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सत्यमेव जयते

क्रम सं/SL No :033124750

पेटेंट कार्यालय,भारत सरकार | The Patent Office, Government Of India

पेटेंट प्रमाण पत्र | Patent Certificate

(पेटेंट नियमावली का नियम 74) | (Rule 74 of The Patents Rules)

पेटेंट सं. / Patent No.	:	434424 (परिवर्धन पेटेंट/ Patent of Addition)
आवेदन सं. / Application No.	:	202233028884
फाइल करने की तारीख / Date of Filing	:	19/05/2022
पेटेंटी / Patentee	:	WEST BENGAL CHEMICAL INDUSTRIES LIMITED
मुख्य पेटेंट संख्या / Main Patent No	:	370845 (201731011640)

प्रमाणित किया जाता है कि पेटेंटी को, उपरोक्त आवेदन में यथाप्रकटित *IMPROVED FERRIC CARBOXYMALTOSE WITH LESS SIDE-EFFECTS OBTAINED COST-EFFECTIVELY* नामक आविष्कार के लिए, पेटेंट अधिनियम, 1970 के उपबंधों के अनुसार आज तारीख मई 2022 के उन्नीसवें दिन

It is hereby certified that a patent has been granted to the patentee for an invention entitled *IMPROVED FERRIC CARBOXYMALTOSE WITH LESS SIDE-EFFECTS OBTAINED COST-EFFECTIVELY* as disclosed in the above mentioned application for a term equal to that of the patent for the main invention and shall remain in force during that term or until cesser of the patent for the main invention in accordance with the provisions of the Patents Act,1970.

अनुदान की तारीख : 13/06/2023
Date of Grant :

पेटेंट नियंत्रक
Controller of Patents

टिप्पणी- परिवर्धन पेटेंट के लिए कोई शुल्क देय नहीं है।

Note.- No fee is payable in respect of a patent of addition.

434424

Indian Patent

Patent Number: 434424
Date of Patent: 13 June, 2023

"Improved Ferric Carboxymaltose With Less Side-effects Obtained Cost-effectively"

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Assignee: **West Bengal Chemical Industries Limited**

Application: 202233028884

Filed: **19 May, 2022**

ABSTRACT:

Development and process of synthesis of better soluble Ferric carboxymaltose attaining desired molecular weight, PDI, high solubility, uniform distribution of the complex through an improved process with less contamination effects for treatment of iron deficiency with less anaphylactic shock. The advanced process of synthesis involves less time taking and preservative free oxidation process by use of ozone.

9 Claims, No Drawings

Claims

1. A pharmaceutical composition obtained from process of synthesis sourced from ozone oxidised Maltodextrin of varied dextrose equivalent 10-15, comprisingferric carboxymaltose wherein not more than 10% of the ferric Carboxymaltose having molecular weight more than 250kDa , less than 10% of ferric Carboxymaltose having molecular weight less than 10kDa and the rest of ferric carboxymaltose falls within the range of 70kDa-250kDa average molecular weight, more specifically the majority of ferric Carboxymaltose within the molecular weight of 70kDa-250kDa having average molecular weight 82.50kDa
2. The pharmaceutical composition as claimed in claim 1 wherein the polymer chain is uniformly distributed justifying the uniformity of the molecular distribution.
3. The pharmaceutical composition as claimed in claim 1 having polydispersity index in the range of 1.38- 1.99, preferably 1.48.
4. The pharmaceutical composition as claimed in claim 1 wherein the dimer content is less than 2.
5. The pharmaceutical composition as claimed in claim 1 having solubility in the range of 50-150 mg/ml, preferably 120mg/ml having therapeutic efficacy in treatment of iron deficiency
6. The pharmaceutical composition as claimed in claim 1 which having negligible amount of ferrous content less than 1%.
7. A process for synthesis of pharmaceutical composition as claimed in claims 1or 5 comprising of the following steps:

a. preparing Ferric hydroxide cake reacting ferric chloride with sodium carbonate;
b. Preparaing oxidized maltodextrin using ozone gas for desired time and at desired temperature;
c. Reacting ferric hydroxide cake with oxidised maltodextrin at desired temperature and for desired time.

