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सत्यमेव जयते

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THE PATENT OFFICE

पेटेंट प्रमाणपत्र
PATENT CERTIFICATE

(Rule 74 Of The Patents Rules)

पेटेंट सं. / Patent No.	:	370845
आवेदन सं. / Application No.	:	201731011640
फाइल करने की तारीख / Date of Filing	:	31/03/2017
पेटेंटी / Patentee	:	WEST BENGAL CHEMICAL INDUSTRIES LIMITED

प्रमाणित किया जाता है कि पेटेंटी को उपरोक्त आवेदन में यथाप्रकटित IMPROVED PROCESS FOR PREPARATION OF FERRIC CARBOXYMALTOSE नामक आविष्कार के लिए, पेटेंट अधिनियम, १९७० के उपबंधों के अनुसार आज तारीख 31st day of March 2017 से बीस वर्ष की अवधि के लिए पेटेंट अनुदत्त किया गया है।

It is hereby certified that a patent has been granted to the patentee for an invention entitled IMPROVED PROCESS FOR PREPARATION OF FERRIC CARBOXYMALTOSE as disclosed in the above mentioned application for the term of 20 years from the 31st day of March 2017 in accordance with the provisions of the Patents Act,1970.

एकस्य कार्यालय THE PATENT OFFICE GOVT.OF INDIA भारत सरकार

अनुदान की तारीख :
Date of Grant : 30/06/2021

पेटेंट नियंत्रक
Controller of Patent

टिप्पणी - इस पेटेंट के नवीकरण के लिए फीस, यदि इसे बनाए रखा जाना है, **31st day of March 2019** को और उसके पश्चात प्रत्येक वर्ष मे उसी दिन देय होगी।

Note. - The fees for renewal of this patent, if it is to be maintained will fall / has fallen due on 31st day of March 2019 and on the same day in every year thereafter.

381772

Indian Patent

Patent Number: 381772
Date of Patent: 12 Nov, 2021

Improve and cost-effective process for preparation Iron - Isomaltoside

Inventor: Niladri Samanta

Assignee: **West Bengal Chemical Industries Limited**

Application: **201731010769**

Filed: **27 March, 2017**

ABSTRACT:

Disclosed herein is improved, cost effective process for preparation of water-soluble Iron isomaltoside complex which is stable, has reduced toxicity useful in the treatment of iron deficiency anaemia.

4 Claims, No Drawings

Claims

1. A simple and cost-effective process for preparation of stable iron isomaltoside with reduced toxicity characterized in that:
   i. adding portion wise sodium borohydride to dextran 5 solution in a ventilated reactor maintaining the temperature below 5°C to obtain reduced dextran, until the concentration of unreduced dextran in the solution is between 0.05 to 0.1%;
   ii. adding reduced dextran to the precipitated aqueous ferric hydroxide followed by addition of citric acid to form citrate iron-isomaltoside complex;
   iii. heating the complex, cooling and adjusting the pH in the range of 7.0-8.0 using ammonia; and
   iv. filtering, drying the filtrate in a spray dryer to obtain the product.
2. The process as claimed in claim 1, wherein the ration of sodium borohydride to dextran 5 is in the range of 0.010 to 0.25:1.
3. The process as claimed in claim 2, wherein the ratio of sodium borohydride to dextran 5 is 0.019:1.
4. The process as claimed in claim 1, wherein the concentration of sodium borohydride is in the range of 0.3 to 0.7 mg/ml.

TITLE OF THE INVENTION:

"IMPROVED AND COST-EFFECTIVE PROCESS FOR PREPARING IRON- ISOMALTOSIDE"

APPLICANT:

NAME: WEST BENGAL CHEMICAL INDUSTRIES LIMITED

NATIONALITY: An Indian Company incorporated under the Companies Act, 1956

ADDRESS: 145/1, Jessore Road, Kolkata 700 089, India.

PREAMBLE TO THE DESCRIPTION:

The following specification describes the invention and the manner in which it is to be performed.

TITLE OF THE INVENTION:

The present invention relates to improved and cost-effective process for preparation of water-soluble Iron isomaltoside which is stable, has reduced toxicity useful in the treatment of iron deficiency anaemia.

