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सत्यमेव जयते

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भारत सरकार
GOVERNMENT OF INDIA
पेटेंट कार्यालय
THE PATENT OFFICE

पेटेंट प्रमाणपत्र
PATENT CERTIFICATE

(Rule 74 Of The Patents Rules)

पेटेंट सं. / Patent No.	:	356552
आवेदन सं. / Application No.	:	201731028196
फाइल करने की तारीख / Date of Filing	:	08/08/2017
पेटेंटी / Patentee	:	WEST BENGAL CHEMICAL INDUSTRIES LIMITED

प्रमाणित किया जाता है कि पेटेंटी को उपरोक्त आवेदन में यथाप्रकटित SOLVENT FREE, COST EFFECTIVE PROCESS FOR PREPARATION OF FERRIC CITRATE नामक आविष्कार के लिए, पेटेंट अधिनियम, १९७० के उपबंधों के अनुसार आज तारीख 8th day of August 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 SOLVENT FREE, COST EFFECTIVE PROCESS FOR PREPARATION OF FERRIC CITRATE as disclosed in the above mentioned application for the term of 20 years from the 8th day of August 2017 in accordance with the provisions of the Patents Act,1970.

एकस्य कार्यालय THE PATENT OFFICE GOVT.OF INDIA भारत सरकार

अनुदान की तारीख : 22/01/2021
Date of Grant :

पेटेंट नियंत्रक
Controller of Patent

टिप्पणी - इस पेटेंट के नवीकरण के लिए फीस, यदि इसे बनाए रखा जाना है, **8th day of August 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 8th day of August 2019 and on the same day in every year thereafter.

356552

Indian Patent

Patent Number: 356552
Date of Patent: 22 Jan, 2021

Solvent Free cost effective process for preparation of Ferric Citrate

Inventor: Niladri Samanta

Assignee: **West Bengal Chemical Industries Limited**

Application: **201731028196**

Filed: **08 Aug, 2017**

ABSTRACT:

Disclosed herein is a solvent free and cost effective process for preparation of pharmaceutical grade Ferric Citrate. The so obtained Ferric citrate is useful for the treatment of HyperPhosphatemia.

4 Claims, No Drawings

Claims

1. A solvent free process for preparation of pharmaceutical grade Ferric Citrate having BET surface area in the range of 12-16.5 m^2/gm with particle size of 20-50 micron characterized in that oxidation is carried out by purging air at 25°c to 35c and pressure at 0.25 to 0.5 kg/m^2 at pH in the range of 4-4.5 comprises aqueous mix of Citric Acid Monohydrate and Iron Powder in a molar ratio from about 0.8 to 1.5 until the Ferric content reaches 21-22% and Ferrous content less than 1% on dried basis.

2. The process as claimed in claim 1, where ratio of citric acid monohydrate to Iron Powder is between 0.8 to 1.5.

3. The process as claimed in claim 1, where oxygen is bubbled till Ferric content reaches between 21 to 22%, on dried basis.

4. The process as claimed in claimed 1, where spray drying is used to isolate Ferric Citrate.

TITLE OF THE INVENTION:

"SOLVENT FREE, COST EFFECTIVE PROCESS FOR PREPARATION OF FERRIC CITRATE"

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 solvent free and cost effective process for preparation of pharmaceutical grade Ferric Citrate. The so obtained Ferric citrate is useful for the treatment of HyperPhosphatemia.

Background of the Invention:
Ferric Citrate is an ionic chemical compound with formula $FeC_6H_5O_7$, consisting of a trivalent Iron anion (Fe^{3+}) and a trivalent Citrate cation (C_6HSO^{3-}). Ferric Citrate is a Phosphate Binder and is indicated for the control of serum Phosphorous levels in patients with chronic kidney disease on dialysis. Ferric Citrate can also be used as food supplement. Ferric Citrate was approved by US FDA in September 2014 with the trade name Auryxia.

According to Merck Index, Ferric Citrate is slowly but completely soluble in cold water and readily soluble in hot water but the solubility diminishes with age. Ferric [Fe^{3+}] iron reacts with ingested phosphate to form an insoluble ferric phosphate complex, which is not absorbed or metabolised during GI transit and is excreted in the stool.

The processes for preparation of Ferric Citrate are known in the art.