8. The process of synthesis as claimed in claim 7 where the pharmaceutica composition is derived by addition of ammonia in the reaction mass at desired time and temperature and further cooled at room temperature and subsequently added ammonia at pH 7.
9. The process of synthesis as claimed in claim 7 where the derived pharmaceutical composition is allowed to settle for 1 hour and spray dried.

TITLE OF THE INVENTION

IMPROVED FERRIC CARBOXYMALTOSE WITH LESS SIDE-EFFECTS OBTAINED COST-EFFECTIVELY

APPLICANT(S)

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PREAMBLE TO THE DESCRIPTION

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

The invention comprises an improvement in, or a modification of the invention claimed in the specification of the main patent granted under the patent No. of 370845

FIELD OF INVENTION

The present invention is directed to advancement in the development and improved ferric carboxymaltose synthesis of improved ferric carboxymaltose with less toxicity, desired polydispersity index and better solubility and less ferrous content and consistent average molecular weight which is suitable for treatment of iron deficiency through both oral as well as parental route through a cost-effective process.

BACKGROUND

Iron carbohydrate complexes are intravenously administered for the treatment of iron deficiency (anaemia) as iron replacement therapies for the patients with serious clinical consequences.

US FDA has approved several iron-carbohydrate complexes for treatment of iron deficiency that are used intravenously in serious clinical conditions. For example, Irongluconate, Iron-sucrose (Venofer), low molecular weight Iron- dextran, high molecular weight Iron-dextran, Iron- Isomaltoside, Ferumoxytol, Ferric Carboxymaltose.

However, the approved iron-carbohydrate complex shows side-effects including but not limited to anaphylactic shocks.

This is because of the lack of stability usually caused due to non-transferrin bound iron, ferrous ion and labile iron content, toxicity in the product and presence of undesired molecular weight.

Polymers can be characterized by a variety of definitions for molecular weight including the number average molecular weight/number of molecule (Mn), the weight average molecular weight (Mw), the size average molecular weight (Mz), or the viscosity molecular weight (Mv).

The Gel permeation chromatography and Size-Exclusion chromatography tests for molecular weight conducted wherein the most prominent peaks determines the molecular weight of majorly distributed molecules along with polymer chains. Further, the average molecular weight is determined on the prominent peaks which are a characteristic of iron carbohydrate complex.

Synthesis of iron-carbohydrate complexes used for the treatment of iron deficiency are known and described in the art. However, the major challenge during the synthesis is to get appropriate molecular weight to retain the stability thus lesser side-effects of iron-carbohydrate complex. For long, dextran and non-dextran complexes have been used to treat iron deficiency with quite some serious side effects resulting from low molecular weights (dimer) than the appropriate molecular weight which affected the physio-chemical stability of the iron complex.

US7612109, US20120214986A1, WO2016151367A, US20210155651A1 disclosed a process for water-soluble ferric carbohydrate complexes obtained by oxidation of maltodextrin followed by coupling with iron (III) chloride. Maltodextrin contained in the mixture lies between 2 and 40 dextrose equivalents which resulted in water soluble iron carbohydrate complex having an average molecular weight of 80,000 to 400,000 Daltons.

