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THE PATENT OFFICE

पेटेंट प्रमाणपत्र
PATENT CERTIFICATE

(Rule 74 of The Patents Rules)

पेटेंट सं. / Patent No.	:	419785
आवेदन सं. / Application No.	:	201731028154
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 PROCESS FOR PREPARATION OF SUCROFERRIC OXYHYDROXIDE नामक आविष्कार के लिए, पेटेंट अधिनियम, 1970 के उपबंधों के अनुसार आज तारीख अगस्त 2017 के आठवें दिन 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 PROCESS FOR PREPARATION OF SUCROFERRIC OXYHYDROXIDE 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.

एकस्व कार्यालय THE PATENT OFFICE GOVT.OF INDIA भारत सरकार

अनुदान की तारीख : 31/01/2023
Date of Grant :

पेटेंट नियंत्रक
Controller of Patent

टिप्पणी - इस पेटेंट के नवीकरण के लिए फीस, यदि इसे बनाए रखा जाना है, अगस्त 2019 के आठवें दिन 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.

419785

Indian Patent

Patent Number: 419785
Date of Patent: 31 January, 2023

Process for preparation of Sucroferric oxyhydroxide

Inventor: **Niladri Samanta**

Assignee: **West Bengal Chemical Industries Limited**

Application: **201731028154**

Filed: **08 August, 2017**

ABSTRACT:

The present invention discloses industrially viable and cost effective process for preparation of SucroFerric Oxyhydroxide with a particle size of upto 50 microns. The invention further discloses pharmaceutical compositions comprising SucroFerric Oxyhydroxide characterised by Bulk Density of about 0.9(g/cm3); particle size distribution in the range of 20 to 50µm, a BET active surface area in the range of 13 to 17m2/gm and Phosphate Binding capacity in the range of 19 to 21 m/m, for use in the treatment of Hyperphosphatemia.

5 Claims, No Drawings

Claims

1. A process for preparation of pharmaceutical grade of SucroFerric Oxyhydroxide which comprises;
    a) dissolving Potato Starch under stirring in water;
    b) adding Ferric Chloride solution and Sodium Carbonate solution slowly and alternatively under stirring followed by filtration to obtain a cake;
    c) washing the cake with water for reducing the Chloride content;
    d) adding Sucrose solution under continuous stirring to the cake till homogeneous mixing lo obtain a cake;
    e) isolating and drying the wet cake at 60 to 75° C followed by milling to obtain the product with a particle size distribution of 20 to 50 µm.
2. The process for preparation of pharmaceutical grade of SucroFerric Oxyhydroxide as claimed in claim 1, wherein, the molar ratio of Sucrose to Potato Starch is in 1: 1 w/w ratio.
3. The process for preparation of pharmaceutical grade of SucroFerric Oxyhydroxide as claimed in claim 1, wherein, the micronized cake is characterized by Bulk Density of about 0.9 (g/cm3); particle size distribution in the range of 20 to 50µm; BET (Brunauer-Emmett-Teller) active surface area in the range of 13 to 17 m2 / gm and Phosphate Binding capacity in the range of 19 Lo 21 mg/ gm.
4. The process for preparation of pharmaceutical grade of SucroFerric Oxyhydroxide as claimed in claim 1, wherein, the product comprises an iron content in the range of 20 to 30 w /w of the product.
5. The process as claimed in the preceding claims, wherein the Iron containing product is in the form of dry powder having a particle size in the range 20 to 50µm.

TITLE OF THE INVENTION:

"PROCESS FOR PREPARATION OF SUCROFERRIC OXYHYDROXIDE"

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.

TECHNICAL FIELD:

This invention relates to industrially viable and cost effective process for preparation of SucroFerric Oxyhydroxide. More particularly, the present invention relates to process for preparation of SucroFerric Oxyhydroxide with a particle size of upto 50 microns using environment-friendly solvent and pharmaceutical compositions containing the same.

BACKGROUND AND PRIOR ART:

Hyperphosphatemia is associated with severe other complications, such as hypocalcemia, decrease in vitamin-D production and metastatic calcification. Hyperphosphatemia further contributes to the increased incidence of cardiovascular disease among dialysis-dependent patients. The Phosphate Binding capacity of Iron Oxide Hydroxides is reported in the art and thus the applicability of the same in patients suffering with Hyperphosphatemia is also known.