BACKGROUND OF THE INVENTION:

Patients with iron deficiency are given iron supplementation both to correct anaemia and to replenish the body stores. Significant proportions of patients are found to benefit by supplementing iron intravenously (IV). There are different IV iron compounds available in the markets which are delivered to patients in a single administration for treatment of anaemia.

The new generation IV iron compound, Iron isomaltoside was developed and manufactured by Pharmacosmos in Denmark and was introduced in Europe in 2010. Iron isomaltoside offers high dosing flexibility with optimized administration convenience. It is a helical inclusion complex with molecular formula Few([C6H10O5]aC6H11O7)x(OH)yOz•nH2O in which individual D-glucose units are linked predominantly by α-1,6 Glycoside linkages forming a Dextran moiety [C6H10O5]a. These Dextran units, in turn, self-repeat themselves in a polymeric chain forming Iron Isomaltoside.It is a non-branched, non-anaphylactic carbohydrate [W. Richter, Hapten inhibition of passive antidextran dextran anaphylaxis in guinea pigs. Role of molecular size in anaphylactogenicity and precipitability of dextran fractions, International Archives of Allergy and Immunology 41(1971) 826–844; K.-G. Ljungström, invited commentary: pretreatment with dextran 1 makes dextran 40 therapy safer, Journal of Vascular Surgery 43 (2006) 1070–1072], structurally different from branched polysaccharides used in iron dextran (Cosmofer).

Iron isomaltoside is marketed under the brand name Monofer® and is disclosed in EP0726272. Iron isomaltoside (IIM) contains a polynuclear Fe(III) oxyhydroxide core which is stabilized by a hydrogenated (reduced) Dextran 1000 (isomaltoside 1000) and a low amount of citrate (Andreasen and Christensen 2001; Medice PharmaGmbH&Co.KG, Iserlohn,Germany 2011;Nordfjeld et al. 2012; Pharmacosmos A/S, Holbaek, Denmark2009).

Synthesis of iron-carbohydrate complexes are known and described in the art. The major challenges during the synthesis are the physical-chemical stability of trivalent iron ions/salts and the use of low molecular weights of the saccharides/polysaccharides. The carbohydrate shell is unique for each preparation since the carbohydrate shell determines the metabolic pathway of the complexes, affecting their pharmacokinetics and pharmacodynamics, as well as their interaction with the innate immune system and, thus, side effects [Koskenkorva- Frank, T.S; et.al The complex interplay of iron metabolism, reactive oxygen and reactive nitrogen species: Insights into the potential of different iron therapies to induce oxidative and nitrosative stress. Free Radic. Biol. Med. 2013, 65, 1174– 1194]. Depending on the carbohydrate shell the preparations can be classified as (a) non-dextran based and (b) dextran/dextran based complexes.

An article titled 'Preparation, Characterization, and Antioxidant Activity of an Isomaltooligosaccharide–Iron Complex (IIC)' by Kai Mao et.al published in Journal of Carbohydrate Chemistry, Volume 34, 2015 - Issue 7, Pages 430-443 disclose oligosaccharide–iron (III) complex prepared under the alkaline condition by mixing ferric chloride solution with isomaltooligosaccharide (IMO) solution.

US6977249 describes a process for producing an iron-dextran compound, in which the molecular weight of a dextran is reduced by hydrolysis, and functional aldehyde terminal groups are converted into alcohol groups by hydrogenation; said dextran as an aqueous solution is combined with at least one water-soluble ferric salt; base is added to the resulting solution to form ferric hydroxide, and the resulting mixture is heated to transform the ferric hydroxide into ferric oxyhydroxide as an association compound with the

dextran. The hydrogenation is only partial, leaving at the most 15% by weight reducing sugar, calculated on the total amount of carbon hydrates, and said dextran before being combined with the ferric salt, and after being subjected to hydrogenation is subjected to an oxidation by means of sodium hypochlorite in basic aqueous solution, said hydrogenation and oxidation being performed to obtain dextran having substantially all aldehyde groups converted into alcohol and carboxylic groups, said so transformed dextran having no functional aldehyde groups or carboxylic acid groups in the intermediate glycosyl groups. The iron-dextran compound has the apparent peak molecular weight (Mp) is 50,000- 150,000 Da with iron content in the range of 15-45% by weight. The use of strong oxidizing agent such as sodium hypochlorite leads to formation of chlorinated by products and breakdown by products of dextran. These impurities are difficult to remove or require costly membrane filtrations using molecular weight cut off membranes.

