well as crystal modification A_2 , there are also further, less stable crystal modifications. Crystal modification A_1 has a melting point range of 140°C to 153°C. It corresponds to the form specified in the patent application EP 643690. By means of more precise Differential Scanning Calorimetry (DSC), it can be shown that it consists of four sub-forms A_{11} , A_{12} , A_{13} and A_{14} with melting points 148°C, 150°C, 152°C and 153°C. These sub-modifications are obtained during the production of the substance in different quantity ratios and together form the crystal modification A_1 .

Crystal modification B may similarly appear during the production of the desferrioxamine-1-decanesulphonate. The melting point thereof in DSC is approximately 142°C, and with a heating rate of 10°C/minute, a transformation into one or several sub-forms of crystal modifications A_1 , namely A_{11} to A_{14} , may be observed.

In detail, the following data are obtained by DSC for the different crystal forms:

A DSC diagram of crystal modification A_2 of desferrioxamine-1-decanesulphonate, sample weight of 2.177 mg and a heating rate of 10.0 °C/min under nitrogen, shows a melting point

$$T_{\text{fus}}^{A_2} = 155 \text{ °C.}$$

A DSC diagram of crystal modification A_{11} , A_{12} and A_{13} of desferrioxamine-1-decanesulphonate, sample weight: 2.747 mg and a heating rate of 10.0 °C/min under nitrogen, re-

veals the following melting points: $T_{\text{fus}}^{A_{11}} = 148 \text{ °C}$; $T_{\text{fus}}^{A_{12}} = 150 \text{ °C}$; and $T_{\text{fus}}^{A_{13}} = 152 \text{ °C}$.

A DSC diagram of crystal modification A_1 of desferrioxamine-1-decanesulphonate, sample weight: 2.683 mg and a heating rate of 10.0 °C/min under nitrogen, reveals the following

melting points: $T_{\text{fus}}^{A_{12}} = 149 \text{ °C}$; $T_{\text{fus}}^{A_{13}} = 151 \text{ °C}$; and $T_{\text{fus}}^{A_{14}} = 153 \text{ °C}$.

A DSC diagram of crystal modification B (mixture with modifications A₁₁ to A₁₃) of desferrioxamine-1-decanesulphonate, sample weight: 2.285 mg and a heating rate of 10.0 °C/min under nitrogen, reveals the following melting point $T_{\text{fus}}^{\text{B}}$: 142 °C.

The crystal modifications may also be distinguished by their X-ray powder patterns, in addition to their melting points. X-ray powder patterns, taken with a Guinier camera in transmission geometry and using Cu-K α_1 radiation, are preferably employed to characterise solids of organic substances. In particular, X-ray diffraction patterns are used successfully to determine the different crystal modifications of a substance. To characterise the present crystal modification A₂ of the desferrioxamine-1-decanesulphonate according to the invention, the measurements are carried out at room temperature and the X-ray films evaluated in an angle range (2 θ) of 3° to 30° . All cited diffraction angles 2 θ in the present disclosure are given in respect to the Cu-K α_1 radiation.

Table 1:

X-ray diffraction pattern (diffraction angle and intensity of most important lines) of crystal modification A₂ of the desferrioxamine-1-decanesulphonate (figure 5)

2 θ	intensity
3.1°	strong
4.2°	strong
7.3°	weak
8.4°	weak
9.4°	weak
10.5°	strong
13.7°	weak
16.8°	weak
17.4°	very weak
18.0°	strong
18.4°	very weak
19.6°	very strong
20.1°	medium

2 θ	intensity
20.9°	medium
22.3°	weak
23.7°	weak
25.1°	strong
25.6°	weak

Tables 2 and 3 reproduce the X-ray diffraction patterns of the above-described crystal modification A₁ and of crystal modification B.

Table 2:

X-ray diffraction pattern (diffraction angle and intensity of the most important lines) of crystal modification A₁ of desferrioxamine-1-decanesulphonate (figure 6)

2 θ	intensity
4.1°	very strong
6.3°	weak
8.4°	weak
10.5°	strong
12.6°	weak
16.9°	weak
18.0°	medium
19.8°	strong
20.8°	medium
22.1°	very weak
25.0°	medium
25.6°	very weak
26.4°	very weak

Table 3:

X-ray diffraction pattern (diffraction angle and intensity of the most important lines) of crystal modification B of desferrioxamine-1-decanesulphonate

2 θ	intensity
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2 θ	intensity
3.5°	weak
7.1°	weak
8.9°	very weak
9.9°	very weak
11.3°	very weak
12.3°	weak
19.0°	strong
21.7°	medium
22.1°	strong
23.8°	medium

The X-ray diffraction patterns confirm that the crystal modifications of desferrioxamine-1-decanesulphonate indicated by A₁, A₂ and B are completely distinct polymorphous forms. In contrast to the DSC method, in which four distinct melting points (see above) could be determined for the crystal modification A₁, the differences in the X-ray diffraction patterns are too small to show significant deviations of the 2 θ values of the reflection angle corresponding to Table 2.

A further appropriate parameter for distinguishing the crystal modifications is frequently their hygroscopicity, from which conclusions may be drawn on the stability of a crystal modification. It is determined for example by weighing the water vapour absorption, whereby the water absorption by the substance to be tested is measured in an atmosphere, preferably a nitrogen atmosphere, of known relative moisture.