US6903235 discloses a method for preparation of pharmaceutical grade Ferric Citrate in solid phase comprising mixing solid Citric Acid with a solid Ferric salt, adding alcohol to the mixture and filtering.

US7767851 discloses synthesis of Ferric Citrate having a formula of $C_6H_5O_7Fe$ and an intrinsic dissolution rate between 1.9 and 4.0 mg/cm^2-min, comprising adding an alkaline metal hydroxide solution to a Ferric Chloride (or its hexahydrate) solution to form a Ferric Hydroxide precipitate; forming a suspension of the precipitate in water, adding Citric Acid to the suspension and forming a Ferric-Citric Acid solution by heating said suspension with said Citric.

Acid; and precipitating the solid form of Ferric Citrate by mixing the Ferric-Citric Acid solution with an organic solvent. Ferric Citrate prepared by the method described in US'851 has a BET active surface area exceeding 16 m^2/gm. The family patent, US8609896, which disclose orally administrable form of ferric citrate of BET surface area exceeding 16m^2/gm however has failed to disclose the phosphate binding capacity of ferric citrate.

WO2016162888 discloses a process for obtaining Ferric Citrate wherein a solution of Ferric salt is treated with an alkali metal carbonate; reacting the resulting mixture with a coagulating agent to obtain Ferric Oxohydride mass followed by heating with Citric Acid to form a solution and adding organic solvent to the heated mixture to obtain Ferric Citrate. The pharmaceutical grade Ferric Citrate that has a BET active surface area of less than 16 m^2/g and a dissolution rate of 4 to 9 mg/cm^2-min.

There still exists a scope to improve the process in terms of cost, industrial applicability and efficacy in the preparation of pharmaceutical grade Ferric Citrate which can effectively bind the soluble Phosphates in the gastrointestinal tract.

Summary of the invention:
To meet the objectives, the present invention provides an improved, cost effective and plant scalable process for preparation of pharmaceutical grade Ferric Citrate characterized in that oxidizing the aqueous mix of Citric Acid Monohydrate and Iron Powder in a molar ratio from about 0.8 to 1.5 until the Ferric content reaches 21-22% and Ferrous content less than 1% on dried basis in the product.

In another aspect, the present invention provides pharmaceutical grade Ferric Citrate having 21.5% Ferric content and less than 1% Ferrous content, characterized by BET surface area of 12-.16.5 m^2/gm, particle size 20-50 micron and Phosphate binding in the range of 19.1 to 19.9 mg of Phosphorous / gm of Ferric Citrate.

Detailed Description of the invention:
The present invention discloses an improved, cost effective and plant scalable process for preparation of pharmaceutical grade Ferric citrate with desired dissolution rate and BET surface area for effective binding of the ferric ions to the soluble phosphates in the gastrointestinal tract.

In an embodiment, the solvent free and cost effective process of the present invention characterized in that oxidizing the aqueous mix of citric acid monohydrate and iron powder in a molar ratio from about 0.8 to 1.5 until the Ferric content reaches 21-22% and Ferrous content less than 1% on dried basis in the product.

Accordingly, to the reactor water, citric acid monohydrate was added and the mixture was continuously stirred until complete dissolution. This was followed by gradual addition of iron powder and the mixture was stirred continuously. The temperature was maintained in the range of 30 to 35^{o}C; pressure was maintained at atmospheric pressure and pH between 4 to 4.5. The ratio of Citric Acid Monohydrate and the Iron Powder was from about 0.8 to 1.5. The air was purged into the reaction mass in the Reactor at same temperature and pressure until the Ferric content reached 21-22% and Ferrous content less than 1% calculated on dried basis. The solution mixture was filtered and spray dried to obtain Ferric citrate.

The Ferric Citrate prepared by the present process is a pharmaceutical grade Ferric citrate with BET surface area 12 to 16.5 m^2/gm, particularly in the range of 16 to 16.5 m^2/gm and mean dissolution rate 2 to 4 mg/cm^2-min as determined by USP intrinsic dissolution assay in water. The particle size is in the range 20-50 micron. The Phosphate binding of the Ferric ions is in the range 84.8 to 87.9 mg of Phosphate / gm of elemental Ferric Ion.

In an embodiment, the present invention provides pharmaceutical grade Ferric citrate having 21-22% ferric content and less than 1% ferrous content, BET surface area 12- 16.5 m^2/gm, particle size in the range 20-50 micron and Phosphate binding in the range of 19.1 to 19.8 mg of Phosphorous / gm of Ferric Citrate.