US3549614 describes a method for manufacturing a mixed complex compound of ferric iron with hydrogenated dextran and citric acid or sodium citrate. The complex is obtained by mixing the precipitated moist ferric hydroxide with dry hydrogenated dextran having the reducing power between 0.02 and 3%, adding citric acid or sodium citrate to the mixture, making the mixture alkaline with an aqueous sodium hydroxide solution and heating with stirring until the product formed is completely soluble in water. US'614 directly uses hydrogenated dextran of reducing power between 0.02% and 3% with average molecular weight of 3000-10,000 Da to form iron-carbohydrate complex. This implies that the commercially used hydrogenated dextran would have to be purified before use, adding to the cost of manufacture. Moreover, the process disclosed in US'614 includes removal of hydroxide of an alkali metal using ion exchange resins. Thus, the process for preparation of iron- carbohydrate complex involves multiple purification steps thereby increasing the cost of manufacture of iron-carbohydrate complex which makes the process industrially non-feasible.

Even though the preparation of trivalent iron-carbohydrate complexes is described in the art, the need still exists to provide cost effective, simple and efficient synthetic method for preparation of trivalent iron-isomaltoside complex with desirable physical-chemical properties useful for treatment of anaemia. This remains the object of the invention.

The present invention provides an improvement over the prior art processes for manufacture of iron-isomaltoside with good stability and reduced toxicity, wherein, the reaction conditions are optimized to provide a process which is cost effective and industrially feasible.

SUMMARY OF THE INVENTION:

Accordingly, the present invention provides a simple and cost-effective process for preparation of iron-isomaltoside complex with high iron content, good stability and reduced toxicity.

In an aspect, the process for synthesis of iron-isomaltoside complex comprises;

i. Adding portion wise sodium borohydride to dextran 5 solution in a ventilated reactor, maintaining the temperature below 5°C to obtain reduced dextran, wherein the concentration of unreduced dextran in the solution is between 0.05 to 0.1%;
ii. Adding reduced dextran to the precipitated aqueous ferric hydroxide followed by addition of citric acid to form citrate iron-isomaltoside complex;
iii. Heating the complex, cooling and adjusting the pH in the range of 7.0-8.0 using ammonia; and
iv. Filtering, drying the filtrate in a spray dryer to obtain the product.

The dextran is selected of molecular weight in the range of 300kda to 500kda, preferably of molecular weight 500kda (dextran-5). The ratio of sodium borohydride to dextran-5 is maintained in the range of 0.010 to 0.25: 1; preferably at 0.019:1.

In an aspect, the reduction process is performed at a controlled condition of residual reducing agent such as sodium borohydride in the reacting solution and at low temperature i.e. below 5o C. The 'in-situ' controlled reduction of dextran avoids the need for costly purification steps to obtain reduced/hydrogenated dextran of molecular weight in the range of 900 to 1200 Da. Further, the low concentration of unreduced dextran in the solution during reduction process diminishes the chances of reduction of ferric ions to undesired ferrous ions, thereby reducing impurity formation.

In another aspect, the Ferric hydroxide obtained by alkaline hydrolysis of ferric chloride is made substantially free of chloride impurities before reacting with reduced dextran. Thus, the process of the present invention reduces the steps of further purification which decreases the cost of manufacturing the iron-isomaltoside of good quality.

DESCRIPTION OF THE INVENTION:

The present invention relates to a simple and cost effective process for preparation of Iron isomaltoside that offers high dosing flexibility with optimized administration convenience to treat patients with iron deficiency.

The present invention is an improvement over the prior art processes resulting in the preparation of iron isomaltoside of good quality with reduced cost of manufacture. The present invention uses organic oxidizing reagent such as citric acid which reduces or ameliorates the disadvantages of sodium hypochlorite used in the art. The present process employs optimal reaction conditions to reduce any undesirable by products due to which iron isomaltoside is obtained in good yield and purity with reduced manufacturing cost.

In a preferred embodiment, the present invention avoids the direct use of commercially available hydrogenated dextran. The commercially available Hydrogenated-Dextran has a molecular weight of 200 to 3000 Da. The process for preparing iron (III) – isomaltoside needs a narrow ”window” of between 900 to 1200 Da, implying that the commercial variety would have to first undergo a costly cleaning process by Membrane Filtration. The improved present process provides an ‘in situ’ reduction of dextran at a controlled condition of a residual reducing agent in the reacting solution.

