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Declarations under Rule 4.17:

- as to the identity of the inventor (Rule 4.17(i))
- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))
- of inventorship (Rule 4.17(iv))

(54) Title: COMPOSITIONS OF FERRIC ORGANIC COMPOUNDS

(57) Abstract: The invention relates to Ferric organic compound containing compositions. The pharmaceutical compositions of the invention which include Ferric citrate as the active ingredient, a disintegrant, and one or more pharmaceutically acceptable excipients, along with an optional film coat wherein the Ferric citrate has BET surface area of 6 - 12 m²/g.



Description

Title of Invention: Compositions of Ferric Organic Compounds

Technical Field

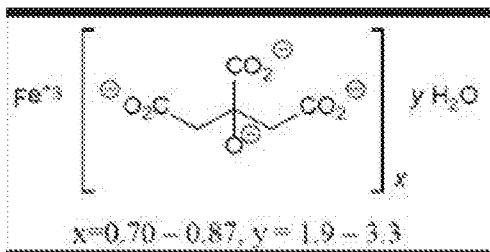
[0001] This invention relates to pharmaceutical composition of pharmaceutical grade ferric organic compounds, such as Ferric citrate.

Background Art

[0002] Ferric iron containing compounds are useful in the treatment of a number of disorders, including, but not limited to, hyperphosphatemia and metabolic acidosis. Ferric iron containing compounds existing in the art are for example Ferric chloride, Ferric oxide, Ferric fluoride, and Ferric citrate. Elevated amounts of phosphate in the blood can be removed by administering compounds such as Ferric citrate. Once in solution, the ferric iron binds phosphate, and the ferric phosphate compounds precipitate in the gastrointestinal tract, resulting in effective removal of dietary phosphate from the body. It is also believed that the absorbed citrate from Ferric citrate is converted to bicarbonate which corrects metabolic acidosis, a condition common in renal failure patients.

[0003] Ferric citrate has the following structure, and can be referred to as FCT.

[0004] [Chem.1]



[0005] The novel form of Ferric citrate has the formula $C_6H_5O_7Fe$ and has novel physical properties as determined by dissolution rates, and has a molecular weight of 244.94 g/mole. Ferric citrate is approved in 2014 in USA, and the NDA applicant is Keryx Pharmaceuticals. Pharmaceutical grade Ferric citrate is suitable for treating hyperphosphatemia, or other disorders characterized by high serum phosphate levels. Specifically, for treating subjects or patients with various renal diseases; e.g., End Stage Renal Diseases (ESRD), Chronic Kidney Disease (CKD) or other related kidney diseases, or subjects and patients who are on dialysis but not limited to hemodialysis. Ferric citrate is characterized as a light brown to beige powder, odorless and slightly ferruginous tasting. According to the Merck Index, Ferric citrate is slowly but completely soluble in cold water and readily soluble in hot water but diminishes in solubility with age.

[0006] US 5,753,706 discloses that Ferric citrate compounds can be used to control

phosphate metabolism and prevent metabolic acidosis in patients. Ferric citrate compounds can be used with patients suffering from renal failure associated with hyperphosphatemia or patients predisposed to development of a hyperphosphatemic condition. Ferric citrate also is used as a food supplement and additive. US 6,903,235 discloses that Ferric citrate is commercially available in the form of a combination of iron and citric acid of indefinite composition. It explains that the indefinite composition is likely due to difficulties encountered in its preparation but that those knowledgeable in the art understand and necessarily accept that commercially available Ferric citrate contains different molar ratios of iron and citric acid and also contains different amounts of water.