Table 4:

Percentage of water absorption at 25°C by crystal modifications A₁ and A₂

% relative moisture	A ₁ water absorption in %	A ₂ water absorption in %
0	0	0
10	0.1	<0.1
20	0.2	<0.1

% relative moisture	A ₁ water absorption in %	A ₂ water absorption in %
30	0.2	0.1
40	0.3	0.1
50	0.3	0.1
60	0.4	0.1
70	0.5	0.2
80	0.6	0.2
90	0.9	0.3
95	2.1	0.5
98	4.7	0.8

The significantly lower water absorption of crystal modification A₂ compared with the form A₁ reflects the higher stability of modification A₂ according to the invention.

The present invention also relates to a process for the production of the crystal modification A₂ of desferrioxamine-1-decanesulphonate according to the invention.

This process is characterised in that, in at least one process step, a suspension of desferrioxamine-1-decanesulphonate of unknown or unspecified morphological composition in a polar solvent is maintained at elevated temperature; or that in at least one process step, a concentrated solution of desferrioxamine-1-decanesulphonate in a polar solvent is prepared at elevated temperature and then crystallised at a cooling rate of 2°C or less per minute.

Polar solvents are for example polar organic compounds such as low alcohols, low ketones, low nitriles and low cyclic ethers, or water or mixtures thereof. The term "low" indicates organic compounds which contain 1 to 4 inclusive carbon atoms and one or two hetero atoms such as oxygen, nitrogen and/or sulphur. Preferred polar organic solvents are water-miscible organic solvents, such as methanol, ethanol, *n*-propanol, isopropanol, acetone, ethyl methyl ketone, acetonitrile, tetrahydrofuran or *p*-dioxane. Especially advantageous for the production of the crystal modification A₂ according to the invention are water or mixtures of water-miscible organic solvents, especially methanol, ethanol, *n*-propanol and/or isopropanol, with water. Water is most particularly preferred.

Elevated temperature indicates the temperature range from room temperature to boiling point of the solvent or solvent mixture, whereby the temperature range of 30°C to 80°C inclusive is preferred, or up to boiling point of the polar solvent, which is also always lower, especially the temperature range of 35°C to 60°C.

Concentrated solution signifies that the solution contains such a quantity of dissolved substance that upon cooling of the solution to a lower temperature the dissolved substance partially crystallises. Preferred concentrated solutions are saturated or slightly supersaturated solutions. Saturated or supersaturated solutions of a substance do not dissolve any further substance without raising the temperature. Supersaturated solutions may be prepared for example by rapid cooling of a saturated solution to a somewhat lower temperature. It is especially advantageous to use saturated solutions.

The preferred cooling rate of a solution is 2°C/minute or less. Cooling rates of 1°C/minute or less are especially advantageous.

In a preferred embodiment of the process, at least one seeding crystal is added.

Appropriate seeding crystals may be produced for example from a less stable form or a mixture of several less stable forms, by maintaining a suspension at an elevated temperature.

In an especially preferred embodiment of the process, a solution of desferrioxamine methane sulphonate in a polar solvent is prepared, heated to the desired temperature, then one part of an equimolar quantity of a 1-decanesulphonic acid salt in solution in the same or another polar solvent is added, at least one seeding crystal is added, maintained until the commencement of crystallisation, then the remainder of the equimolar quantity of the 1-decanesulphonic acid salt in solution in the same or another polar solvent is slowly added, and then maintained at the desired temperature; or a hot-saturated solution of desferrioxamine-1-decanesulphonate in a polar solvent is produced at an elevated temperature, then after adding at least one seeding crystal it is cooled at a rate of 1°C/minute or less to a lower elevated temperature, during which time crystallisation takes place, and the crystal suspension is maintained at this lower temperature.

The salts used as 1-decanesulphonic acid salts may be for example all salts of 1-decanesulphonic acid that have better solubility in the chosen polar solvent than desferrioxamine-1-decanesulphonate. These salts are salts with bases, such as corresponding alkali metal salts, e.g. sodium or potassium salts, or salts with ammonia or organic amines, such as cyclic amines, such as mono-, di- or tri-lower-alkylamines, such as hydroxy-lower-alkylamines, e.g. mono-, di- or trihydroxy-lower-alkylamines, hydroxy-lower-alkyl-lower-alkylamines or polyhydroxy-lower-alkylamines. Cyclic amines are e.g. morpholine, thiomorpholine, piperidine or pyrrolidine. The mono-lower-alkylamines may be for example ethyl- and *tert*-butylamine, the di-lower-alkylamines may be for example diethyl- and diisopropylamine, and the tri-lower-alkylamines may be for example trimethyl- and triethylamine. Corresponding hydroxy-lower-alkylamines are e.g. mono-, di- and triethanolamine; hydroxy-lower-alkyl-lower-alkylamines are e.g. N,N-dimethylamino- and N,N-diethylamino-ethanol, and polyhydroxy-lower-alkylamine may be e.g. glucosamine. Preference is given to pharmaceutically acceptable salts, especially the sodium salt.

Working up may be effected in a basically known manner, by separating the crystallisate from the mother liquor, for example by filtration, with or without the assistance of pressure and/or vacuum, or by centrifugation, with subsequent drying.

