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FERROUS CHELATE COMPOSITIONS FOR ORAL ADMINISTRATION

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6 Claims. (Cl. 167—68)

This invention relates to compositions useful for the oral administration of iron in therapeutic or prophylactic dosage. More particularly it relates to compositions containing chelated iron in oral dosage unit form and to a method of compounding same.

The need for iron in the daily diet of the average individual is fully established and the conditions which result from a failure to supply the necessary minimum amount of iron per day are well known. Iron deficiency or iron anemia is a condition which occurs in a large segment of the population, particularly in females. The treatment of iron deficiency by injections of iron compounds and oral administration of iron is widespread but is attended with disadvantages to the patient. In oral administration of iron compounds for example, the incidence of nausea and other undesirable side reactions is quite prevalent. It has been necessary in order to obtain favorable iron response in an iron deficient patient to administer a comparatively large amount of iron per day to the adult patient. This large amount of iron, usually administered in the form of ferrous sulfate, often results in undesirable side reactions such as nausea and vomiting. In order to overcome this tendency it has become common practice to administer tablets containing only a small portion of the total dosage at intervals and to thereby spread the total intake of iron over the full day. This in itself is inconvenient to the patient and does not always solve the problem of eliminating the undesirable side reactions.

It is an object of this invention to provide a composition which will give a high iron response in relatively small dosage and with a minimum of side effects.

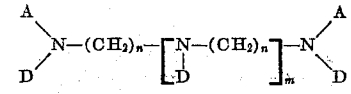
Another object of the invention is to provide a convenient dosage unit form suitable for oral administration and capable of giving a high iron response.

In the accomplishment of the foregoing objects and in accordance with the practice of the present invention there is now provided a new iron composition useful for oral administration and containing as the active ingredient a chelated iron compound which may be associated with a solid pharmaceutical carrier. It was an unexpected finding of this invention that a highly favorable response could be obtained in humans using a relatively small dosage of a chelated iron composition because experiments in rats had proved unsatisfactory. It was found, for example, that a favorable iron response comparable to that obtained when ferrous sulfate is used as the source of elemental iron could be obtained using only ¼ to ⅛ the amount of elemental iron in the form of a chelated iron complex or co-ordination compound.

By favorable iron response is meant a significant increase in the hemoglobin count of a blood sample. Other criteria are also employed to show a favorable iron response and measured by any of these criteria the chelated iron composition of the present invention gives a highly favorable response.

By chelated iron as the term is used herein it is desired

to include iron derivatives of compounds which fall within the scope of the formula



wherein n is 2 to 6 inclusive, m is 0 to 2 inclusive, D is $-CH_2COOH$, $-CH_2CH_2COOH$ or the alkali metal salts thereof (sodium, potassium and $-NH_4$), and A is the same as D, or lower alkyl or hydroxy lower alkyl. As examples of the carboxylic poly- or diamino acids specifically included within the above formula may be mentioned ethylene diamine N,N′ tetraacetic acid, propylene 1,2-diamine N,N′ tetraacetic acid, 1,3-diaminopropanol-2-N,N′ tetraacetic acid, diethylenetriamine N,N′ tetraacetic acid, diethylenetriamine N,N′N″ pentaacetic acid, hexamethylenediamine N,N′ tetraacetic acid, β-hydroxyethylethylenediamine-N,N′ triacetic acid. Iron forms a stable complex or co-ordination compound with the above identified polycarboxylic amino acids and salts thereof and the iron is readily released from such compositions upon oral ingestion. The compounds referred to in this paragraph may also be conveniently named alkylenepolyamine polyacetic acids.

The solid pharmaceutical carrier to which the invention pertains may take the form of tablets, powders, capsules or other dosage forms which are particularly useful for oral ingestion. Solid diluents and/or tablet adjuvants such as corn starch, lactose, talc, stearic acid, magnesium stearate, gums and the like are all included in this class. In fact, any of the tableting materials used in ordinary pharmaceutical practice may be employed where there is no incompatibility with the chelated iron of this invention. The iron chelates used herein have between about 9% and 17% elemental iron and the bulk represented by the substantially inactive polycarboxylic amino acid residue may take the place of a diluent or filler in the oral dosage form. The material may be tableted with or without adjuvants but it will ordinarily be better practice to employ at least the lubricating compounds such as talc, stearic acid and magnesium stearate. Alternatively the active material with or without its adjuvant materials may be placed in a capsule such as the usual gelatin capsule and administered in that form. In still another embodiment the active chelated iron composition may be put with or without adjuvants into powder packets or in powdered form and administered in this manner.

The amount of chelated iron in the composition in this invention may be varied to suit certain individual situations. It is necessary, however, that the active ingredient constitute a proportion such that a suitable dosage will be obtained. It will be apparent that several unit dosage forms may be administered at the same time or at intervals. Hence, it will be apparent that any small but significant amount of chelated iron may be employed in each dosage unit. As a practical matter it is desirable to have at least about 5 milligrams of elemental iron present in each dosage unit and the amount may be varied upwardly from that point at will. One particularly useful dosage unit which will be described in detail in the following examples contains sufficient chelated iron to provide about 16⅔ milligrams of elemental iron per tablet. In this manner the patient may obtain 50 milligrams of elemental iron by taking one tablet three times a day. It has been found that this schedule of treatment will provide iron response comparable to that obtained with far greater amounts of elemental iron administered in the form of ferrous sulfate according to previously known practices.