The enhanced binding capacity of ferric citrate obtained by the process of the present invention with large surface area is depicted below in Table 1 and Table 2 respectively.

Table 1: Relation between BET Active surface area and Particle size of Ferric Citrate

Particle size (micron)	BET Active surface area (m^2/gm)
261	0.39
148	3.89
101	8.02
45	15.77
39	16.03
22	16.12

Table 2: Relation between BET Active surface area and Phosphate binding capacity of Ferric Citrate

BET Active surface area (m^2/gm)	Phosphate binding capacity (mg P/ferric citrate)
15.77	19.16
16.03	19.32
16.12	19.84

It can be seen from above that BET active surface area increases with decrease in particle size of Ferric citrate, which enhances the phosphate binding of the ferric ions. Ferric citrate with BET surface area of 16.12m^2/gm shows maximum.

Phosphate binding capacity of 19.84mg of phosphorous per gram of ferric citrate which the prior art has failed to achieve.

In an embodiment, the present invention provides pharmaceutical composition comprising Ferric citrate with 21-22% ferric content and less than 1% ferrous content, a BET surface area of 12 to 16.5m^2/gm, particle size in the range of 20-50 microns and phosphate binding in the range of 19.1 to 19.8 mg of Phosphorous / gm of Ferric Citrate along with pharmaceutically acceptable excipients for the treatment of HyperPhosphatemia.

The pharmaceutical compositions of ferric citrate in accordance with the present invention can be formulated in the form of tablets, granules, powder, capsules, caplets etc and can be administered to the subject in need orally. The compositions may be prepared by the method known in the art.

In another embodiment, the present invention relates to the use of ferric citrate with 21.5% ferric content and less than 1% ferrous content, a BET surface area of 12 to 16.5m^2/gm, particle size in the range of 20-50 microns and phosphate binding in the

range of 19.1 to 19.8 mg of Phosphorous / gm of Ferric Citrate for treatment of HyperPhosphatemia.

The invention further relates to a method for treating hyperphosphatemia in a subject, comprising administering to said subject an effective amount of ferric citrate prepared by the present process. In an embodiment, the subject is a human being.

The advantage of the present process includes use of water as solvent in the process, avoidance of coagulating agent, avoids use of iron salts thereby reducing the process steps of purification. Direct reaction of iron powder and citric acid is carried out in aqueous solution without using solvent as precipitating agent.

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

Example 1: Preparation of Ferric citrate
To the Reactor vessel was added 2000 Lt of water, 375 kg of Citric Acid and the mixture was stirred continuously at temperature 30 to 35°C and atmospheric pressure until complete dissolution. 130 kg of Iron Powder was added to the mixture with continuous stirring and air was purged into the Reactor vessel till the Ferric content reaches 21.5% and Ferrous content is less than 1% analysed on dried basis. The solution was then filtered using Sparkler Filter and the filtrate was spray dried. The inlet temperature of the Dryer was maintained at 275°C and the outlet temperature at 105°C to obtain dried Ferric Citrate.

Yield: 500 kg
Purity: 98.21%

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

We Claim;

1. A solvent free process for preparation of pharmaceutical grade Ferric Citrate having BET surface area in the range of 12-16.5 m^2/gm with particle size of 20-50 micron characterized in that oxidation is carried out by purging air at 25°c to 35c and pressure at 0.25 to 0.5 kg/m^2 at pH in the range of 4-4.5 comprises aqueous mix of Citric Acid Monohydrate and Iron Powder in a molar ratio from about 0.8 to 1.5 until the Ferric content reaches 21-22% and Ferrous content less than 1% on dried basis.

2. The process as claimed in claim 1, where ratio of citric acid monohydrate to Iron Powder is between 0.8 to 1.5.

3. The process as claimed in claim 1, where oxygen is bubbled till Ferric content reaches between 21 to 22%, on dried basis.

4. The process as claimed in claimed 1, where spray drying is used to isolate Ferric Citrate.

Solvent Free, Cost Effective Process for Preparation of Ferric Citrate

ABSTRACT

Disclosed herein is a solvent free and cost effective process for preparation of pharmaceutical grade Ferric Citrate. The so obtained Ferric citrate is useful for the treatment of HyperPhosphatemia.