The present invention also relates to pharmaceutical preparations comprising as active ingredient crystal modification A₂ of desferrioxamine-1-decanesulphonate and a pharmaceutically acceptable carrier, preferably as described hereinbefore and hereinafter. The invention also relates to the preparation of such a pharmaceutical preparation, preferably as described hereinbefore. The invention also relates to the use of crystal modification A₂ of desferrioxamine-1-decanesulphonate for the treatment of a disease selected from the group comprising iron-overload disease, aluminium overload, Alzheimer's disease, malaria, reperfusion injury and cancer, especially thalassemia, or for the preparation of a pharmaceutical preparation for the treatment of such a disease. The invention furthermore relates to a method of treatment of a disease selected from the group comprising iron-overload disease, aluminium overload, Alzheimer's disease, malaria, reperfusion injury and cancer, especially thalassemia, which comprises administering to a patient in need of such treatment a dose of crystal modification A₂ of desferrioxamine-1-decanesulphonate that is pharmaceutically effective in the treatment of said disease.

In all cases, the doses and percentages of the active ingredient are in accordance with the customary ones, especially those as described hereinbefore and hereinafter.

Examples:

The invention is illustrated by the following Examples in which parts are by weight unless otherwise specified. The invention is not restricted by the examples.

Desferrioxamine-B n-decansulphonate, Preparation I used in the Examples is prepared as follows: An aqueous 10% solution of 1-decanesulfonic acid sodium salt is added at 0-5 °C over 60 minutes to an aqueous 20% solution of desferrioxamine-B methanesulphonate, the molar ratio of the decanesulphonate salt to the methanesulphonate being 1:1. Desferrioxamine-B n-decansulphonate precipitates. The suspension is agitated for another 1-2 hours at 0-5 °C before the product is collected by filtration. The product is washed with water, dried in vacuum at 40 °C for 20 hours and finally de-agglomerated over a sieve.

Desferrioxamine-B n-decansulphonate, Preparation II used in the Examples is prepared as follows: Desferrioxamine-B methanesulphonate (12.3 parts) is dissolved in water (47 parts) at 30-40 °C. A solution of sodium n-decansulphonate (0.7 parts) in water (12.0 parts) is added at 50 °C over a few minutes. The solution is seeded by the addition of desferrioxamine-B n-decansulphonate (0.08 parts) and, after stirring the resulting suspension for 30 min at 50 °C, a further solution of sodium n-decansulphonate (3.8 parts) in water (64 parts) is added slowly with stirring over 3 to 4 hours at 50-52 °C. The suspension obtained is stirred for a further 1-2 hours at 50-52 °C and then cooled overnight to 40 °C. The product is collected by filtration, washed with water, dried under vacuum at 50 °C for 20 hours and then de-agglomerated over a sieve.

Desferrioxamine-B n-decansulphonate, Preparation III used in the Examples is prepared as follows: Crude desferrioxamine-B n-decansulphonate prepared by reacting n-decansulphonic acid with desferrioxamine-B free base as described in Example 1 of WO93/24451 (548g) is dissolved in a mixture of ethanol (3000ml) and water (600ml) at 40 °C. The solution is filtered and the filtrate concentrated by distillation at 40 °C under reduced pressure (40 mbar). The thick suspension obtained is diluted with water (3000ml) and the product is

collected by filtration, washed with water, dried in a vacuum at 50°C/20mbar for 20 hours and de-agglomerated over a sieve.

In Examples 1 to 16, parenterally injectable compositions of the desferrioxamine-B salts mentioned therein are obtained. The resulting mean particle diameters and particle size distributions of the respective suspended desferrioxamine-B salt are given as "Result".

Example 1: Composition A

Desferrioxamine-B n-decansulphonate, Preparation I (1g) is mixed with sesame oil (3.75ml) and polyoxyethylene (20) sorbitan mono-oleate (0.02ml) until a lump-free suspension is obtained. Ethyl oleate (1.25ml) is added to the resulting suspension and mixed thoroughly therewith using pestle and mortar. Result: Mean particle diameter of 59.18µm; particle size distribution: 90% less than 113.19µm, 50% less than 55.08µm and 10% less than 5.41µm.

Example 2: Composition B

Example 1 is repeated, using 2.5ml of sesame oil and 2.5ml of ethyl oleate instead of the amounts used in Example 1. Result: Mean particle diameter of 66.34µm; particle size distribution: 90% less than 121.78µm, 50% less than 62.34µm and 10% less than 6.49µm.

Example 3: Composition C

Example 1 is repeated, using 1.25ml of sesame oil and 3.75ml of ethyl oleate instead of the amounts used in Example 1. Result: Mean particle diameter of 68.97µm; particle size distribution: 90% less than 119.31µm, 50% less than 66.97µm and 10% less than 7.97µm.

Example 4: Composition D

Example 2 is repeated, using 0.043ml of polyoxyethylene (20) sorbitan mono-oleate instead of the amount used in Example 2. Result: Mean particle diameter of 57.02µm; particle size distribution: 90% less than 107.45µm, 50% less than 54.65µm and 10% less than 4.99µm.

Example 5: Composition E

Example 2 is repeated, but omitting the polyoxyethylene (20) sorbitan mono-oleate. Result: Mean particle diameter of 60.04µm; particle size distribution: 90% less than 112.84µm, 50% less than 56.42µm and 10% less than 5.25µm.