SucroFerric Oxyhydroxide is non-calcium, iron-based Phosphate Binder used for the control of serum Phosphorus levels in adult patients with chronic kidney disease (CKD) on haemodialysis (HD) or peritoneal dialysis (PD). SucroFerric Oxyhydroxide is available under the brand name, as Velphoro 500mg, in the form of chewable tablets.

US3821192 first reports the synthesis of an Iron-Saccharide complex from the reaction of Fe3+ and a low molecular Dextrin. The disadvantages of the process described in US'192 is the high toxicity of Methanol and high cost of the investment and operation having to use a high-speed Centrifuge, which is not suitable for industrial scale production of the Iron-polysaccharide complex according to the ICH guidelines (1997).

US6174442 discloses a process for preparation of an adsorbent for adsorbing Phosphate from aqueous medium which comprises; mixing an aqueous solution of a base with an aqueous solution of an Iron (III) salt containing Chloride ions with formation of a suspension in the pH range of 3 to 10; allowing the suspension to stand; washing a precipitate obtained with water; suspending the still moist precipitate in water with formation of a suspension with an Iron content of up to 6% by weight, and adding at least one member selected from the group consisting of one or more carbohydrates and humic acid in an amount such that a solid obtained contains a maximum of 40% by weight of Iron.

US20090169645 discloses a process for preparation of Iron Sulfate-Based Phosphate Adsorbent which process comprises; a) adding at least one base to an aqueous, sulfate and/or nitrate-containing Iron III) salt solution to form a precipitate of Iron Hydroxide; (b) optionally washing the resulting precipitate one or more times with water, yielding an aqueous suspension of the Iron Hydroxide, (c) contacting the aqueous suspension and at least one constituent that inhibits ageing of the Iron Hydroxide, and (d) drying the composition obtained in step (c).

WO2016038541 discloses a process for the preparation of an Iron containing Phosphate adsorbent, which process comprises the steps of: (1) Mixing an aqueous solution of an Iron (III) salt with an aqueous solution of a base optionally in the presence of solvent-1 to form a precipitate; (2) isolating the precipitate and optionally washing with water; (3) Slurrying the precipitate in water to obtain a suspension; (4) Adding a carbohydrate and/or humic acid to the suspension; (5) Adding solvent-2 to the suspension to obtain an Iron containing Phosphate adsorbent; and (6) Isolating the Iron containing Phosphate adsorbent.

The solvents 1 and 2 as disclosed in WO'541 are organic solvents. While the solvent 1 is selected from methanol, ethanol, isopropanol, n-propanol, butanol and a combination thereof; solvent 2 is selected from an alcohol, ketone, ether, ester and a mixture thereof. The use of organic solvents in different stages has the disadvantages such as inherent toxicity associated with the solvent as well as the escalation of the manufacturing cost of the product. The iron containing adsorbent is characterized by a PSD d(0.9) in the range of 20 µm to 80 µm, a BET active surface area less than 15 m2/g and a phosphate binding capacity in the range of 35 to 60 mg/g.

Some prior arts (US8252310), use alcoholic solvents

such as ethanol during the addition of sucrose in the manufacturing process of the Iron-based absorbent.

In order to obtain a pharmaceutical grade of an Iron-based absorbent, it is necessary to provide the product which is free of any toxic substances including toxic solvents. Moreover, it is necessary to provide the product in powder form having good BET surface area which enables maximum phosphate adsorption thereby results in increased therapeutic effect upon administration.

Therefore, there exists a need for a scalable and industrially viable process for the manufacture of pharmaceutical grade of SucroFerric Oxyhydroxide, a Phosphate adsorbent that is devoid of use of organic solvent.

SUMMARY OF THE INVENTION:

In line with the above, the present invention provides an industrially scalable process for preparation of pharmaceutical grade of SucroFerric Oxyhydroxide, a Phosphate adsorbent, wherein, the process is free from the use of organic solvents.

More particularly, the present invention provides an iron (III) based phosphate adsorbent containing polynuclear iron (III) oxide hydroxides wherein the polynuclear iron oxide hydroxide contains polynuclear gamma-iron oxide hydroxides, and optionally traces of ferrihydrite, stabilized by carbohydrate.