In an embodiment, the process for preparation of iron-isomaltoside complex involves the preparation of Ferric hydroxide and reduced dextran.

(a) Preparation of Ferric hydroxide:

The salt of trivalent iron (38%w/w) was dissolved in water followed by addition of base (about 30%) and the mixture was stirred until pH of the solution was in the range of 4.0-5.0. The solution mixture was filtered; the precipitate of ferric hydroxide was washed with water to reduce the salt content and transferred to another reactor for further processing.

The trivalent iron salt is preferably selected from ferric chloride; the base is selected from alkali or alkaline metal carbonates such as sodium carbonate, potassium carbonate, calcium carbonate and the like; preferably sodium carbonate.

(b) Preparation of reduced dextran:

In an embodiment of the present process, it is imperative to inhibit the reduction of ferric to ferrous ion. The propensity of reduction of ferric to ferrous ion comes from the use of dextran. To inhibit the reduction of Ferric, the present invention provides a technique to hydrogenate dextran itself thus eliminating or diminishing its reducing property. Consequently, reduction of dextran was performed under ‘in- situ’ controlled condition of residual sodium borohydride in the reacting solution. The concentration of sodium borohydride was maintained between 0.3 to 0.7mg/ml; preferably at 0.5mg/ml and the temperature below 5°C. The reduction was carried using a ventilated reactor to exhaust the inflammable hydrogen gas produced during the reduction reaction. The process was continued until the unreduced dextran concentration in the solution was in the range of 0.05 to 0.1%.

The ratio of sodium borohydride to dextran-5 was maintained in the range of 0.010 to 0.25: 1; preferably at 0.019:1.

According to the reaction, Dextran of molecular weight in the range of 300kda to 500kda, preferably of molecular weight 500kda (dextran-5) was added to the solvent selected from lower alcohols in a well-ventilated glass reactor and cooled to 0°C. To the dextran solution was added portion wise reducing agent selected from alkali metal borohydride complexes such as lithium borohydride, sodium borohydride; preferably sodium borohydride maintaining the temperature below 5°C. The reduced dextran was filtered and washed.

(c) Formation of iron-isomaltoside complex:

The ferric hydroxide of step (a) was added to water with continuous stirring. Reduced dextran of step (b) was later added to the precipitate of ferric hydroxide and the solution was stirred for about 25-35 mins. This was followed by slow addition of citric acid or its salt and the mixture was stirred for about an hour. The iron-isomaltoside citric acid complex was heated and the temperature was maintained at 75°C-80°C for 6-7 hours. The reaction mass was cooled to temperature of about 40°C and the pH was adjusted in the range of 7.0-8.0 by addition of ammonia. The solution was filtered, excess ammonia was removed and the solution was transferred to the spray dryer for drying the reaction mass. The inlet temperature of the dryer was maintained at about 140°C and the outlet temperature at about 115°C to obtain brown red powder with iron content in the complex in the range of 25-30%w/w and molecular weight of the complex in the range of 50kDa to 150kDa. The product was readily soluble in water and was used for preparation of parenteral compositions.

In an embodiment, the citric acid induced oxidation of reduced dextran provides iron isomaltoside of high purity. Citric acid or its salt is used preferably in amount of 100-125% of the amount of hydrogenated dextran used in the reaction. The citrate complexes of ferric ion with hydrogenated dextran form an integral part of the helical inclusion complex exhibiting large capability to solubilize in water which can be used directly for preparation of fresh solutions.

The aqueous solution of iron-isomaltoside was suitably used for preparation of injections by adjusting the concentration of iron and by adding suitable amount of sodium chloride in order to make the solution isotonic. The solution thus prepared was filtered; the filtrate was placed in ampoules, vials and adequately sterilized.

The iron-isomaltoside content obtained by the process of the present invention is stable having iron content of 25-30%w/w with reduced toxicity. The iron-isomaltoside so obtained can be safely used for parenteral administration to the patients suffering from iron deficiency anaemia.

The invention is further illustrated by means of the following non-limiting examples.