Example 6: Composition F

Example 1 is repeated, using 2.5ml of sesame oil, 2.5ml of ethyl oleate and 0.043ml of polyoxyethylene (20) sorbitan mono-oleate instead of the amounts used in that Example, and additionally mixing the ingredients with sorbitan trioleate (0.057ml) in the first stage of the procedure. Result: Mean particle diameter of 60.36 μ m; particle size distribution: 90% less than 109.36 μ m, 50% less than 58.14 μ m and 10% less than 5.12 μ m.

Example 7: Composition G

Example 2 is repeated, replacing the polyoxyethylene (20) sorbitan mono-oleate used in that Example by soy lecithin (0.011g) . Result: Mean particle diameter of 43.13 μ m; particle size distribution: 90% less than 93.62 μ m, 50% less than 34.26 μ m and 10% less than 4.98 μ m.

Example 8: Composition H

Example 7 is repeated, using 0.027g of soy lecithin, instead of the amount used in that Example. Result: Mean particle diameter of 52.07 μ m; particle size distribution: 90% less than 117.62 μ m, 50% less than 39.98 μ m and 10% less than 5.99 μ m.

Example 9: Composition I

Desferrioxamine-B n-decansulphonate, Preparation II (1g) is mixed with sesame oil (2.5ml) and polyoxyethylene (20) sorbitan mono-oleate (0.02ml) until a lump-free suspension is obtained. Ethyl oleate (2.5ml) is added to the resulting suspension, and mixed thoroughly therewith. Result: Mean particle diameter of 41.48 μ m and the following particle size distribution: 90% less than 99.19 μ m, 50% less than 26.31 μ m and 10% less than 5.24 μ m.

Example 10: Composition J

Example 9 is repeated, using 0.004ml of polyoxyethylene (20) sorbitan mono-oleate in place of the amount used in that Example. Result: Mean particle diameter of 43.60 μ m; particle size distribution: 90% less than 104.11 μ m, 50% less than 26.63 μ m and 10% less than 5.22 μ m.

Example 11: Composition K

Example 9 is repeated, using 0.043ml of polyoxyethylene (20) sorbitan mono-oleate in place of the amount used in that Example. Result: Mean particle diameter of 30.60 μ m; particle size distribution: 90% less than 73.40 μ m, 50% less than 17.18 μ m and 10% less than 5.22 μ m.

Example 12: Composition L

Example 9 is repeated, but omitting the polyoxyethylene (20) sorbitan mono-oleate used in that Example. Result: Mean particle diameter of 43.75 μ m and the following particle size distribution: 90% less than 104.80 μ m, 50% less than 25.32 μ m and 10% less than 5.36 μ m.

Example 13: Composition M

Example 9 is repeated, using 3.75ml of sesame oil and 1.25ml of ethyl oleate instead of the amounts used in that Example and omitting the polyoxyethylene (20) sorbitan mono-oleate used in that Example. Result: Mean particle diameter of 50.52 μ m; particle size distribution: 90% less than 118.97 μ m, 50% less than 31.87 μ m and 10% less than 6.91 μ m.

Example 14: Composition N

Example 9 is repeated, using 1.25ml of sesame oil and 3.75ml of ethyl oleate instead of the amounts used in that Example and omitting the polyoxyethylene (20) sorbitan mono-oleate used in that Example. Result: Mean particle diameter of 35.83 μ m; particle size distribution: 90% less than 86.60 μ m, 50% less than 19.85 μ m and 10% less than 5.92 μ m.

Example 15: Composition O

Example 9 is repeated, but omitting the polyoxyethylene (20) sorbitan mono-oleate used in that Example. Result: Mean particle diameter of 39.50 μ m; particle size distribution: 90% less than 96.33 μ m, 50% less than 22.08 μ m and 10% less than 6.23 μ m.

Example 16: Composition P

Example 9 is repeated, using 5.00ml of ethyl oleate instead of the amount used in that Example and omitting the sesame oil used in that Example. Result: Mean particle diameter

of 35.44 μ m; particle size distribution: 90% less than 79.52 μ m, 50% less than 19.79 μ m and 10% less than 5.85 μ m.

Example 17: Plasma Levels in hamsters I

Desferrioxamine-B n-decansulphonate, Preparation I (1g) is ground in a triple roll mill with a mixture of sesame oil (2.5ml), ethyl oleate (2.5ml), polyoxyethylene (20) monolaurate (0.057ml) and polyoxyethylene (20) sorbitan mono-oleate (0.043ml) which is added slowly to the salt. The resulting parenterally injectable suspension is tested for in vivo release of the desferrioxamine-B salt as follows:

Male golden Syrian hamsters weighing 100g $\pm$ 20g are injected subcutaneously in the nape of the neck with the suspension at a dosage of 1ml per kg. At various time intervals the animals are terminally anaesthetised, and blood samples are obtained by cardiac puncture, the blood being collected in heparinised syringes and centrifuged. The plasma is removed and the combined concentration of desferrioxamine-B and metabolite B in the plasma is determined by immunoassay. The results, expressed as the average results for 3 animals for each time interval, are as follows:

<u>Time (hours)</u>	<u>Combined concentration of Desferrioxamine-B and metabolite B in Plasma (μg/ml)</u>
3	24.57
6	14.36
24	0.53
30	0.58
48	2.31
54	0.77
72	0.48
168	0.45

The immunoassay is done by a solid phase enzyme based immunoassay that is capable of detecting the presence of the iron chelating compound DesferalTM and its major metabolite, Metabolite B, in biological fluids such as plasma and urine. For that purpose, a polyclonal

rabbit antibody was developed. It can distinguish between the parent molecule desferrioxamine (DFO) and the chelated form, Ferrioxamine (FO). The principle of the method is as follows: FO is coated onto wells of a 96 well-plate (Nunc Maxisorb) via a biotin/streptavidin link. A standard curve of DFO or Metabolite B is prepared in the diluted (1/20 in buffer) biological fluid (serum, urine etc.) containing ferric citrate (1 mM) as the iron source. Test samples are diluted accordingly in the same fluid. Appropriately diluted anti-ferrioxamine antibody is added and allowed to react. Unbound antibody is removed by washing. Bound antibody is detected using a goat anti-rabbit IgG Fc horseradish peroxidase conjugated antibody and a peroxidase substrate. The amount of colour produced is inversely proportional to the amount of DFO/MetB in the sample.

The antibody is produced as follows:

Immunogenic bovine serum albumin (BSA)/desferrioxamine conjugate is produced according to standard procedures (activation of BSA with N-succinimidyl 3-(2-pyridyldithio)propionate (SPDP), removal of the DPDP excess by dialysis, reduction with dithiothreitol to obtain BSA with attached sulfhydryl groups, dialysis, then addition of SPDP, DFO and N-methylmorpholine, after 1 h centrifugation at 1000 g for 5 min and dialysis against PBS at 4 °C for 17 h, storing the resulting solution at -80 °C. A keyhole limpet hemocyanin (KLH)/DFO conjugate is obtained in an analogous way. These conjugates are then injected s.c. into Dutch rabbits (Harlan-Olac) with alternating BSA-DFO and KLH conjugates mixed (1:1) with incomplete Freund's adjuvant (450 µg BSA-DFO month 0, 300 µg KLH-DFO month 1, 250 µg BSA-DFO month 2, 150 µg KLH-DFO month 3, 150 µg BSA-DFO month 6, 150 µg KLH-DFO month 10). Blood is isolated and serum prepared and stored at -20 °C. The antibodies are isolated over protein A-agarose by routine methods.

Biotin-FO/DFO conjugate is prepared by reaction of biotin-LC-NHS in water/dimethylformamide with FO in the presence of N-Methylmorpholine.

The competition assay relies on the drug in the sample competing with the bound drug for the binding of the antibody which is then detected with a horseradish peroxidase conjugated anti-species antibody. The concentration of drug is measured using a standard curve of DFO and a standard curve of Metabolite B (MetB) (at molar equivalent concentrations) diluted in the appropriate biological fluid/buffer mix. The antibody recognizes only the iron

bound forms of DFO or any of the iron chelating metabolites, which are converted in situ by addition of 1 mM ferric citrate to the sample buffer. The assay is performed in two different buffers, 0.3 M PBS pH 6.4 or 0.3 M Borate pH 7.4. The plasma or urine samples are also converted to the iron bound form by the addition (1/2) of 1 mM ferric citrate.

Streptavidin is diluted to 1 µg/ml in 0.1 M carbonate coating buffer pH 9.6, added to the wells of a microtiter plate (100 µl/well) and incubated overnight at 22 °C. The wells are washed four times with PBS/Tween (Tween 20, Sigma, Poole, Dorset). Residual adsorption sites on the plate are saturated by incubation with 200 µl of PBS containing 0.1% casein for 1 h at 37 °C. The wells are washed four times with PBS/Tween. Biotin-FO (427 µg/ml) is diluted (1 ng/ml) in PBS/casein and incubated in the wells (100 µl/well) for 2 h at 22 °C. The wells are washed four times with PBS/Tween. DFO and MetB standards (range 2.80500 to 0.00273 / 0.00000 µM) are added (50 µl/well) to 12 sets of duplicate wells. The rabbit anti-ferrioxamine antibody is diluted 1/800 in either pH 6.4 or 7.4 buffer and added (50 µl/well) to the same set of wells, mixed in a micro shaker for 30 seconds and incubated for 2 h at 22 °C. The samples are diluted in either buffer and treated the same way as the FO standards. The wells are washed four times with PBS/Tween. A horseradish peroxidase conjugated anti-rabbit IgG Fc antiserum (Biogenesis, Poole, Dorset) is diluted 1/2500 and incubated in the wells (100 µl/well) overnight at 4 °C. The wells are washed four times with PBS/Tween. The enzyme conjugated antiserum that has remained bound after washing is developed by incubating the plate with 100 µl/well o-phenyldiamine dihydrochloride for 20 min in the dark. The reaction is stopped with the addition of 100 µl/well 1M HCl. The colour is measured using a Dynatech MR600 colourimeter at 490 nm.