[0007] WO 2004/074444 discloses processes for making Ferric organic compounds, such as Ferric citrate, with enhanced dissolution rates, WO 2007/022435 is a continuation-in-part of WO 2004/074444 and discloses processes for making Ferric organic compounds soluble over a wide pH range and having a large surface area. WO 2007/089577 is directed to methods of treating soft tissue calcification using Ferric organic compounds, such as a Ferric citrate. WO 2007/089571 is directed to methods of treating chronic kidney disease using Ferric organic compounds, such as Ferric citrate. Where in US 7,767,851 relates to Ferric citrate having intrinsic dissolution of 1.9 to 4 mg/cm²/min, US 8,299,298 B2/ US 8,754,258 B2 relate to Ferric citrate having BET active surface area of at least 16 sq. m/g, US 8,338,642 B2/ US 8,901,349 B2/ US 8,609,896 B2 relate to Ferric citrate having BET active surface area greater than 16 sq. m/g. US 8,754,257 B2, US 9,328,133 and US 8,093,423 relate to FCT having intrinsic dissolution rate of 1.88-4.0 mg/cm²/min. US 8,754,258 B2/ US 8,846,976 B2/ US 9,050,316 B2 relate to FCT having intrinsic dissolution rate of at least 1.88 mg/cm² / min.

[0008] US 9,387,191/US 2013/274328 A1/US 2016/0263075 A relates to a composition of Ferric citrate comprising Pregelatinized starch, a lubricant and coating. IN 2016/28011726 which is an equivalent of US 9,387,191 relates to Ferric citrate tablet wherein the mean surface area to mass ratio of said granule particles is equal to or greater than 1 m²/g. IN 305/MUMNP/2012 which is an equivalent of US 9,387,191 relates to a tablet containing Ferric citrate with a mean surface area to mass ratio of 1 m²/g, and a binder, with LOD limitation. US 2016/0263038 which is assigned to Keryx pharma relates to FCT composition containing Pregelatinized starch. US 2009/0186939 which is an equivalent of US 7,767,851 relates to Ferric citrate having BET surface area $\geq 16\text{m}^2/\text{g}$. WO2016/162794 relates to FCT tablet, wherein Ferric citrate having a specific surface area less than $16\text{m}^2/\text{g}$. WO2016/162888 relates to Ferric citrate having a BET active surface area of less than $16\text{m}^2/\text{g}$. WO 2015/110968 relates to Ferric citrate having a BET active surface area in the range of 1-15 m²/g. WO

2015/198304 discloses FCT tablet preparation and process for preparation FCT composition using wet granulation. IN241/MUM/2014 / IN 201627024694 relates to Ferric citrate having a BET active surface area in the range of 1-15 m²/gm. IN 996/DEL/2015 relates to pharmaceutical grade Ferric citrate having a BET active surface area of less than 16 m²/g and a mean dissolution rate of 4 to 9 mg/cm²/min. IN 253106 which is an equivalent of WO 2007/022435 relates to Ferric citrate having intrinsic dissolution of 1.9 to 4 mg/cm²/min, and BET active surface area greater than 16 m²/g.

[0009] Accordingly, there exists a need for improved/technologically advanced/economically feasible/scalable compositions of Ferric organic compounds or Ferric citrate for human use.

Summary of Invention

[0010] The main aspect of the invention is to provide a pharmaceutical composition comprising Ferric citrate, along with disintegrant and other pharmaceutically acceptable excipients. According to other object of invention, the composition disintegrates within 15 minutes, and the BET surface area of Ferric citrate of the composition is the in the range of 6-12 m²/g.

[0011] The other aspect of the present invention is to provide an oral pharmaceutical composition of Ferric organic compound such as Ferric citrate. The other aspect of the invention provides a pharmaceutical composition comprising: Ferric organic compound; and a disintegrant.

[0012] In another aspect, the invention provides a pharmaceutical composition in the form of a tablet that comprises Ferric organic compound, a disintegrant selected from crospovidone, low substituted hydroxypropyl cellulose, cross linked cellulose, sodium starch glycolate, and microcrystalline cellulose or a combination thereof, and one or more pharmaceutically acceptable excipients, for example, a binder, a lubricant or any combination thereof.

[0013] In yet another aspect, the invention provides a pharmaceutical composition consisting of a tablet that comprises a powder blend or granules comprising Ferric organic compound; a disintegrant, and one or more pharmaceutically acceptable excipients, for example, a binder, and a lubricant.