It is evident from published methods that the ferric carbohydrate complexes prepared from dextrin having a varying dextrose equivalents unit. Broadly, it involved two steps or in situ one step processes where both require the oxidation of maltodextrin and coupling with iron salts. The oxidation methods include sodium hypochlorite with without sodium bromide, hydrogen peroxide, sodium hypochlorite + hydrogen peroxide, sodium tungstate etc. In the second stage, iron salts were used for coupling to yield ferric carboxymaltose. The maltodextrins were used with varying dextrose units ranging from 5 to 20 DE which gave varying

molecular weights of ferric carboxymaltose. All the processes in the previous art suffer from the following drawbacks, formation of iron carbohydrate complexes with inconsistent average molecular weight and iron content, formation of undesired chlorinated by-products such as chlorides, metal bromides, and carbonates. Thus, generating a large quantity of chemical waste which is difficult to treat and hence, unsuitable for the commercial scale. The dextrin with varying dextrose equivalents used in the reported methods can be obtained according to the literature methods. However, the methods used various combinations of dextrin's from 5 to 20 DE which significantly affect the average molecular weight of the ferric carboxymaltose.

In order to avoid the variations and to maintain the consistency of the product stability, the present invention which further improves the IN370845 through a robust and novel oxidation process have been used which gives consistency in the product average molecular weight throughout all the batches.

The improved process makes an improvement in the final product having high solubility, better polydispersity index, uniform distribution of the complex which is suitable for injectables having less side-effects.

OBJECTIVE OF THE INVENTION

It is thus the primary object of the present invention to provide for improved ferric carboxymaltose suitable for formulations having desired molecular weight, polydispersity index and good solubility for treatment of iron deficiency with less anaphylactic shock.

Yet another objective of the present invention is to provide a process which is free of preservatives.

Yet another object of the present invention is to provide a process for the advancement in the manufacture of said Ferric carboxymaltose involving selective oxidation by ozone to maintain the consistency of molecular weight.

Another object of the present invention is to provide the process for the advancement in manufacture of said Ferric carboxymaltose wherein the ferrous content is negligible.

Yet another object of the present invention is to provide the process for the advancement in manufacture of Ferric Carboxymaltose having improved solubility and high efficacy.

Another object of the present invention is to provide the process for the advancement in manufacture of said Ferric Carboxymaltose which can be completed faster and in lesser time.

SUMMARY OF THE INVENTION

A pharmaceutical composition obtained from process of synthesis sourced from ozone oxidised Maltodextrin of varied dextrose equivalent 10-15, comprising ferric carboxymaltose wherein not more than 10% of the ferric Carboxymaltose having molecular weight more than 250kDa , less than 10% of ferric Carboxymaltose having molecular weight less than 10kDa and the rest of ferric carboxymaltose falls within the range of 70kDa-250kDa average molecular weight, more specifically the majority of ferric Carboxymaltose within the molecular weight of 70kDa-250kDa having average molecular weight 82.50kDa

The polydispersity index is also a major area of concern which vary from process to process and if it is more than 2 then results in poor patients compliance. It is seen than when polydispersity index is lesser than 2, it improves Patients compliance. So the process insures better Polydispersity index less than 2 which is specifically1.48.

The solubility of the ferric carboxymaltose in terms of iron derived is in the range of 50-150 mg/ml, preferably 120 mg/ml having therapeutic efficacy in treatment of iron deficiency with less anaphylactic shock.

Free and labile iron are important factor for anaphylactic shock because of induction of non-specific oxidative stress, hence becomes a challenge to produce FCM having less free/labile iron.

The derived Ferric Carboxymaltose which is substantially free of Ferrous content is less than 1%.

DETAILED DESCRIPTION OF THE INVENTION

The present invention thus provides for a process for synthesis of the said formulation which includes the following steps wherein,

a) Preparing Ferric hydroxide cake reacting ferric chloride with sodium carbonate;
b) Preparing oxidized maltodextrin using ozone gas for desired time and at desired temperature;
c) Reacting ferric hydroxide cake with oxidised maltodextrin at desired temperature and for desired time.

Step (a): Preparation of Ferric hydroxide

38% w/w Ferric chloride is taken and added to 600 L of Water for injection; taken in a reactor and further the solution was cooled to 15˚C. The solution transmission was checked and the clarity of the solution was justified to ensure no insoluble matter are present emphasizing good quality raw material. Sodium carbonate solution (20%w/w) was added slowly to ferric chloride solution under stirring until the pH was 4.0. 3000 L of water was further added in 3-4 succession to the mixture and the ferric hydroxide precipitate was allowed to settle for 8 hours. 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. The water of the upper layer after final washing was decanted. The ferric hydroxide precipitate cake was free of sodium chloride.