In accordance with the same, the process for preparation of pharmaceutical grade of SucroFerric Oxyhydroxide which comprises;

a) dissolving Potato Starch under stirring in water;
b) adding Ferric Chloride solution and Sodium Carbonate solution slowly and alternatively to the solution of step a) under stirring, followed by filtration to obtain a cake;
c) washing the cake with process water for reducing the Chloride content;
d) adding Sucrose solution under continuous stirring to the cake till homogeneous mixing to obtain a cake;
e) drying the wet cake at 60 to 75°C followed by milling to obtain pharmaceutical grade of SucroFerric Oxyhydroxide with a particle size distribution of 20 to 50 µm.

In another aspect, the invention provides micronized SucroFerric Oxyhydroxide, which is characterised by Bulk Density of about 0.9(g/cm3); particle size distribution in the range of 20 to 50µm, a BET active surface area in the range of 13 to 17m2/gm and Phosphate Binding capacity in the range of 19 to 21 m/m, prepared in accordance with the process of the present invention.

In another aspect, the invention provides pharmaceutical composition comprising micronized SucroFerric Oxyhydroxide characterised by Bulk Density of about 0.9(g/cm3); particle size distribution in the range of 20 to 50µm, a BET active surface area in the range of 13 to 17m2/gm and Phosphate Binding capacity in the range of 19 to 21 m/m, according to claim 6, for use in the treatment of Hyperphosphatemia.

DETAILED DESCRIPTION:

The invention will now be described in detail in connection with certain preferred and optional embodiments, so that various aspects thereof may be more fully understood and appreciated.
Accordingly, the present invention provides a process for preparation of pharmaceutical grade of SucroFerric Oxyhydroxide which comprises;

a) dissolving Potato Starch under stirring in water;
b) adding Ferric Chloride solution and Sodium Carbonate solution slowly and alternatively under stirring to the solution of step a), followed by filtration to obtain a cake;
c) washing the cake with water for reducing the Chloride content;
d) adding Sucrose solution under continuous stirring to the cake till homogeneous mixing to obtain a cake;
e) isolating and drying the wet cake at 60 to 75° C followed by milling to obtain pharmaceutical grade of SucroFerric Oxyhydroxide a particle size distribution of 20 to 50 µm.

The beauty of the process lies in non-use of organic solvent in the entire process and also lies in obtaining the product having Bulk Density of about 0.9 (g/cm3), particle size distribution in the range of 20 to 50µm, a BET (Brunauer-Emmett- Teller) active surface area in the range of 13 to 17 m2/gm and Phosphate Binding capacity in the range of 19 to 21 m/m.

The process is simple and easy to scale up for commercial production. Also, the process is free of toxic solvents and further avoids costly equipment.

In an aspect, the molar ratio of Sucrose and Potato Starch is taken preferably in 1:1 w/w ratio.

According to the present invention, the amount of the

Sodium Carbonate is used to obtain the desired pH and to obtain the precipitate of Ferric Hydroxide as a wet cake. The desired pH as referred herein is in the range of 6 to 8.

All the process steps except the drying of the product in step (e) have been conducted at ambient temperatures.

Isolation of the product is carried out using the conventional techniques known in the art such as filtration or centrifugation.

The product is dried at about 60 to 75°C, preferably at 70°C for upto 7 to 8 hours.

The Iron containing Phosphate adsorbent obtained in accordance with the invention comprises an iron content in the range of 20 to 30 w/w of the product.

According to the present invention, the Iron containing Phosphate adsorbent thus obtained having high Phosphate Binding capacity in the range of 19-21 m/m, in form of a dry powder having particle size distribution in the range of 20 to 50 µm.

According to the invention the cake is micronized using Air Jet Mill equipment and the particle size distribution is analysed using MASTERSIZER 2000 equipment.

The Particle Size Distribution of the micronized cake having Bulk Density of about 0.9 (g/cm3), particle size distribution in the range of 20 to 50 µm, a BET (Brunauer-Emmett-Teller) active surface area in the range of 13 to 17 m2/gm and Phosphate Binding capacity in the range of 19 to 21 m/m.

As used herein, "Particle Size Distribution (PSD)" means the cumulative volume size distribution of equivalent spherical diameters as determined by laser diffraction in Malvern Master Sizer equipment or its equivalent.

In yet another embodiment, the invention provides micronized SucroFerric Oxyhydroxide which is characterised by Bulk Density of about 0.9 (g/cm3), particle size distribution in the range of 20 µm to 50µm, a BET active surface area is in the range of 13 to 17 m2/gm and Phosphate Binding capacity in the range of 19 to 21 m/m.