The following examples are presented in order to define

the invention more clearly but it will be understood that the invention is not intended to be limited in any way by these examples.

Example I

1200 tablets were made up according to the following directions:

	Grams
Sequestrene H_2Fe (an iron complex with ethylenediaminetetraacetic acid containing about 17% elemental ferrous iron)	120
Talc	6
Stearic acid	4
Magnesium stearate	2

Add 3 grams of talc and 2 grams of stearic acid to the sequestrene H_2Fe (Alrose Chemical Company) through a 40-mesh screen. Mix well and slug. Grind the slugs through a 4-mesh screen and then through a 16-mesh screen. Add the remainder of lubricants through a 40-mesh screen and blend well. Compress on a convex punch so that 10 tablets weigh about 1.1 grams.

Add sufficient coats of cellulose acetate phthalate in solution, dusting with talc, until the tablets meet the U. S. P. disintegration test for enteric coatings. Sub-coat with gelatin and acacia and sub-coating powder. Apply syrup and polish.

The tablets contain about 16⅔ milligrams of elemental ferrous iron per tablet and when taken three times daily to provide a daily dose of 50 milligrams of elemental iron the composition results in a high iron response as evidenced by a substantial increase in the hemoglobin count in the blood of patients taking the tablets. The response is equal to or superior to that obtained when 200 milligrams per day of elemental iron is given in the form of ferrous sulfate. The side reactions, vomiting and nausea, are far less in the composition of this invention.

Lactose, corn starch and other diluents or adjuvants may also be added if desired, and if added, they do not substantially alter the response obtained.

Example II

1200 tablets were made up according to the following directions:

	Grams
Sequestrene H_2Fe (containing about 17% elemental ferrous iron)	60
Talc	3
Stearic acid	2
Magnesium stearate	1

The ingredients were compounded in the manner set forth in Example I and 10 such tablets weighed 0.55 gram. The tablets were sub-coated with gelatin and acacia solution and sub-coating powder. Then a suitable syrup coating was applied and polished.

The tablets contained approximately 8⅓ milligrams of elemental ferrous iron per tablet and three tablets per day were administered to provide a daily dose of 25 milligrams of elemental iron. Favorable iron response was noted and there were no important side reactions.

Lactose, corn starch and other diluents and adjuvants may also be added if desired in order to make the tablet a desirable size and shape.

Example III

1500 tablets were made up according to the following directions:

	Grams
Sequestrene H_2Fe (containing about 10% elemental ferrous iron)	250
Carbowax 6000	50
Talc	15
Stearic acid	9
Magnesium stearate	6

The chelated iron is passed through a 40-mesh screen and massed with the melted Carbowax. The mass is allowed to set for about 4 hours at about 25° C. It is then granulated through a 16-mesh screen, talc, stearic acid, and magnesium stearate are added through a 40-mesh screen and the composition is blended well. When compressed on an 11/32" convex punch 10 such tablets weigh 2.2 grams.

A special clear, colored enteric coating of cellulose acetate phthalate resin was applied to the tablets until they would meet the U. S. P. test for enteric coating. It is not necessary to apply sub-coating and sugar-coating to these tablets since their appearance is highly satisfactory.

These tablets contain about 16⅔ milligrams of elemental ferrous iron per tablet.

Example IV

A multiple viamin-mineral tablet was prepared according to the following directions:

Sequestrene H_2Fe (containing about 10% elemental ferrous iron)	grams	200
Ascorbic acid (as sodium ascorbate)	do	35.8
Nicotinamide	do	6.0
Pyridoxine hydrochloride	do	0.6
Polyvinylpyrrolidone	do	10
Anhydrous alcohol, q. s	cc	100
Intrinsic factor concentrate	grams	3
Vitamin B_{12} oral grade powder (500 mcg./gm.)	grams	12
Folic acid	do	0.79
Thiamin mononitrate	do	1.38
Riboflavin	do	1.19
Calcium pantothenate	do	2.89
Talc	do	2.73
Stearic acid	do	5.46

Blend the chelated iron, sodium ascorbate, nicotinamide and pyridoxine hydrochloride and pass through a 40-mesh screen. Mass with 10% polyvinylpyrrolidone in anhydrous alcohol. Granulate through a 4-mesh screen and dry at 120° F. for 18 hours. Pass the dried granulation through a 16-mesh screen and blend in the intrinsic factor concentrate, vitamin B_{12} powder, folic acid, thiamin mononitrate, riboflavin, calcium pantothenate, talc, stearic acid and pass through a 40-mesh screen into the main granulation. Mix well and compress on a ½" convex punch. 10 such tablets weighed 6.91 grams.

