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(54) **METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON**

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(51) **Int. Cl.**

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| ***A61K 31/7016*** | (2006.01) |
| ***A61K 31/715*** | (2006.01) |
| ***A61K 31/721*** | (2006.01) |
| ***C07H 23/00*** | (2006.01) |

(52) **U.S. Cl.**

CPC ..... ***C07H 23/00*** (2013.01); ***A61K 31/715*** (2013.01); ***A61K 31/721*** (2013.01)

USPC ..... **514/502**; 514/53; 514/54; 514/58; 514/59

(58) **Field of Classification Search**

USPC ..... 514/53, 54, 58, 59, 502

See application file for complete search history.

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(57) **ABSTRACT**

The present invention generally relates to treatment of iron-related conditions with iron carbohydrate complexes. One aspect of the invention is a method of treatment of iron-related conditions with a single unit dosage of at least about 0.6 grams of elemental iron via an iron carbohydrate complex. The method generally employs iron carbohydrate complexes with nearly neutral pH, physiological osmolarity, and stable and non-immunogenic carbohydrate components so as to rapidly administer high single unit doses of iron intravenously to patients in need thereof.

**20 Claims, 2 Drawing Sheets**

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FIGURE 1

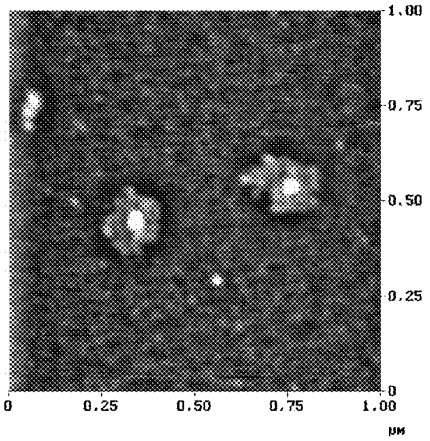



FIG. 1B

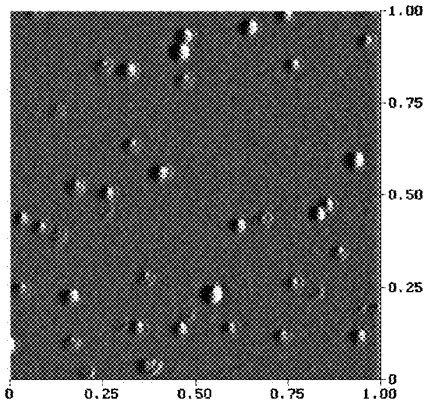



FIG. 1A

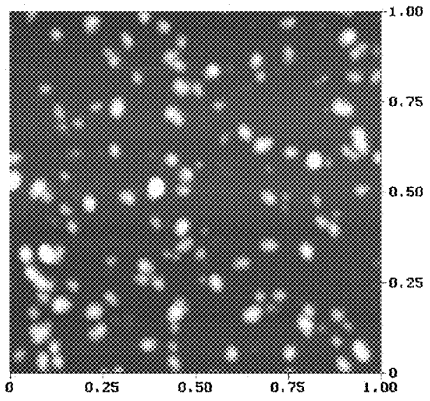
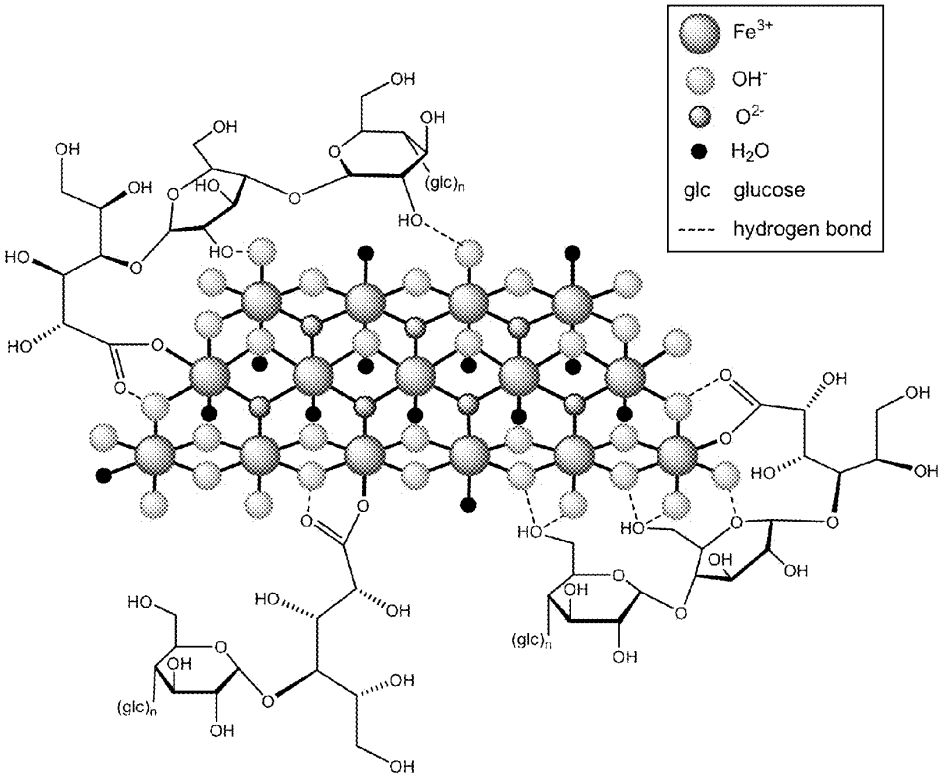



FIG. 1C

FIGURE 2



# METHODS AND COMPOSITIONS FOR ADMINISTRATION OF IRON

## CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a Continuation Application that claims priority to U.S. Non-Provisional application Ser. No. 13/847,254, filed 19 Mar. 2013; U.S. Non-Provisional application Ser. No. 12/787,283, filed 25 May 2010, issued as U.S. Pat. No. 