Step (b): Preparation of oxidized Maltodextrin:

Step 1: 400 litre of Water for injection was added to Maltodextrin of dextrose equivalent 10-15 taken in a reactor at 25-30˚C and stirred for 1 hour at the same temperature.

Step 2: The obtained aqueous solution of Maltodextrin oxidized by purging ozone gas at 30-40˚C for different times periods to obtain the completely oxidized Maltodextrin.

Example 1:
The obtained aqueous solution of Maltodextrin oxidized by purging ozone gas at 30-40˚C for 2 hours. 1-2 ml of the oxidized Maltodextrin was collected in a test tube and added to 1 ml of Fehling's solution. The same was heated in water bath, after around 10 minutes, a red ppt. was observed below, showing that the oxidation was not complete.

Example 2:
The obtained aqueous solution of Maltodextrin oxidized by purging ozone gas at 30-40˚C for 4 hours. 1-2 ml of the oxidized Maltodextrin was collected in a test tube and added to 1 ml of Fehling's solution. The same was heated in water bath, after around 10 minutes, a red ppt. was seen below, showing that the oxidation was not complete.

Example 3:
The obtained aqueous solution of Maltodextrin oxidized by purging ozone gas at 30-40˚C for 5 hours. 1-2 ml of the oxidized Maltodextrin was collected in a test tube and added to 1 ml of Fehling's solution. The same was heated in water bath, no red ppt was found.

Example 4:
The obtained aqueous solution of Maltodextrin oxidized by perching ozone gas at 30-40˚C for 8 hours. 1-2 ml of the oxidized Maltodextrin was collected in a test tube and added to 1 ml of Fehling's solution. The same was heated in water bath, no red ppt was found.

Thus, it is clear that by ozonisation for 6 hours, the Maltodextrin is completely oxidized which is further justified by FT-IR report. The report of the oxidized Maltodextrin obtained from the process in Example 3 does not have the peak of 1636 cm-1 proving conversion of maltodextrin to its oxidized form.

Step (c): involves preparation of Ferric Carboxymaltose

The ferric hydroxide cake is added to the oxidized maltodextrin obtained and heated at different temperature for different time period, the reaction was is then cooled at 40˚C, followed by addition of ammonia till pH 7.5 was obtained. The reaction mass was then allowed to settle down for 1 hour and the solution from the upper layer was filtered using 1.2 micron filter. The filtered material was transferred to the spray dryer. The inlet temperature of the dryer was maintained at 275˚C and outlet temperature at 115˚C to obtain ferric carboxymaltose of desired molecular weight.

Example 1:
The ferric hydroxide cake is added to the oxidized maltodextrin obtained and heated at 80-85˚C temperature for 1.5 hour and the reaction was carried out adopting the same process as described in step c. The product obtained was analyzed for its molecular weight and PDI using Gel Permeable Chromatography (GPC).

The apparent weight average molecular weight is predominantly 85113 Dalton and the less prominent peak obtained is of weight average molecular weight as 11910 Da

PDI: 1.48
Solubility: 120 mg in 1 ml of water

No dimer content is detected in the above example.

Example 2:
The ferric hydroxide cake is added to the oxidized maltodextrin obtained and heated at 75-80˚C temperature for 2 hours and the reaction was carried out adopting the same process as described in step c.

The product obtained was analysed for its molecular weight and PDI using Gel Permeable Chromatography (GPC).

Apparent molecular weight is predominantly 245000 Da while other less prominent peaks showing are 290000 Da and 6000 Da.

