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सत्यमेव जयते

क्रमांक : 033116496
SL No :

भारत सरकार
GOVERNMENT OF INDIA
पेटेंट कार्यालय
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.

370845

Indian Patent

Patent Number: 370845
Date of Patent: 22 Jan, 2021

Improved process for preparation of Ferric Carboxymaltose

Inventor: **Niladri Samanta**

Assignee: **West Bengal Chemical Industries Limited**

Application: **201731011640**

Filed: **31st Mar, 2017**

ABSTRACT:

Disclosed herein is improved, cost effective process for preparation of water soluble Ferric Carboxymaltose with reduced impurity suitable for preparation of medicament without involving further purification. Particularly, the present invention discloses the process of manufacturing Ferric Carboxymaltose obtained by reaction of aqueous iron (III) salt and an aqueous solution of oxidation product of maltodextrin having dextrose equivalent 10-20 using citric acid as mild oxidizing and cross linking agent.

4 Claims, No Drawings

Claims

1. A simple, cost effective process for preparation of water soluble Ferric Carboxymaltose in good yield and purity comprising;
   i. Adding maltodextrin of dextrose equivalent in the range of 10-20 to the suspension of ferric hydroxide obtained from mixture of FeCl3 and NaOH wherein NaCl with sodium chloride level not more than 45ppm and the chloride content not more than 2.5%w/w;
   ii. Adding citric acid to the solution of step (i) in an amount of 0.4 to 1.2 equivalent of one aldehyde group per molecule of maltodextrin oxidized followed by heating to a temperature in the range of 75-80^{o}C;
   iii. Adjusting the pH in the range of 7.0-8.0 using ammonia;
   iv. Filtering and drying to obtain water soluble Ferric Carboxymaltose.

2. The process as claimed in claim 1, wherein the citric acid in step (ii) is used in amount of 0.72 equivalent of one aldehyde group per molecule of maltodextrin oxidized.

3. The process as claimed in claim 1, wherein the mean molecular weight of Ferric Carboxymaltose is 82,000 Da and the iron content is 34.55%.

4. A pharmaceutical composition for treatment of iron deficiency by Parental administration comprising more than 90% Ferric Carboxymaltose prepared by the process as claimed in claim 1 having molecular weight of 82 KDa with iron content 34.55% and less than 10% Ferric Carboxymaltose complex having molecular weight less than 10,000 Da.

TITLE OF THE INVENTION:

"IMPROVED PROCESS FOR PREPARATION OF FERRIC CARBOXYMALTOSE"

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.

FIELD OF THE INVENTION:

The present invention relates to improved, cost effective process for preparation of water soluble ferric carboxy maltose with reduced impurity suitable for preparation of medicament without involving further purification.

BACKGROUND OF THE INVENTION:

Ferric carboxymaltose is a stable, non-dextran iron complex consisting of ferric hydroxide core stabilized by a carbohydrate shell. Ferric carboxymaltose is commercially available in market under the brand name Ferinject® and is administered intravenously in single doses to treat iron deficiency anaemia.

US2006/0205691 discloses a process for water soluble iron-carbohydrate complexes comprising reacting aqueous solution of iron (III) salt and aqueous solution of one or more oxidation products of maltodextrin. The oxidation of maltodextrin is carried out using aqueous hypochlorite solution at a pH-value within the alkaline range. The drawback of the process is that it involves the use of large amount of toxic ferric chloride and sodium carbonate generating a large quantity of undesired sodium chloride and unacceptable impurities of sodium carbonate resulting in poor quality of iron (III)-carbohydrate complex.

US20120214986 discloses a process for preparation of iron (III) carboxymaltose complex wherein a mixture of one or more maltodextrins, ferric hydroxide and water are heated and the resulting iron maltodextrin complex is oxidized using aqueous sodium hypochlorite solution to yield iron (III) carboxymaltose.

WO2016151367 describes a process for preparation of iron (III) carboxymaltose complex which include reacting aqueous solution of iron (III) salt with aqueous solution of oxidation product of at least one maltodextrin. The oxidation of maltodextrin is carried out in presence of catalyst and phase transfer catalyst in alkaline medium.