[0014] In another aspect the pharmaceutical composition of the invention disintegrates within 15 minutes.

[0015] In another aspect, the pharmaceutical composition is directed to a tablet comprising Ferric citrate having a BET surface area in the range of 6-12 m²/g.

Description of Embodiments

[0016] The present invention relates to the pharmaceutical composition comprising Ferric organic compound, and disintegrant, which is prepared by either dry granulation or wet

granulation.

- [0017] In one aspect, the Ferric organic compounds, which include Ferric citrate, Iron Sucrose, Sucroferric Oxyhydroxide, preferably Ferric citrate.
- [0018] In other aspect, the pharmaceutical composition is directed to a tablet comprising Ferric citrate, having a BET surface area of compound is in the range of 6-12 m²/g.
- [0019] In another aspect, the tablet can include at least 70 weight percent Ferric citrate, at least 80 weight percent Ferric citrate, or at least 90 weight percent Ferric citrate.
- [0020] In yet another aspect, the disintegrant can be one or more of crospovidone, low substituted hydroxypropyl cellulose, cross linked cellulose, microcrystalline cellulose, crospovidone, sodium starch glycolate or a combination thereof.
- [0021] In another aspect, the tablet can include various additional components including, for example, one or more binders and/or one or more lubricants, and optionally other pharmaceutical excipients.
- [0022] Pharmaceutical excipients include excipients, for example, diluents, glidants etc.... Specific examples of pharmaceutically acceptable carriers and excipients that may be used to formulate oral dosage forms are described in the Handbook of Pharmaceutical Excipients, American Pharmaceutical Association (1986).
- [0023] Pharmaceutical grade ferric citrate contains a definite composition and a definite hydrate.
- [0024] In yet another aspect, the binder can be selected from one or more of hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose (HPMC), sodium alginate, alginic acid, guar gum, acacia gum, xanthan gum, carbopol, cellulose gum (carboxymethyl cellulose), ethyl cellulose, PVP/VA, povidone, starch (partially or fully pregelatinized starch) and methyl cellulose. The lubricant can be one or more of magnesium stearate, calcium stearate, sodium stearyl fumarate, polyethylene glycol (molecular weight above 3350), talc, mineral and vegetable oil.
- [0025] In one aspect, disclosed herein are compositions and process for the preparation of compositions containing Ferric organic compounds, which can include Ferric citrate. In various aspects, the formulations can include Ferric citrate as the active ingredient and a disintegrant.
- [0026] In another aspect, disclosed herein are pharmaceutical compositions and a process for the preparation of compositions containing Ferric organic compounds which can include Ferric citrate.
- [0027] According to one aspect, the composition can be prepared by dry granulation, where roller compactor is widely used as one of dry granulation process.
- [0028] In another aspect a dry granulation is prepared by compacting a dry powder blend of the drug and inactive tableting ingredients using roller compactor or slugging by using compression machine, milling the compacts and blending the resultant granulation

with other inactive ingredients followed by lubrication. This method is commonly used for drug substance that has better or moderate compressibility but not having good flow characteristics.

