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(54) PROCESS FOR THE MANUFACTURE OF IRON-POLYISOMALTOSE COMPLEX FOR THERAPEUTICAL PURPOSES

(57) Abstract:

This invention relates to a process for the preparation of iron-polyisomaltose complexes suitable for parenteral injection.

It is known that a colloidal iron dextran complex can be prepared by dissolving, with heating if necessary, a suitable water-soluble dextran of a particular intrinsic viscosity, i.e. a dextran (polyisomaltose) having a molecular weight within a particular range, in a solution or suspension of an iron salt, adding an excess of alkali, or by dissolving the dextran in an alkali and then adding the iron compound in solution or suspension. The partly depolymerized dextran used in the manufacture of these iron dextran complexes is obtained by hydrolyzing crude dextran in the usual manner, for example with dilute mineral acid, and precipitating and isolating from the aqueous solution, the desired dextran residue with the help of water-miscible organic liquids, such as alcohols or ketones. Residues of this nature with intrinsic viscosities of 0.025 to 0.25 at 25°C. have been described as useful starting material. (See Canadian Patent 556,877, London et al, May 6, 1958, the disclosure of which is hereby incorporated into the present application by reference.)

In contrast to ~~the~~ this two-stage process in which dextran of a particular intrinsic viscosity must be employed, the present invention makes it possible to use crude dextran of any particle size, preferably one having an intrinsic viscosity of between 0.25 to 0.75 at 25°C.

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This is done according to the process of the present invention in a single stage by heating the solution or suspension of the crude dextran together with an acidic solution of a ferric (iron III) salt until the intrinsic viscosity at 25°C. is at the most 0.1, and subsequently treating the mixture with an alkali and then isolating and purifying the resulting ferric complex by known means.

In a preferred procedure according to the invention there can be added to the acid-reacting solution of the iron salt to inhibit hydrolysis, an acid with the same anion. It is also of advantage to make the solution of the iron-polyisomaltose complex isotonic by dialysis against water or by ion exchange. For the preparation of a solid iron-polyisomaltose complex according to preferred aspects of the invention, the solution of the iron-polyisomaltose is concentrated in vacuum, or the complex precipitated, isolated and dried by the addition of a suitable water-miscible solvent. The alkaline solution of the iron-polyisomaltose complex can be neutralized before purification and isolation by addition of a solid, liquid or gaseous acid, for example, an ion-exchanger, sulfuric acid or hydrochloric acid.

The preparation of the iron-polyisomaltose complex according to the invention does away with the time-consuming, technically difficult, and low-yield preparation of exactly defined, low polymer homologs of dextran for use as starting material. It makes possible the preparation in a single-stage of iron-polyisomaltose complexes suitable for therapeutic application from higher molecular weight

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dextrans or their homologous polymers. In contrast to the usual two-stage process, the one-stage process of the invention provides an iron-polyisomaltose complex which is more heterogenous in particle size, but surprisingly of lower toxicity, better pharmacological properties, compatible and of higher therapeutic efficacy than the iron-dextran complexes hitherto known.

A preparation made according to the invention provided the following results in an acute toxicity test on rabbits. At a dose of 690 mg Fe/kg intramuscular, all animals survived. With the same dose and the same method of application of a commercial preparation, two-thirds of the animals died within eight weeks. Intramuscular application into young pigs a few days after birth, of prior preparations of iron-dextran in a dosage of 100 mg Fe/animal, caused either the death of all animals (H. Behrens, Mh. Veterinärmed. 12.422, 1957), or led after four weeks to a medium gain in weight of only +0.81 kg compared with the controls (M.I.Swenson et al., J. Am.Vet. Med. Assoc. 131, 146, 1957). On the other hand, the iron-polyisomaltose of the invention led with the same arrangement of tests to an average gain in weight of + 2.55 kg.

The"iron-polyisomaltose" of the invention is a complex compound consisting of iron hydroxide and polyisomaltose, a polyhexosan. In analogy to the nomenclature in Chemical Abstracts (e.g. polyhexosan ⟶ glucosan ⟶ dextran ⟶ polyisomaltose) the compound could be designated "polyisomaltose iron (III) hydroxide". While "polyisomaltose" is a term used loosely for "dextran", the latter is a compound of very high molecular weight, whereas

polyisomaltose is a degradation product of dextran. Moreover the polyisomaltose in the applicants' complex lacks the disadvantages of certain clinical dextrans.

The process according to the invention is explained in more detail by the following examples:

EXAMPLE I

50 g dextran (intrinsic viscosity 0.34) were dissolved in water to make 420 cm^3. 80 cm^3 of 30% by weight $FeCl_3.6\ H_2O$ were added, and the solution, being 0.206 molar-solution in regard to $FeCl_3$, was boiled with reflux until the relative viscosity of a reaction solution, diluted to 2% dextran, was 1.095 - 1.105. The acidic turbid liquid was cooled, poured while stirring to 50 cm^3 of 15-N caustic soda, heated for 20 minutes in a boiling water bath, whereupon the cooled reaction mixture was separated from undissolved particles by centrifuging. The alkaline solution was neutralized with hydrochloric acid, precipitated with isopropanol in the proportion of 1.1 parts aqueous solution + 1.5 parts alcohol, and the mixture stored for 20 minutes in the refrigerator. The supernatant solution was decanted, the iron complex deposit dissolved in water to make the original volume of the neutralized solution and the precipitation repeated with isopropanol in the proportion of 1.1 parts solution + 1.3 parts alcohol. The deposit was dried in vacuo after decanting, or ground in a mortar with isopropanol, drawn off by suction, washed with a little ether, and dried in vacuo. The substance was made into an aqueous, sterile, blood-isotonic solution containing 5% trivalent iron.

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