The processes in the art require catalysts, phase transfer catalysts for performing oxidation of maltodextrin which add to the manufacturing cost. The use of sodium hypochlorite as the oxidizing agent lead to formation of undesired chlorinated by products. The processes in the art thus suffer from the drawbacks of formation of inorganic impurities such as metal bromides, chlorides and carbonates which impact the yield and purity of iron (III)-carboxymaltose.

The problem to be solved by the present invention is to reduce the impurity formation and provide ferric carboxymaltose which will be suitable for preparation of medicament without involving further purification. Also, the preparation to be provided by the present invention should provide ferric carboxymaltose which is stable, less toxic, avoids dangerous anaphylactic shocks that can be induced by dextran so as to enable a high applicable dosage of ferric carboxymaltose.

The present inventors were of the view that the drawbacks of the prior art processes can be resolved on the basis of oxidation products of maltodextrin using citric acid which functions both as mild oxidizing and cross-linking agent. Maltodextrin individually and independently polymerize using citric acid as cross-linkage agent under mild conditions and the resultant polymers obtained are hydrophilic, forming helical inclusion complexes thereby exhibiting larger capability to solubilize in water.

SUMMARY OF THE INVENTION:

In accordance with the above, the present invention provides simple, cost effective process for preparation of ferric carboxy maltose in good yield and purity comprising;

i. adding maltodextrin of dextrose equivalent in the range of 10-20 to the suspension of ferric hydroxide with sodium chloride level not more than 45ppm and the chloride content not more than 2.5%w/w;

ii. adding citric acid to the solution of step (i) in an amount of 0.4 to 1.2 equivalent of one aldehyde group per molecule of maltodextrin oxidized followed by heating;

iii. adjusting the pH in the range of 7.0-8.0 using ammonia;

iv. filtering and drying to obtain water soluble ferric carboxy maltose.

DESCRIPTION OF THE INVENTION:

The present invention relates to simple, cost effective process for preparation of ferric carboxy maltose having mean molecular weight 70,000 to 90,000Da in good yield and purity. The ferric carboxymaltose obtained by the present process has iron content of 26% to 35% and is suitable for preparation of medicament without employing costly Membrane Filtration process using Molecular Weight Cut-off Membranes.

The present inventors observed that natural α, β and γ Dextrins, Maltodextrin and Dextran can individually and independently polymerize when citric Acid was used as cross-linkage agent under mild conditions. The resultant polymers were hydrophilic, forming helical inclusion complexes thereby exhibiting larger capability to solubilize in water.

Accordingly, the carbohydrate for complex formation with iron was selected from maltodextrin having dextrose equivalent which lies between 10 and 20. The citric acid was used in amount of 0.4 to 1.2 equivalent, preferably of amount 0.6 to 0.8 equivalent of one aldehyde group per molecule of maltodextrin oxidized. The oxidation takes place at the terminal aldehyde group of the maltodextrin. Accordingly, the reactivity caused by glucose content of maltodextrin was lowered to 0.5 % or less. The oxidized maltodextrin polymerizes in presence of citric acid and forms helical inclusion complexes when reacted with iron (III) solutions to obtain water soluble iron-carbohydrate complex.

In an embodiment, the process for preparation of ferric carboxy maltose in good yield and purity is described in detail in the following paras.

Step (i) of the process comprises preparation of ferric hydroxide with reduced impurity levels. Accordingly, to the cooled aqueous ferric chloride solution (38%w/w) was added sodium carbonate solution (20%) slowly with continuous stirring until the pH was in the range of 3.5-4.5. Water was added to the mixture and the solution was allowed to settle for about 7-9 hours. After settling down, the upper layer of the water was decanted and the settled precipitate was filtered and thoroughly washed with water until the sodium chloride content in the rinsed water was not more than 45ppm and the chloride content of ferric hydroxide precipitate was not more than 2.5%w/w. The sodium chloride free ferric hydroxide precipitate was collected and suspension was prepared using water for further reaction.

Step (ii) comprises adding maltodextrin of dextrose equivalent in the range of 10 to 20 slowly to the ferric hydroxide suspension under stirring conditions for complete dissolution. Citric acid was slowly added to the mixture under stirring. The iron-carboxymaltose citric acid complex was heated at 75-80°C for about 8 hours, the reaction mass was cooled to temperature in the range of 35-45°C. Ammonia was then added into the reaction mass to adjust the pH in the range of 7.0-8.0 and allowed to settle.