- [0029] In yet another aspect, a typical granulation is prepared by blending Ferric organic compound with inactive tableting ingredients in a blender, compacting the blend using a roller compactor, milling to a desired particle size and lubrication. Dry granulation is usually described as a method of controlled crushing of precompact powders densified by either slugging or passing the material between two counter-rotating rolls. More specifically, powdered components that may contain very fine particles are typically mixed prior to being compacted to yield hard slugs which are then milled and sieved before the addition of other ingredients and finally compressed into tablets. Although dry granulation would in many cases appear to be the best way to produce products such as tablets containing APIs, it has been relatively little used because of the challenges in producing the desired kind of granules as well as managing the granulated material in the manufacturing process. Known dry granulation methods, as well as the known issues related to them are well described in scientific articles, such as the review article "Roll compaction / dry granulation: pharmaceutical applications" written by Peter Kleinebudde and published in European Journal of Pharmaceutics and Biopharmaceutics 58 (2004) at pages 317-326.
- [0030] In one aspect, a wet granulation technique requires preparation of a blend, wetting the blend with a binder solution to get a wet mass, milling the wet mass into moist granules agglomerated with a binder and drying the granules, followed by further milling and blending with other inactive ingredients. For drugs that are not compressible and lack required flow characteristics, this process of agglomeration with a binder results in a compressible granulation. A typical granulation is prepared in a conventional granulator, high sheer granulator or fluid bed granulator. Drying of the wet granular mass is usually achieved in a fluid bed dryer.
- [0031] In yet another aspect, this invention relates to an improved process for preparing Ferric organic compound tablets by a modified wet granulation technique; and especially, but not exclusively, tablets which have a high active matter content, in particular, tablets containing poorly compressible medicinally active matter. There is much art and skill in practicing the wet granulation technique; but in outline, it involves no more than the incorporation of a granulating fluid into the mixed, powdery tablet ingredients (including at least some tableting aids) in such an amount and manner as to convert them into a uniform, moist, coherent, non-pasty mass, which then is formed into moist granules of fairly uniform size, usually by forcing the mass through a screen. Thereafter the moist granules are dried and rescreened to break down agglomerates, and finally blended with other tableting aids so as thus to arrive at the

granulate ready for tableting.

[0032] According to another aspect, the invention provides a process for making the pharmaceutical compositions described herein by roller compaction process comprising the steps of weighing Ferric organic compound and excipients, screening, blending Ferric organic compound and excipients for a suitable amount of time; roller compacting the blend into ribbons and milling the ribbons into granules; blending the granules with extra-granular excipients for a suitable amount of time; compressing the blend into tablets; coating the tablets.

[0033] According to yet another embodiment, the method for producing a pharmaceutical composition comprises providing an admixture of solid forms, e.g. an admixture of powdered ingredients, the admixture comprising Ferric organic compound, a disintegrant and one or more excipients selected from: a dry binder, a glidant, a diluent, a lubricant, and a filler; mixing the admixture until the admixture is substantially homogeneous, and compressing/compacting the admixture into a granular form using a roller compactor using a dry granulation composition as set forth in the Examples below.

[0034] According to yet another embodiment, the method for producing a pharmaceutical composition comprises providing an admixture of solid forms, e.g. an admixture of powdered ingredients, the admixture comprising Ferric organic compound, a disintegrant and one or more excipients selected from: a binder, a glidant, a diluent, a lubricant, and a filler; mixing the admixture until the admixture is substantially homogeneous, and compressing/compacting the admixture into a granular form using a wet granulation composition as set forth in the Examples below.

[0035] The following examples illustrate various aspects of the present invention. They are not to be construed to limit the claims in any manner whatsoever.

Examples

[0036] **Example 1: Ferric citrate formulation was prepared by using dry granulation technique, where L-HPC has been used as the disintegrant.**

[0037]

[Table I]

Excipients	mg/unit	% w/w
Core Tablet		
Ferric citrate	1000.0	88.50
L-HPC	20.0	1.77
Calcium Stearate	10.0	0.88
Extragranular Part		
L-HPC	80.0	7.08
Calcium Stearate	20.0	1.77
Tablet weight	1130	100.00
Film coating		
Opadry	20.0	
Purified water	QS	
Total	1150.0	100.00

[0038] **Example 2: Ferric citrate formulation was prepared by using dry granulation technique, where Crospovidone has been used as the disintegrant.**

[0039] [Table II]

Excipients	mg/unit	% w/w
Core Tablet		
Ferric citrate	1000.0	88.50
Hydroxypropyl methyl cellulose	20.0	1.77
Magnesium Stearate	10.0	0.88
Extragranular Part		
Crospovidone	80.0	7.08
Magnesium Stearate	20.0	1.77
Tablet weight	1130	100.00
Film coating		
Opadry	20.0	
Purified water	QS	
Total	1150.0	100.00