It is important that the lower the particle size the higher the active surface area and thus greater phosphate binding capacity due to the large surface area.

In yet another embodiment, the present inventors have carried out tests to analyse the relation between the BET active surface area and the particle size for SucroFerric Oxyhydroxide. The data is presented in table 1.

Relation between BET Active surface area and Particle size of Sucroferric oxyhydroxide:

Table 1

Particle size (micron)	**BET Active surface area (m^2/gm)**
250	1.2
150	6.7
105	9.45
50	13.97
37	15.81
20	16.04

As shown in table 1, the SucroFerric Oxyhydroxide particles (20 to 50 µm) obtained in accordance with the process of the present invention exhibits greater BET active surface area when compared to the particles of the prior art methods, the particle size of which are greater than the particle size of the present invention and thus possesses lower BET surface area.

Similarly, in a further embodiment, the present inventors have carried out tests to analyse the relation between the phosphate binding capacity and the BET active surface area of the particle of SucroFerric Oxyhydroxide. The data is presented in table 2.

Relation between BET Active surface area and Phosphate binding capacity of Sucroferric oxyhydroxide:

Table 2

BET Active surface area (m^2/gm)	**Phosphate binding capacity (m/m)**
13.97	19.01
15.81	19.38
16.04	20.12

As shown in table 2, the SucroFerric Oxyhydroxide particles (20 to 50 µm) obtained in accordance with the process of the present invention exhibits greater phosphate binding capacity due its higher BET active

surface area when compared to the particles of the prior art methods. The particle size of SucroFerric Oxyhydroxide produced by the prior art methods are greater than the particle size of the present invention and thus possesses lower BET active surface area and thus lesser phosphate binding capacity.

Accordingly, in a further embodiment, the invention provides pharmaceutical compositions comprising micronized SucroFerric Oxyhydroxide characterised by Bulk Density of about 0.9 (g/cm3), particle size distribution in the range of 20 to 50µm, a BET active surface area in the range of 13 to 17 m2/gm and Phosphate Binding capacity in the range of 19 to 21 m/m in association, with one or more pharmaceutical excipients, for use in the treatment of Hyperphosphatemia.

The pharmaceutical compositions prepared out of the SucroFerric Oxyhydroxide provided in accordance with the invention can be administered orally, in the form of tablets, chewable tablets, mini-tablets (micro-tablets), granules, capsules, caplets, granules, powders etc. The compositions may be prepared by conventional means or enabling technologies.

The following examples, which include preferred embodiments, will serve to illustrate the practice of this invention, it being understood that the particulars shown are by way of example and for purpose of illustrative discussion of preferred embodiments of the invention.

EXAMPLE 1

To 30 L of Process Water in a 100 L Reactor, added Potato Starch (3.35 Kg) under stirring. Ferric Chloride solution (17.72 Kg in 7.5 L water) and Sodium Carbonate solution (10.1 Kg in 50 L water) were added slowly and alternatively under stirring conditions. Then total solution sent to a PolyPropylene Filter Press for filtration. The cake thus obtained was washed with process water for reducing the Chloride content. Unloaded the material and sent for further processing to a Pan Mixer. Sucrose solution (3.35 kg in 6.7 L water) was added under continuous stirring to the cake till homogeneous mixing to obtain SuccroFerric OxyHydroxde as a cake. The product thus obtained was dried at 70°C and micronized to obtain the product with a particle size in the range of 20 to 50 µm.

Yield: 10 Kg
Purity: 98.35%
Chloride ion content: 2.01% w/w
Iron content: 25.6% w/w

Title: PROCESS FOR PREPARATION OF SUCROFERRIC OXYHYDROXIDE

ABSTRACT:

The present invention discloses industrially viable and cost effective process for preparation of SucroFerric Oxyhydroxide with a particle size of upto 50 microns. The invention further discloses pharmaceutical compositions comprising SucroFerric Oxyhydroxide characterised by Bulk Density of about 0.9(g/cm3); particle size distribution in the range of 20 to 50µm, a BET active surface area in the range of 13 to 17m^2/gm and Phosphate Binding capacity in the range of 19 to 21 m/m, for use in the treatment of Hyperphosphatemia.