Example 18: Plasma levels in hamsters II

Example 17 is repeated, but grinding the salt with the other components of the suspension using an agate pestle and mortar instead of the triple roll mill used in Example 17. The resulting parenterally injectable suspension is tested as in Example 17. The results are as follows:

	Combined concentration of Desferrioxamine-B and metabolite B
<u>Time (hours)</u>	<u>in Plasma (µg/ml)</u>

3	18.19
6	10.72
24	0.91
30	0.63
48	0.53
54	1.06
72	0.51
168	1.69

Example 19: Plasma levels in hamsters III

Example 17 is repeated, using Desferrioxamine-B n-decansulphonate, Preparation III (1g) instead of the Desferrioxamine-B Salt I used in that Example. The resulting parenterally injectable suspension is tested as in Example 17. The results are as follows:

<u>Time (hours)</u>	<u>Combined concentration of Desferrioxamine-B and metabolite B in Plasma (µg/ml)</u>
3	20.50
6	18.03
24	1.06
30	1.09
48	1.05
54	1.96
72	0.84
168	0.78

Example 20: Plasma levels in hamsters IV

Example 18 is repeated, using Desferrioxamine-B n-decansulphonate, Preparation III (1g) instead of the Desferrioxamine-B Salt I used in that Example. The resulting parenterally injectable suspension is tested as in Example 17. The results are as follows:

Combined concentration of
Desferrioxamine-B and metabolite B

<u>Time (hours)</u>	<u>in Plasma ($\mu\text{g/ml}$)</u>
3	17.61
6	17.15
24	0.67
30	0.41
48	0.60
54	0.88
72	0.50
168	0.47

Example 21: Plasma levels in hamsters V

Desferrioxamine-B n-decansulphonate, Preparation III (1g) is ground, using an agate pestle and mortar, with a mixture of sesame oil (2.5ml), ethyl oleate (2.5ml), sorbitan trioleate (0.075ml) and polyoxyethylene-4-lauryl ether (0.025ml) which is added slowly to the salt. The resulting parenterally injectable suspension is tested as in Example 17. The results are as follows:

Combined concentration of Desferrioxamine-B and metabolite B	
<u>Time (hours)</u>	<u>in Plasma ($\mu\text{g/ml}$)</u>
3	5.93
6	14.10
24	7.91
30	0.41
48	4.91
54	0.89
96	0.17

Example 22: Composition Q

Desferrioxamine-B n-decansulphonate, Preparation II (12.15 parts) is added to Miglyol 812 (47.25 parts). The suspension obtained is homogenised using a colloid mill until the mean particle size of the suspended salt is 5 to 10 microns, thereby producing a parenterally injectable suspension.

Example 23: Effect on Bile Secretion

Example 22 is repeated using 19.8 parts of Desferrioxamine-B n-decansulphonate, Preparation II and 99 parts of Miglyol 812 instead of the amounts used in that Example. The resulting parenterally injectable suspension is tested for its effect on iron excretion in bile duct cannulated rats. After collecting control bile and urine samples for 3 hours, the rats (male Fischer) are injected subcutaneously with the suspension (591 μ l/kg, corresponding to a desferrioxamine dosage of 117 mg/kg). Bile samples are then collected at 3 hour intervals and their iron content determined. The results for rats injected with the suspension are shown below (average for 3 animals):

<u>Time After Injection (hours)</u>	<u>Bile Fe Content (mg/kg)</u>
0	11.0
3	86.9
6	111.8
9	105.1
12	96.1
15	92.7
18	88.2
21	86.2
24	92.0
27	76.7
30	67.0
33	52.7
36	35.5
39	16.1
42	9.6
45	8.4
48	7.2

Example 24: Composition R

After milling of Desferrioxamine-B n-decansulphonate, Preparation II, using an air jet mill (median particle size 5 - 10 μ m), the resulting material is mixed in the oil phase (ratio and ingredients as in example 22 or 23). The homogeneous suspension is filled in a container

(glass vial, prefilled syringe or bottelpack container) and sterilized by gamma or beta irradiation or heat treatment

Example 25: Iron elimination in hamsters

A mixture of sesame oil (2.0ml), ethyl oleate (2.0ml), sorbitan trioleate (75 μ l) and polyoxyethylene-4-lauryl ether (25 μ l) is added slowly to desferrioxamine-B n-octanesulphonate (1g), while grinding with an agite pestle and mortar, to give a parenterally injectable suspension. The suspension is tested for its affect on iron elimination in male golden Syrian hamsters iron-loaded by intravenous injection of ^{59}Fe labelled ferritin (100 μ l). The suspension under test is administered by subcutaneous injection, at a desferrioxamine dosage of 150 μ mol/kg, one hour after administration of the ferritin. The ^{59}Fe content of urine and faeces is determined using a gamma-counter after 24 hours and 48 hours. The results for hamsters injected with the suspension (average for 6 animals) and control hamsters receiving no iron chelator (average for 5 animals) are shown below:

<u>Elimination</u>	<u>% of ^{59}Fe Dose</u>	
	<u>Injected Hamsters</u>	<u>Control</u>
Urine 24 hours	0.74	0.026
Faeces 24 hours	7.09	1.14
Urine 48 hours	0.052	0.037
Faeces 48 hours	2.59	1.00

Example 26: Crystalline Modification A₂

To produce seeding crystals, 84 g of desferrioxamine-1-decanesulphonate, consisting of a mixture of crystal modification B and crystal modification A₁, are added to 820 ml of distilled water containing a trace of tinovetin (a mixture of lauryl ether sulphate and ethoxylated nonylphenol) as wetting agent. The suspension formed is maintained isothermally in a water bath for 1 hour at 80°C whilst stirring. The suspension is subsequently filtered through a suction filter whilst still warm. The filtered substance is dried at room temperature whilst passing through a nitrogen atmosphere. The seeding crystals obtained are tested for chemical purity and morphological uniformity, and if no pure form of crystal modification A₂ is present, the above process is repeated. The title compound is thus obtained.