[0040] **Example 3: Ferric citrate formulation was prepared by using dry granulation technique, where Croscarmellose sodium has been used as the disintegrant.**

[0041] [Table III]

Excipients	mg/unit	% w/w
Core Tablet		
Ferric citrate	1000.0	88.50
Hydroxypropyl methyl cellulose	20.0	1.77
Magnesium Stearate	10.0	0.88
Extragranular Part		
Croscarmellose sodium	80.0	7.08
Magnesium Stearate	20.0	1.77
Tablet weight	1130	100.00
Film coating		
Opadry	20.0	
Purified water	QS	
Total	1150.0	100.00

[0042] **Example 4: Ferric citrate formulation was prepared by using dry granulation technique, where L-HPC has been used as the disintegrant.**

[0043]

[Table IV]

Excipients	mg/unit	% w/w
Core Tablet		
Ferric citrate	1000.0	88.50
Hydroxypropyl cellulose	20.0	1.77
Magnesium Stearate	10.0	0.88
Extragranular Part		
L-HPC	80.0	7.08
Magnesium Stearate	20.0	1.77
Tablet weight	1130	100.00
Film coating		
Opadry	20.0	
Purified water	QS	
Total	1150.0	100.00

[0044] Manufacturing Process:

a) The drug substance and dry binder were sifted and loaded into blender and blended for about 10 min,

b) The intragranular lubricant was sifted and added to above step and blended for about 5 min,

c) The above material was loaded into hopper of Compactor and compacted with suitable hardness of ribbons with preset roller RPM, GAP, Vertical and horizontal feeder screw speed.

d) The above flakes were milled in multimill fitted with suitable screen at suitable speed and suitable direction,

e) The milled material was sifted using suitable ASTM mesh. The compaction followed by milling process will be continued till desired particle size of granules obtained.

f) The above material loaded in blender and blended for 5 min,

g) The extragranular material was sifted through # 40 ASTM and loaded to above step and blended for 5 min,

h) The above lubricated material compressed into tablets with suitable punches,

i) The core tablets are coated with opadry and evaluated for physicochemical properties.

[0045] **Example 5: Ferric citrate formulation was prepared by using wet granulation technique, where L-HPC has been used as the disintegrant.**

[0046] [Table V]

Excipients	mg/unit	% w/w
Core Tablet		
Ferric citrate	1000.00	90.9
L- Hydroxypropyl cellulose	10.00	0.9
Hydroxypropyl cellulose	20.00	1.8
Extragranular Part		
L- Hydroxypropyl cellulose	55.00	5.0
Calcium Stearate	15.00	1.4
Tablet weight	1100.00	100.00
Film coating		
Opadry	30.00	
Purified water	QS	
Total	1130.0	-

[0047] **Example 6: Ferric citrate formulation was prepared by using wet granulation technique, where crospovidone has been used as the disintegrant.**

[0048]

[Table VI]

Excipients	mg/unit	% w/w
Core Tablet		
Ferric citrate	1000.00	90.9
Hydroxypropyl cellulose	20.00	1.8
Extragranular Part		
Crospovidone	65.00	5.9
Calcium Stearate	15.00	1.4
Tablet weight	1100.00	100.00
Film coating		
Opadry	30.00	
Purified water	QS	
Total	1130.0	-

[0049] **Example 7: Ferric citrate formulation was prepared by using wet granulation technique, where crospovidone has been used as the disintegrant.**

[0050] [Table VII]

Excipients	mg/unit	% w/w
Core Tablet		
Ferric citrate	1000.00	90.91
Crospovidone	5.00	0.45
Hypermellose	15.00	1.36
Extragranular Part		
Crospovidone	60.00	5.45
Calcium Stearate	20.00	1.82
Tablet weight	1100.00	100.00
Film coating		
Opadry	30.00	
Purified water	QS	
Total	1130.0	-

[0051] **Example 8: Ferric citrate formulation was prepared by using wet granulation technique, where L-HPC has been used as the disintegrant.**

[0052] [Table VIII]