PDI: 1.58
Solubility: 100 mg in 1 ml of water

Example 3:

The ferric hydroxide cake is added to the oxidized maltodextrin obtained and heated at 60-65˚ C temperature for 2 hours and the reaction was carried out adopting the same process as described in step c. The product obtained was analysed for its molecular weight and PDI using Gel Permeable Chromatography (GPC).

The apparent weight average molecular weight is predominantly 73234 Da while other less prominent peaks showing are 280073 Da and 2985 Da.

PDI: 1.56
Solubility: 87 mg in 1 ml of water

The dimer content of the above example is 0.84%

From the comparative trials with respect to change in the operative parameters regarding Step (c): preparation of Ferric Carboxymaltose

Finally, 1 gm of obtained product from Step c is taken as a sample and 100 ml of water is added which is mixed properly. Freshly prepared 5.0% of potassium ferrocyanide solution is added in the properly mixed solution of the product in water.

There is no colour change, which is an indication of the absence of free iron.

According the advancement of the present invention clearly and sufficiently demonstrate the advancement including reaching to the desired ferric carboxymaltose having:-

i. Desired molecular weight and polydispersity index justifying the statement on less anaphylactic shock;
ii. Ferrous content of the ferric carboxymaltose less;
iii. Oxidation by ozone is less toxic and free of preservatives;
iv. High solubility of the product;
v. V) Polymer chain uniformly distributed hence the molecular distribution is also uniform;
vi. Filtration through micron filter reduces the possibility of contamination with free ions; and
vii. The reaction is completed in a lesser time, which could not be attained prior to the present advancement.

We Claims

1. A pharmaceutical composition obtained from process of synthesis sourced from ozone oxidised Maltodextrin of varied dextrose equivalent 10-15, comprisingferric carboxymaltose wherein not more than 10% of the ferric Carboxymaltose having molecular weight more than 250kDa , less than 10% of ferric Carboxymaltose having molecular weight less than 10kDa and the rest of ferric carboxymaltose falls within the range of 70kDa-250kDa average molecular weight, more specifically the majority of ferric Carboxymaltose within the molecular weight of 70kDa-250kDa having average molecular weight 82.50kDa
2. The pharmaceutical composition as claimed in claim 1 wherein the polymer chain is uniformly distributed justifying the uniformity of the molecular distribution.
3. The pharmaceutical composition as claimed in claim 1 having polydispersity index in the range of 1.38- 1.99, preferably 1.48.
4. The pharmaceutical composition as claimed in claim 1 wherein the dimer content is less than 2.
5. The pharmaceutical composition as claimed in claim 1 having solubility in the range of 50-150 mg/ml, preferably 120mg/ml having therapeutic efficacy in treatment of iron deficiency
6. The pharmaceutical composition as claimed in claim 1 which having negligible amount of ferrous content less than 1%.
7. A process for synthesis of pharmaceutical composition as claimed in claims 1or 5 comprising of the following steps:

a. preparing Ferric hydroxide cake reacting ferric chloride with sodium carbonate;
b. Preparaing oxidized maltodextrin using ozone gas for desired time and at desired temperature;
c. Reacting ferric hydroxide cake with oxidised maltodextrin at desired temperature and for desired time.

8. The process of synthesis as claimed in claim 7 where the pharmaceutica composition is derived by addition of ammonia in the reaction mass at desired time and temperature and further cooled at room temperature and subsequently added ammonia at pH 7.
9. The process of synthesis as claimed in claim 7 where the derived pharmaceutical composition is allowed to settle for 1 hour and spray dried.

TITLE: IMPROVED FERRIC CARBOXYMALTOSE WITH LESS SIDE- EFFECTS OBTAINED COST-EFFECTIVELY

ABSTRACT

Development and process of synthesis of better soluble Ferric carboxymaltose attaining desired molecular weight, PDI, high solubility, uniform distribution of the complex through an improved process with less contamination effects for treatment of iron deficiency with less anaphylactic shock. The advanced process of synthesis involves less time taking and preservative free oxidation process by use of ozone.