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Date: May 27, 2015

To whom it may concern:

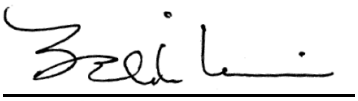
This is to certify that the attached translation from German into English is an accurate representation of the documents received by this office.

The documents are designated as:

- WO2004037865

Belinda Lai attests to the following:

"To the best of my knowledge, the aforementioned documents are a true, full and accurate translation of the specified documents."



Signature of Belinda Lai

Abstract

Disclosed is a water-soluble iron-carbohydrate complex obtained from an aqueous iron(III)-salt solution and an aqueous solution of the product obtained by oxidizing one or several maltodextrins with an aqueous hypochlorite solution at an alkaline pH value. The dextrose equivalent of the maltodextrin ranges from 5 to 20 if a single maltodextrin is used while the dextrose equivalent of the mixture of several maltodextrins ranges from 5 to 20 and the dextrose equivalent of each individual maltodextrin contained in the mixture ranges from 2 to 40 if a mixture of several maltodextrins is used. Also disclosed are a method for the production of said complex and medicaments for the treatment and prophylaxis of iron deficiencies.

Water-soluble iron-carbohydrate complexes, their production, and medications containing them

The object of the present invention is water-soluble iron-carbohydrate complexes, which are suitable for therapy of iron-deficiency anemia, as well as their production, medications containing them, and their use in the prophylaxis or therapy of iron deficiency anemia. The medications are particularly suitable for parenteral use.

Anemia caused by iron deficiency can be treated or prevented by administration of medications containing iron. For this purpose, the use of iron-carbohydrate complexes is known. A preparation frequently successfully used in practice is based on a water-soluble iron (III) hydroxide saccharose complex (Danielson, Salmonson, Derendorf, Geisser, Drug Res., Vol. 46: 615 – 621, 1996). In the state of the art, iron-dextran complexes as well as complexes on the basis of pullulans (WO 02/46241), which are difficult to access and must be produced under pressure at high temperatures and with the inclusion of hydrogenation steps, are described. Other iron-carbohydrate complexes for oral administration are common.

The present invention has set itself the task of making available an iron preparation, which can preferably be administered parenterally, and can be sterilized in comparatively simple manner; this is because the previous preparations that can be administered parenterally, based on saccharose or dextran, were stable only at temperatures up to 100°C, making sterilization difficult. Furthermore, the preparation to be made available according to the invention is supposed to demonstrate reduced toxicity and to prevent the dangerous anaphylactic shocks that can be induced by dextran. Also, the preparation to be made available is supposed to demonstrate great complex stability, so that a large application dose or a high application speed is made

possible. Also, it is supposed to be possible to produce the iron preparation from starting products that are easy to obtain, without special effort.

It has been shown that this task is accomplished by means of iron (III) carbohydrate complexes on the basis on the oxidation products of maltodextrins. Therefore water-soluble iron-carbohydrate complexes that can be obtained from an aqueous iron (III) salt solution and an aqueous solution of the product of oxidation of one or more maltodextrins with an aqueous hypochlorite solution at an alkaline pH of 8 to 12, for example, form an object of the invention, wherein when using one maltodextrin, its dextrose equivalent ranges from 5 to 20, and when using a mixture of several maltodextrins, the dextrose equivalent of the mixture ranges from 5 to 20 and the dextrose equivalent of the individual maltodextrins contained in the mixture ranges from 2 to 40.

A further object of the invention is formed by a method for the production of the iron-carbohydrate complexes according to the invention, in which one or more maltodextrins are oxidized in an aqueous solution, at an alkaline pH of 8 to 12, for example, using an aqueous hypochlorite solution, and the solution obtained is reacted with the aqueous solution of an iron (III) salt, wherein when using one maltodextrin, its dextrose equivalent ranges from 5 to 20, and when using a mixture of several maltodextrins, the dextrose equivalent of the mixture ranges from 5 to 20 and the dextrose equivalent of the individual maltodextrins contained in the mixture ranges from 2 to 40.

The maltodextrins that can be used are easily accessible starting products that are commercially available.

For the production of the ligands of the complexes according to the invention, the maltodextrins are oxidized in aqueous solution, with hypochlorite solution.

Suitable solutions are, for example, solutions of alkaline hypochlorites, such as sodium hypochlorite solution. The concentrations of the hypochlorite solutions are, for example, at least 13 wt.-%, preferably on the order of 13 to 16 wt.-%, calculated as active chlorine, in each instance. The solutions are preferably used in such an amount that about 80 to 100%, preferably about 90% of an aldehyde group are oxidized per maltodextrin molecule. In this manner, the reduction capacity caused by the glucose component of the maltodextrin molecules is reduced to about 20% or less, preferably 10% or less.

Oxidation takes place in an alkaline solution, for example at a pH of 8 to 12, e.g. 9 to 11. For oxidation, it is possible to work at temperatures on the order of 15 to 40°C, preferably 25 to 35°C, for example. The reaction times are on the order of 10 minutes to 4 hours, e.g. 1 to 1.5 hours, for example.

By means of the method of procedure described, the degree of polymerization of the maltodextrins used is kept at a minimum. Without stating a binding theory, it is assumed that oxidation primarily takes place at the end-position aldehyde group (or acetal or hemiacetal group) of the maltodextrin molecules.

It is also possible to catalyze the oxidation reaction of the maltodextrins. The addition of bromide ions, for example in the form of alkali bromides, for example sodium bromide, is suitable for this purpose. The amount of bromide added is not critical. It is kept as low as possible, in order to obtain an end product (Fe complex) that can be purified as easily as possible. Catalytic amounts are sufficient. As has been mentioned, the addition of bromide is possible but not necessary.

Furthermore, it is also possible, for example, to use the known ternary oxidation system hypochlorite/alkali bromide/2,2,6,6-tetramethyl piperidine-1-oxyl (TEMPO) for oxidation of the maltodextrins. The method of procedure for oxidizing maltodextrins with catalysis by alkali bromides or with the ternary

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