Excipients	mg/unit	% w/w
Core Tablet		
Ferric citrate	1000.00	90.91
Povidone	30.00	2.73
Extragranular Part		
L-Hydroxy propyl cellulose	50.00	4.55
Magnesium Stearate	20.00	1.82
Tablet weight	1100.00	100.00
Film coating		
Opadry	30.00	
Purified water	QS	
Total	1130.0	-

[0053] PROCESS:

a) The drug substance along with intragranular ingredients was sifted through # 20 ASTM.

b) The binding agent was dissolved in purified water under stirring to get clear solution.

c) Step no 1 material was loaded into top bowl of fluid bed processor and coated with step no b binder solution until consistence granules obtained. The set bed temperature during the process is $40^{\circ}\text{C} \pm 10^{\circ}\text{C}$.

d) The above material was dried at set inlet temperature $50^{\circ}\text{C} \pm 10^{\circ}\text{C}$ till target LOD achieved.

e) The dried granules were sifted through # 18 ASTM mesh and retained are milled in multimill fitted with suitable screen at optimum speed and milled granules were sifted through # 18 ASTM.

f) The shifted material was loaded in blender and blended for 5 min.

g) The extragranular material was sifted through # 40 ASTM and loaded to above step and blended for 5 min.

h) The above lubricated material was compressed into tablets.

i) The core tablets were coated with opadry and evaluated for physicochemical properties.

Claims

- [Claim 1] A pharmaceutical composition comprising: (a) a core comprising Ferric organic compound, disintegrant selected from the group comprising of crospovidone, low substituted hydroxypropyl cellulose, and cross linked cellulose, or a combination thereof and one or more pharmaceutically acceptable excipients (b) optionally a coating the core with a film coating material.
- [Claim 2] According to claim 1, the Ferric organic compound is selected from the group comprising of Ferric citrate, Iron Sucrose, Sucroferric Oxyhydroxide, preferably Ferric citrate.
- [Claim 3] According to claim 1, pharmaceutically acceptable excipients include binders, glidants, lubricants, fillers and combinations thereof.
- [Claim 4] According to claim 1 the pharmaceutical composition is prepared using wet granulation or dry granulation techniques.
- [Claim 5] A Ferric citrate composition comprising: (a) a core comprising disintegrant selected from the group consisting of crospovidone, low substituted hydroxypropyl cellulose, and cross linked cellulose, and a combination thereof, and one or more pharmaceutically acceptable excipients (b) optionally coating the core with a film coating material, wherein the Ferric citrate has BET surface area of 6 - 12 m²/g. This is a sample Claim. Since separate searches and examinations are required for distinctly different inventions, additional fees are required if the international search or international preliminary examination is to cover two or more inventions (or groups of inventions linked as just described).
- [Claim 6] A pharmaceutical composition comprising Ferric citrate having BET surface area of 6-12 m²/g, wherein the composition is prepared by dry granulation or wet granulation, wherein the finished product disintegrates within 15 minutes.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2018/050441

A. CLASSIFICATION OF SUBJECT MATTER
A61K31/295 Version=2018.01

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

TotalPatent One, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, Y	WO2016162794 A1 (LEIUTIS PHARMACEUTICALS PVT LTD [IN]) 13 october 2016 (13-10-2016) the whole document	1; 2-6
Y	WO2004074444 A2 (GLOBOASIA LLC [US]) 02 september 2004 (02-09-2004) examples claims 24, 25, 34-42, 51 -55	1-6
Y	WO2015110968 A1 (LUPIN LTD [IN]) 30 july 2015 (30-07-2015) claims 1, 7-10, examples	1-6

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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"P" document published prior to the international filing date but later than the priority date claimed	"&" document member of the same patent family

Date of the actual completion of the international search

31-10-2018

Date of mailing of the international search report

31-10-2018

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INTERNATIONAL SEARCH REPORT
Information on patent family members

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Citation	Pub.Date	Family	Pub.Date
WO 2004074444 A2	02-09-2004	AU 2004213819 A 1	02-09-2004
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