Step (iii) comprises filtering the solution of the upper layer and drying the clear solution using spray dryer to obtain water soluble ferric carboxymaltose.

The feature of the present invention is that it avoids the contamination of the impurities such as sodium chloride, sodium bromide, organic metal catalyst and excess sodium carbonate in the final complex by providing a substantially pure ferric hydroxide solution for complexing with maltodextrin having dextrose equivalent of 10-20.

The ferric carboxymaltose prepared by the process of the present invention has iron content 26%-35%w/w which can safely be used for preparation of medicament to treat the patients suffering from iron deficiency anaemia.

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

Example 1: Preparation of Ferric hydroxide

Ferric chloride solution (38%w/w; 1315 kg) was added to 600lt of water taken in a reactor and the solution was cooled to 15°C. Sodium carbonate solution (20%w/w) was added slowly to ferric chloride solution under stirring until the pH was 4.0. 3000lt of water was further added to the mixture and the ferric hydroxide precipitate was allowed to settle for 8 hours. Decanted the upper layer of water and the precipitate was transferred to the filter assembly. The ferric hydroxide precipitate was thoroughly washed with water until the sodium chloride in the rinsed

water was not more than 45ppm and the chloride content of ferric hydroxide precipitate was not more than 2.5%w/w. Collected the sodium chloride free ferric hydroxide precipitate and water (6000lt) was added to make a suspension in the reactor.

Example 2: Preparation of Ferric carboxymaltose
To the ferric hydroxide suspension (of example 1) in the reactor was added maltodextrin (162 kg) of dextrose equivalent 10-20 slowly under stirring conditions for complete dissolution to obtain a homogeneous solution of maltodextrin. Citric acid (125kg) was added to the solution under stirring and the ferric carboxy maltose citrate complex was heated to a temperature in the range of 75-80°C for 8 hours. Cooled the reaction mass to 40°C. This was followed by addition of ammonia till pH 7.5 was attained. The reaction mass was allowed to settle down for 5 hours and the solution from the upper layer was filtered using suitable filtration assembly. The clear solution after filtration was transferred to the spray dryer. The inlet temperature of the dryer was maintained at 275°C and the outlet temperature at 115°C to obtain dried ferric carboxymaltose.

Yield: 92%
Purity: 96.88%
Iron content: 34.55%
Mol. wt of the complex: 82,000Da

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.

We Claims:

1. A simple, cost effective process for preparation of water soluble Ferric Carboxymaltose in good yield and purity comprising;
   i. Adding maltodextrin of dextrose equivalent in the range of 10-20 to the suspension of ferric hydroxide obtained from mixture of FeCl3 and NaOH wherein NaCl with sodium chloride level not more than 45ppm and the chloride content not more than 2.5%w/w;
   ii. Adding citric acid to the solution of step (i) in an amount of 0.4 to 1.2 equivalent of one aldehyde group per molecule of maltodextrin oxidized followed by heating to a temperature in the range of 75-80°C;
   iii. Adjusting the pH in the range of 7.0-8.0 using ammonia;
   iv. Filtering and drying to obtain water soluble Ferric Carboxymaltose.

2. The process as claimed in claim 1, wherein the citric acid in step (ii) is used in amount of 0.72 equivalent of one aldehyde group per molecule of maltodextrin oxidized.

3. The process as claimed in claim 1, wherein the mean molecular weight of Ferric Carboxymaltose is 82,000 Da and the iron content is 34.55%.

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"IMPROVED PROCESS FOR PREPARATION OF FERRIC CARBOXYMALTOSE"

ABSTRACT

Disclosed herein is improved, cost effective process for preparation of water soluble ferric carboxymaltose with reduced impurity suitable for preparation of medicament without involving further purification. Particularly, the present invention discloses the process of manufacturing ferric carboxymaltose obtained by reaction of aqueous iron (III) salt and an aqueous solution of oxidation product of maltodextrin having dextrose equivalent 10-20 using citric acid as mild oxidizing and cross-linking agent.