Example 1: Preparation of iron-isomaltoside

(a) Preparation of Ferric hydroxide

Ferric chloride solution (315kg; 738 moles; 38%w/w) containing 0.13mg/ml of iron in 1ml was added to 450lt of water in a reactor. Sodium carbonate solution (146.5kg in 500lt water; 1382 moles; 30%) was added to the mixture under stirring until the pH was 4.0. The ferric hydroxide precipitate obtained was filtered and the precipitate was washed with water (500lt) several times until the washings were free from chlorides. The precipitate was filtered and transferred to another reactor for further processing.

(b) Preparation of Reduced dextran

Dextran 5 (25kg) was added to methanol (150lt) in ventilated glass reactor and the solution was cooled to 0°C. Sodium borohydride (0.488kg; 12.89 moles) was divided into 5 parts and each part was added to the dextran 5 solution gradually maintaining the temperature between 0oC- 5°C until the unreduced dextran concentration in the solution was between 0.05 to 0.1%. The reduced dextran was washed and taken for further reaction.

The Mol. wt of reduced dextran is 1200Da (average) with reducing capability of dextran of about 0.093%.

(c) Formation of iron isomaltoside complex

To the reactor containing water (500lt) ferric hydroxide (of step a) was added with continuous stirring. Reduced dextran (of step b) was added after 15 min addition of the precipitate ferric hydroxide and the mixture was stirred for 30 min. Solid citric acid (31.5kg) was added to the mixture slowly and the mixture was further stirred for 1 hr. The temperature of the mixture was raised to 75-80°C and maintained for 6-7 hours to obtain reaction mass which was completely soluble in water. The reaction mass was cooled to temperature of 40°C by an efficient cooling system. The pH was adjusted to 7.5 by adding ammonia. Excess of ammonia was removed and the solution was filtered and transferred to the spray dryer. The inlet temperature of the dryer was maintained at 140°C and the outlet temperature at 115°C to obtain red brown iron isomaltoside powder.

Yield: 94%; Purity: 97%; Iron content: 27.88%w/w; Mol. wt of the complex: 78kDa The 'in situ' controlled/ gradual reduction of the free aldehydic group of Dextran using sodium borohydride at concentration between 0.3 to 0.7mg/ml; preferably at 0.5mg/ml simultaneously reduces the tendency of conversion of ferric ions to undesired ferrous ion. The oxidation of reduced dextran using mild oxidizing agent such as citric acid in the present process avoids the formation of chlorinated by products (by using strong oxidizing agent such as sodium hypochlorite) which are difficult to remove or require costly purification processes. The use of optimum reaction conditions in the present process provides iron-isomaltoside complex of better quality over the prior art processes. The present process reduces the steps of purification thus reducing the cost of manufacture and can be directly adapted for commercial scale production of iron-isomaltoside. The as prepared iron isomaltoside can suitably be used in preparation of parenteral composition to administer to patients for treatment of iron deficiency with reduced or no side effects.

It will be understood that the above description is intended to be illustrative and not restrictive. The embodiments will be apparent to those in the art upon reviewing the above description. The scope of the invention should therefore, be determined not with reference to the above description but should instead be determined by the appended claims along with full scope of equivalents to which such claims are entitled.

Claims

1. A simple and cost-effective process for preparation of stable iron isomaltoside with reduced toxicity characterized in that:
   i. adding portion wise sodium borohydride to dextran 5 solution in a ventilated reactor maintaining the temperature below 5°C to obtain reduced dextran, until the concentration of unreduced dextran in the solution is between 0.05 to 0.1%;
   ii. adding reduced dextran to the precipitated aqueous ferric hydroxide followed by addition of citric acid to form citrate iron-isomaltoside complex;
   iii. heating the complex, cooling and adjusting the pH in the range of 7.0-8.0 using ammonia; and
   iv. filtering, drying the filtrate in a spray dryer to obtain the product.

2. The process as claimed in claim 1, wherein the ration of sodium borohydride to dextran 5 is in the range of 0.010 to 0.25:1.
3. The process as claimed in claim 2, wherein the ratio of sodium borohydride to dextran 5 is 0.019:1.
4. The process as claimed in claim 1, wherein the concentration of sodium borohydride is in the range of 0.3 to 0.7 mg/ml.

Improve and cost-effective process for preparation Iron - Isomaltoside

ABSTRACT

Disclosed herein is improved, cost effective process for preparation of water-soluble Iron isomaltoside complex which is stable, has reduced toxicity useful in the treatment of iron deficiency anaemia.