8,431,549 on 30 Apr. 2013: and U.S. Non-Provisional application Ser. No. 11/620,986, filed 8 Jan. 2007, issued as U.S. Pat. No. 7,754,702 on 13 Jul. 2010, both of which claim priority to U.S. Provisional Application Ser. No. 60/757,119, filed 6 Jan. 2006, each of which is incorporated herein by reference in their entireties.

## FIELD OF THE INVENTION

The present invention generally relates to treatment of iron-related conditions with iron carbohydrate complexes.

## BACKGROUND

Parenteral iron therapy is known to be effective in a variety of diseases and conditions including, but not limited to, severe iron deficiency, iron deficiency anemia, problems of intestinal iron absorption, intestinal iron intolerance, cases where regular intake of an oral iron preparation is not guaranteed, iron deficiency where there is no response to oral therapy (e.g., dialysis patients), and situations where iron stores are scarcely or not at all formed but would be important for further therapy (e.g., in combination with erythropoietin). Geisser et al., Arzneimittelforschung (1992) 42(12), 1439-1452. There exist various commercially available parenteral iron formulations. But many currently available parenteral iron drugs, while purportedly effective at repleting iron stores, have health risks and dosage limitations associated with their use.

Currently available parenteral iron formulations approved for use in the U.S. include iron dextran (e.g., InFed, Dexferrum), sodium ferric gluconate complex in sucrose (Ferrlecit), and iron sucrose (Venofer). Although serious and life-threatening reactions occur most frequently with iron dextran, they are also known to occur with other parenteral iron products. In addition, non-life threatening reactions such as arthralgia, back pain, hypotension, fever, myalgia, pruritus, vertigo, and vomiting also occur. These reactions, while not life-threatening, often preclude further dosing and therefore iron repletion.