Example 27: Crystalline Modification A₂

145 mg of a mixture of desferrioxamine-1-decanesulphonate crystal modification B and crystal modification A₁ (consisting of a little A₁₁ and the two forms A₁₂ and A₁₃ in about equal parts) are suspended in 1.2 ml of distilled water containing a trace of tinovetin as wetting agent. The suspension is maintained isothermally in a water bath for 2 hours at 80 °C whilst stirring. The suspension is subsequently filtered through a suction filter whilst still warm. The filtered substance is dried at room temperature whilst passing through a nitrogen atmosphere. The title compound is thus obtained.

Example 28: Crystalline Modification A₂

20.1 kg of desferrioxamine methane sulphonate are dissolved in water at room temperature and heated to 50°C. One part (15%) of 7.3 kg of sodium-1-decanesulphonate is dissolved in water at 50°C and the solution added in one go to the desferrioxamine methane sulphonate solution. The solution is seeded with A₂ crystals and afterwards stirred for 30 minutes at 50°C, whereby crystallisation commences. Then, the second portion of aqueous sodium-1-decanesulphonate solution (85%) is measured into the existing warm suspension over the course of 3 to 4 hours and thus completes crystallisation. The suspension is stirred for a further 90 minutes at 50°C and is then slowly cooled to 40°C. The product is filtered off through a filter drier, washed with water and dried in a vacuum, yielding the title compound.

Example 29: : Crystalline Modification A₂

12.3 kg of desferrioxamine methane sulphonate are dissolved in 47.0 kg of water at 30-40 °C. The solution is sterile-filtered and the filtrate transferred to a crystallisation kettle. A sterile solution of 0.7 kg of sodium-1-decanesulphonate in 12.0 kg of water is added at 45-50°C over the course of a few minutes, and crystallisation is initiated by adding 0.08 kg of desferrioxamine-1-decanesulphonate, crystal modification A₂. After stirring for 30 minutes at 50°C, a further sterile-filtered solution of 3.8 kg of sodium-1-decanesulphonate in 64.0 kg of water is slowly added with gentle stirring over the course of 3 to 4 hours at approximately 50°C to 52°C. The suspension is then left for a further 1 to 2 hours at 50°C to 52°C and is subsequently cooled over night to about 40°C. The product is filtered off by suction under sterile conditions, washed with 54 kg of water in several portions, and dried at reduced pressure (<20 hPa) at 50°C for 24 to 40 hours. The title compound is thus obtained.

Example 30: Crystalline Modification A₂

20.0 kg of desferrioxamine-1-decanesulphonate are dissolved at reflux temperature (ca. 78°C) in 80.0 kg of absolute ethanol and the solution is filtered. The filtrate which is supplemented with 8.0 kg of ethanolic rinsing solution is cooled to 40°C over the course of 1 to 2 hours, whereby the clear solution is seeded at ca. 75°C with a little crystalline desferrioxamine-1-decanesulphonate, crystal modification A₂. Crystallisation thereby commences. The suspension is maintained at 40°C for 30 minutes, then cooled further to 0°C over the course of ca. 1 hour, and stirred at this temperature for another 1 to 2 hours. The product is filtered off by suction, washed with 24.0 kg of ethanol in several portions and dried at reduced pressure (<20 hPa) at 50°C. The title compound is thus obtained.

Example 31: Crystalline Modification A₂

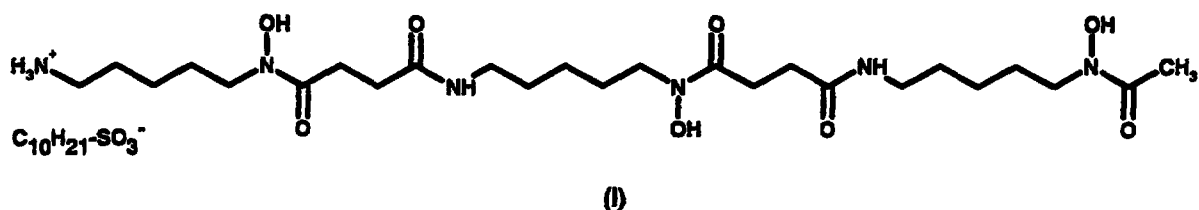
20.0 kg of desferrioxamine-1-decanesulphonate are dissolved at reflux temperature (ca. 78°C) in 80.0 kg of absolute ethanol and the solution is sterile-filtered. The filtrate which is supplemented with 8.0 kg of ethanolic rinsing solution is cooled stepwise to 44°C over the course of approximately 2 hours, whereby the clear solution is seeded at ca. 68°C with a little crystalline desferrioxamine-1-decanesulphonate, crystal modification A₂. Crystallisation thereby commences. The suspension is maintained at 44°C for 30 minutes, then cooled further to 0°C over the course of about 1 to 2 hours, and stirred at this temperature for approximately 1 further hour. The product is filtered off by suction, washed with ethanol in several portions and dried at reduced pressure (<20 hPa) at 50°C.