Tablets of this type are highly suitable for either therapeutic or prophylactic treatment of vitamin and iron deficiencies. The tablets can be marketed uncoated, or they can be sugar coated or enteric coated as desired.

Example V

461 capsules were prepared according to the following directions:

	Grams
Sequestrene H_2Fe (containing 12% elemental ferrous iron)	130
Lactose	26

Pass the chelated iron and the lactose through a 40-mesh screen and encapsulate into gelatin capsules. Each capsule contains about 33.3 milligrams of elemental ferrous iron.

Example VI

2,000 tablets were prepared according to the following directions:

Sequestrene H_2Fe	grams	412
Cane sugar	do	103
Starch, for paste	do	15
Distilled water	cc	100
Magnesium stearate	grams	12.78
Dry starch	do	95.9

Charge the sequestrene iron and cane sugar into a mixer and blend well. Prepare a hot starch paste and

add a sufficient amount to mass the ingredients. Granulate through a 4-mesh screen and dry at 120° F. overnight. Grind the dry granulation through a 14-mesh screen and blend in the dry starch and magnesium stearate. Compress into tablets.

Each tablet contains about 25 mg. of ferrous iron and may be coated in any one of the several ways described in preceding examples.

The sequestrene H_2Fe previously referred to is a product of the Alrose Chemical Company and a typical example of it analyzes as follows:

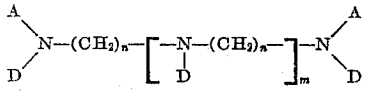
	Percent
Ethylenediamine tetraacetic acid	72.1
Total iron	13.3
Ferrous iron	13.2
Theoretical iron content for trihydrate	13.9

The theoretical iron content may vary between about 9% and 17% in different samples.

Others may practice the invention in any of the numerous ways which will be suggested to one skilled in the art. It is contemplated that all such practices of the invention shall be covered hereby provided they fall within the scope of the appended claims.

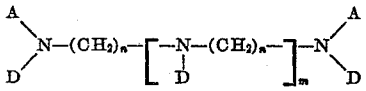
I claim:

1. A solid composition for oral administration in dosage unit form for administering iron comprising at least about 5 mg. of a physiologically acceptable chelated ferrous iron in which the chelating compound is represented by the formula



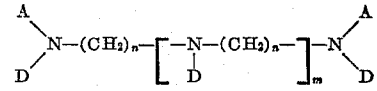
wherein n is 2 to 6 inclusive, m is 0 to 2 inclusive, D is selected from the group consisting of $-CH_2COOH$, $-CH_2CH_2COOH$, and the alkali metal salts thereof, A is selected from the group consisting of lower alkyl, hydroxy lower alkyl, $-CH_2COOH$, $-CH_2CH_2COOH$, and the alkalimetal salts thereof, and a non-toxic, solid pharmaceutical carrier.

2. A solid composition for oral administration for treatment of iron deficiencies comprising at least about 5 milligrams of elemental iron in the form of a ferrous salt of a chelating compound represented by the formula



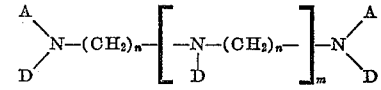
wherein n is 2 to 6 inclusive, m is 0 to 2 inclusive, D is selected from the group consisting of $-CH_2COOH$, $-CH_2CH_2COOH$, and the alkali metal salts thereof, A is selected from the group consisting of lower alkyl, hydroxy lower alkyl, $-CH_2COOH$, $-CH_2CH_2COOH$, and the alkali metal salts thereof.

3. As a new article of manufacture a solid composition for oral administration comprising a capsule of encapsulating material containing at least about 5 milligrams of elemental iron in the form of a ferrous salt of a chelating compound represented by the formula



wherein n is 2 to 6 inclusive, m is 0 to 2 inclusive, D is selected from the group consisting of $-CH_2COOH$, $-CH_2CH_2COOH$, and the alkali metal salts thereof, A is selected from the group consisting of lower alkyl, hydroxy lower alkyl, $-CH_2COOH$, $-CH_2CH_2COOH$, and the alkali metal salts thereof.

4. A tablet for oral administration for the treatment of iron deficiencies containing a non-toxic, solid pharmaceutical carrier and at least about 5 milligrams of elemental iron in the form of a ferrous salt of a chelating compound represented by the formula



wherein n is 2 to 6 inclusive, m is 0 to 2 inclusive, D is selected from the group consisting of $-CH_2COOH$, $-CH_2CH_2COOH$, and the alkali metal salts thereof, A is selected from the group consisting of lower alkyl, hydroxy lower alkyl, $-CH_2COOH$, $-CH_2CH_2COOH$, and the alkali metal salts thereof.

5. A tablet for oral administration for therapeutic and prophylactic use containing a non-toxic, solid pharmaceutical carrier and at least about 5 milligrams of elemental iron in the form of a ferrous salt of ethylenediamine tetraacetic acid.

6. A solid composition for oral administration of iron which comprises at least about 5 milligrams of elemental iron in dosage unit form, said iron being in the form of the ferrous salt of β-hydroxyethylethylenediamine-N,N' triacetic acid.

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