Iron dextran, the first parenteral iron product available in the United States (US), has been associated with an incidence of anaphylactoid-type reactions (i.e., dyspnea, wheezing, chest pain, hypotension, urticaria, angioedema). See generally Fishbane, Am J Kidney Dis (2003) 41(5 Suppl), 18-26: Landry et al. (2005) Am J Nephrol 25, 400-410, 407. This high incidence of anaphylactoid reactions is believed to be caused by the formation of antibodies to the dextran moiety. Other parenteral iron products (e.g., iron sucrose and iron gluconate) do not contain the dextran moiety, and the incidence of anaphylaxis with these products is markedly lower. Fishbane, Am J Kidney Dis (2003) 41(5 Suppl), 18-26: Geisser et al., Arzneimittelforschung (1992) 42(12), 1439-52. However, the physical characteristics of, for example, iron gluconate and iron sucrose lead to dosage and administration rate limitations. Negative characteristics include high pH, high osmolarity, low dosage limits (e.g., maximum 500 mg iron once per week, not exceeding 7 mg iron/kg body weight), and the long duration of administration (e.g., 100 mg iron over at least 5 minutes as an injection; 500 mg iron over at least 3.5 hours as a drip infusion). Furthermore, injectable high molecular mass substances produce more allergic reactions than the corresponding low molecular mass substances. Geisser et al. (1992) *Arzneimittelforschung* 42: 1439-1452.



Ferumoxytol is a newer parenteral iron formulation but limited information is available as to its efficacy and administration. See e.g., Landry et al. (2005) Am J Nephrol 25, 400-410, 408: and Spinowitz et al. (2005) Kidney Intl 68, 1801-1807: U.S. Pat. No. 6,599,498.

Various pharmacokinetic studies suggest that doses of iron complexes higher than 200 mg of iron are generally unsuitable and that the conventional therapy model prescribes repeated applications of lower doses over several days. See Geisser et al., (1992) *Arzneimittelforschung* 42: 1439-1452. For example, to achieve iron repletion under current therapy models, a total dose of 1 g typically requires 5 to 10 sessions over an extended period of time. These delivery modes incur significant expense for supplies such as tubing and infusate, costly nursing time, multiple administrations, and patient inconvenience.

## SUMMARY OF THE INVENTION

Among the various aspects of the present invention is the provision of a method of treatment of iron-associated diseases, disorders, or conditions with iron formulations. Briefly, therefore, the present invention is directed to use of iron carbohydrate complexes that can be administered parenterally at relatively high single unit dosages, thereby providing a safe and efficient means for delivery of a total dose of iron in fewer sessions over the course of therapeutic treatment.

The present teachings include methods of treating a disease, disorder, or condition characterized by iron deficiency or dysfunctional iron metabolism through the administration of at least 0.6 grams of elemental iron via a single unit dosage of an iron carbohydrate complex to a subject that is in need of such therapy.

In various embodiments, the method treats anemia. In some embodiments, the anemia is an iron deficiency anemia, such as that associated with chronic blood loss; acute blood loss; pregnancy; childbirth; childhood development; psychomotor and cognitive development in children; breath holding spells; heavy uterine bleeding; menstruation; chronic recurrent hemoptysis; idiopathic pulmonary siderosis; chronic internal bleeding; gastrointestinal bleeding; parasitic infections; chronic kidney disease; dialysis; surgery or acute trauma; and chronic ingestion of alcohol, chronic ingestion of salicylates, chronic ingestion of steroids; chronic ingestion of non-steroidal anti-inflammatory agents, or chronic ingestion of erythropoiesis stimulating agents. In some aspects, the anemia is anemia of chronic disease, such as rheumatoid arthritis; cancer; Hodgkins leukemia; non-Hodgkins leukemia; cancer chemotherapy; inflammatory bowel disease; ulcerative colitis thyroiditis; hepatitis; systemic lupus erythematosus; polymyalgia rheumatica; scleroderma; mixed connective tissue disease; Sojgren's syndrome; congestive heart failure/cardiomyopathy; or idiopathic geriatric anemia. In some embodiments, the anemia is due to impaired iron absorption or poor nutrition, such as anemia associated with Crohn's Disease; gastric surgery; ingestion of drug products that inhibit iron absorption; and chronic use of calcium. In

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