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(54) Title: IRON DEXTRAN FORMULATIONS

(57) Abstract

Ferric oxyhydroxide-dextran compositions for treating iron deficiency having ellipsoidal particles with a preferred molecular weight range of about 250,000 to 300,000 daltons.

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IRON DEXTRAN FORMULATIONS

Field of the Invention

The present invention relates to improved iron dextran formulations for the treatment of iron deficiency, and to methods for preparing such formulations.

Background of the Invention

The intravenous or intramuscular injection of sterile solutions of an iron dextran complex is clinically indicated for the treatment of patients with documented iron deficiency in whom oral administration is unsatisfactory or impossible.

Iron dextran is absorbed from the injection site after intramuscular injection, for example, into the capillaries and the lymphatic system. Circulating iron dextran is cleared from the plasma by cells of the reticuloendothelial system, which split the complex into its components of iron and dextran. IMFERON®, for example, a product previously marketed by Fisons Pharmaceuticals, is released to the blood after uptake by the phagocytic activity of macrophages. See Henderson, *et al.*, *Blood* 34:357-375 (1969). The iron immediately is bound to available protein moieties to form hemosiderin or ferritin, the physiological forms of iron or, to a lesser extent, to transferrin. This iron, which is subject to physiological control, replenishes the iron component of hemoglobin and other depleted iron stores.

The major benefit of the clinical use of iron dextran is that, due to its large molecular weight (*i.e.*, greater than 70,000 daltons), the iron dextran complex is not excreted by the kidneys. Therefore almost the entire dose of iron dextran remains bioavailable as the iron dextran is metabolized in the liver. The major portion of an intramuscular injection of iron dextran is absorbed within 72 hours. Most of the remaining iron is absorbed over the ensuing 3 to 4 weeks.

Iron dextran for parenteral administration currently is marketed by Steris Pharmaceuticals, Inc. under the brand name INFeD®. As formulated, this product is a dark brown and slightly viscous sterile liquid complex of ferric oxyhydroxide, beta-FeO(OH), and is a low molecular weight dextran derivative in approximately 0.9% weight per volume sodium chloride for intravenous or intramuscular use. It contains the equivalent of 50 mg of elemental iron (as an iron dextran complex) per ml. Sodium chloride may be added for tonicity. The pH of the solution is between 5.2 and 6.5.

Under electron microscopy, IMFERON® has been shown to have an inner electron-dense FeO(OH) core with a diameter of approximately 3 nm and an outer moldable plastic dextran shell with a diameter of approximately 13 nm. Almost all of the iron, about 98-99% is present as a stable ferric-dextran complex. The remaining iron represents a very weak ferrous complex.

The dextran component of conventional iron dextran products is a polyglucose that either is metabolized or excreted. Negligible amounts of iron are lost via the urinary or alimentary pathways after administration of iron dextran. Staining from inadvertent deposition of iron dextran in subcutaneous and cutaneous tissues usually resolves or fades within several weeks or months. Various studies have reported that the half life of iron dextran in iron deficient subjects ranges from 5 to more than 20 hours. Notably, these half-life values do not represent clearance of iron from the body because iron is not readily eliminated from the body. See, for example, the package inserts for IMFERON® and INFeD®, or Hamstra, *et al.* *JAMA* 243:1726-1731 (1980).

U.S. Patent No. 2,820,740 and its reissue RE 24,642 to London *et al.* describe colloidal injectable iron preparations suitable for parenteral injection formed of a nonionic ferric hydroxide, partially depolymerized dextran complex. Current commercial iron dextran products, based on these two prior patents do not have sufficient purity (see Figs. 1 and 2) and needed thermal

stability (see Figs. 3 and 4) to safeguard safety and sterility concerns. Also, these commercial products have a relatively short plasma residence time which could cause a potential risk of iron overload in specific organs. See, Carthew, R. E., *et al. Hepatology* 13(3):534-538 (1991); Pitts, T. O., *et al. Nephron* 22:316 (1978); Weintraub, L. R., *et al. Brit. J. Hematology* 59:321 (1985); and Fletcher, L. M., *et al., Gastroenterology* 97:1011 (1989).

Similarly, U.S. Patent No. 2,885,393 to Herb also discloses iron dextran complexes. The most suitable range in molecular weight of the partially depolymerized dextran for injection was found to be 30,000 to 80,000 daltons or lower. A subsequent patent to Herb, U.S. Patent No. 4,180,567, discloses other iron preparations and methods for making and administering such preparations; however, the method disclosed does not teach the heating of iron dextran complexes above 100°C.

Other methods for the production of iron dextran complexes have been described, for example, in U.S. Patent No. 4,599,045 to Muller *et al.* regarding iron (III) hydroxy/dextran complexes that are produced using an alkali carbonate, ammonium carbonate or a carbonate of an organic base added to an acid solution containing a partially depolymerized dextran and an iron (III) salt. Thereafter, an alkali metal hydroxide or ammonium hydroxide is added. The suspension so formed is then converted into a solution by heating, and the solution worked up in a known manner.

Alternatively, ferric chloride and dextran can be reacted in aqueous solution in the presence of citric acid as disclosed in U.S. Patent No. 3,697,502 or by treating reactive trivalent iron with a complex-forming agent consisting of sorbitol, gluconic acid and certain oligosaccharides, in particular proportions and amounts as taught in U.S. Patent No. 3,686,397.

U.S. Patent No. 4,749,695 and its divisional, U.S. Patent No. 4,927,756, both to Schwengers, disclose a

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