**Claims**

1. A parenterally injectable composition comprising particles of a desferrioxamine-B salt of an aliphatic sulphonic acid having at least 8 carbon atoms suspended in a parenterally administrable oil.
2. A composition according to claim 1, in which the salt is a salt of n-octanesulphonic acid or n-decanesulphonic acid.
3. A composition according to claim 1, in which the salt is desferrioxamine-B n-decane-sulphonate in a crystal form having a melting point of 154 to 158 °C and the following characteristic diffraction lines (2θ in angular degrees $\pm 0.1^\circ$) in the X-ray diffraction pattern thereof : 3.1 °, 7.3 °, 9.4 °, 13.7 ° and 23.7 °.
4. A composition according to any one of claims 1 to 3, in which the salt particles have a mean diameter from 5 to 10 microns.
5. A composition according to any one of claims 1 to 4, in which the oil comprises at least one vegetable oil or ester of a fatty acid obtained from a vegetable oil.
6. A composition according to any one of claims 1 to 5, in which the parenterally administrable oil comprises a triglyceride of a mixture of caprylic and capric acid, the weight ratio of caprylic acid to capric acid being from 10:9 to 13:6.
7. A composition according to any of claims 1 to 6 which also contains a surfactant.
8. A method of preparing a composition according to any of claims 1 to 7 which comprises mixing particles of the desferrioxamine-B salt with the parenterally administrable oil and, where present, the surfactant.
9. A method of treating an iron-overload disease, aluminium overload, Alzheimer's disease, malaria, reperfusion injury or cancer which comprises parenterally injecting a composition according to any of claims 1 to 8 into a warm-blooded mammal in need of such treatment.



10. A crystal modification of desferrioxamine-1-decanesulphonate (N-[5-{3-[(5-aminopentyl)-hydroxycarbamoyl]-propionamido}-pentyl]-3-[[5-(N-hydroxyacetamidopentyl)-carbamoyl]-propionohydroxamic acid-1-decanesulphonate) of formula I



which in Differential Scanning Calorimetry has a melting point range of 154°C to 158°C inclusive, at a heating rate of 10°C/min under nitrogen and possesses the following characteristic diffraction lines (2θ in angular degrees ± 0.1°) in its X-ray pattern: 3.1°, 7.3°, 9.4°, 13.7° and 23.7°.

11. A crystal modification according to claim 10, which possesses the following characteristic diffraction lines (2θ in angular degrees ± 0.1°) in its X-ray pattern: 3.1°, 4.2°, 7.3°, 8.4°, 9.4°, 10.5°, 13.7°, 16.8°, 17.4°, 18.0°, 18.4°, 19.6°, 20.1°, 20.9°, 22.3°, 23.7°, 25.1° and 25.6°.

12. Process for the production of the crystal modification according to claim 10 or 11, characterised in that in at least one process step, a suspension of desferrioxamine-1-decanesulphonate of unknown or unspecified morphological composition in a polar solvent is maintained at elevated temperature; or that in at least one process step, a concentrated solution of desferrioxamine-1-decanesulphonate in a polar solvent is prepared at elevated temperature and then crystallised at a cooling rate of 2°C or less per minute.

13. Process according to claim 12, characterised in that the polar solvent is lower alcohol, water or a mixture of water and lower alcohol, and that the elevated temperature lies between room temperature and boiling point of the polar solvent.

14. Process according to claim 13, characterised in that at least one seeding crystal is added.



15. Process according to claim 14, characterised in that a solution of desferrioxamine methane sulphonate in a polar solvent is prepared, heated to the desired elevated temperature, then one part of an equimolar quantity of a 1-decanesulphonic acid salt in solution in the same and/or other polar solvent is added, at least one seeding crystal is added, maintained until the commencement of crystallisation, then the remainder of the equimolar quantity of the 1-decanesulphonic acid salt in solution in the same and/or other polar solvent is slowly added, and then maintained at the desired elevated temperature; or a hot-saturated solution of desferrioxamine-1-decanesulphonate in a polar solvent is produced at an elevated temperature, then after adding at least one seeding crystal it is cooled at a rate of 1°C/minute or less to a lower elevated temperature, during which time crystallisation takes place, and the crystal suspension is maintained at this lower temperature.

16. A pharmaceutical preparations comprising as active ingredient crystal modification A₂ of desferrioxamine-1-decanesulphonate according to any one of claims 12 and 13 and a pharmaceutically acceptable carrier.

17. The use of crystal modification A₂ of desferrioxamine-1-decanesulphonate according to any one of claims 12 and 13 for the preparation of a pharmaceutical preparation for the treatment of a disease selected from the group comprising iron-overload disease, aluminium overload, Alzheimer's disease, malaria, reperfusion injury and cancer.

18. A method of treatment of a disease selected from the group comprising iron-overload disease, aluminium overload, Alzheimer's disease, malaria, reperfusion injury and cancer, which comprises administering to a patient in need of such treatment a dosis of crystal modification A₂ of desferrioxamine-1-decanesulphonate according to any one of claims 12 and 13 that is pharmaceutically effective in the treatment of said disease.