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FERROUS CITRATE COMPLEX

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This invention relates to a new therapeutically effective compound for providing a source of iron in the diet and more particularly relates to a new therapeutic compound in the nature of a ferrous salt of citric acid.

Heretofore, it has been the established practice to administer iron in the form of ferrous sulfate to provide a source of iron in the diet of humans where indicated. Supplemental sources of iron are frequently required by anemic, pregnant, and aged patients.

It has been frequently observed that the administration in the diet of ferrous compounds such as ferrous sulfate consistently causes some degree of digestive discomfort. Youmans, Journal of the American Medical Association, volume 143, page 1252, 1950; summarized the undesirable features due to the addition of ferrous compounds in the diet by stating that patients undergoing such treatment traditionally complain of gastro-intestinal symptoms, nausea, cramps, diarrhea and epigastric distress from taking iron; but if the patients persist in continuing to take iron, the symptoms usually disappear, probably due to an acquired tolerance.

Iron preparations in liquid form, and solutions of ferrous sulfate in particular, are offensive to taste. Ferrous compounds are unstable and are readily oxidized to the ferric form on exposure to the atmosphere.

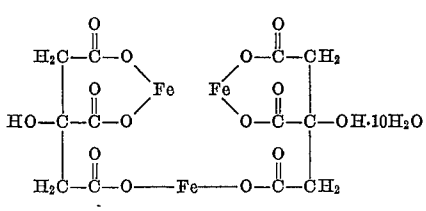
It is an object of this invention to provide a stable, therapeutic compound in the nature of a ferrous salt of citric acid.

It is another object of this invention to provide a stable, therapeutic compound containing all of the chemically bound iron in the ferrous state which upon oral administration is utilized normally without gastro-intestinal disturbances, constipation or diarrhea.

It is still another object of this invention to provide a new and improved therapeutic tablet effective by oral administration in providing a supplemental source of iron in the diet.

Other and further objects of this invention will be apparent from the description to follow, the examples and the appended claims.

It has now been discovered that a compound having the empirical formula $Fe_3(C_6H_5O_7)_2 \cdot 10H_2O$ and the structural formula



in which the ten molecules of water are bound by coordinate covalences, may be prepared from citric acid or ferrous acid citrate by reacting either compound with the stoichiometric quantity of powdered iron required to produce triferrous dicitrate. The complex is a very slightly colored powder and is very stable to air oxidation, the ferrous content remaining substantially unchanged after six months of storage in air at ordinary temperatures in the absence of direct light. However, removal of the water by vacuum desiccation at elevated or room temperature results in spontaneous auto-oxidation of the complex with the conversion of the ferrous iron of the complex to the ferric state. The dehydrated compounds continue to oxidize to the ferric state when allowed to stand at room temperature even in the absence of light. The structure of the dehydrated compound or of the mixture of compounds formed on dehydration is not known but X-ray diffraction patterns and chemical analysis show it to be an entirely different chemical entity from that of the hydrated material having the above formula.

The following examples are set forth for the purpose of illustrating the method of preparing the ferrous citrate complex and compositions of matter in dosage unit form according to this invention but are not to be construed as a limitation. All parts are given by weight unless otherwise indicated.

EXAMPLE I

Triferrous dicitrate decahydrate

In a reaction kettle equipped with a stirrer, reflux condenser, and gas inlet, tube reaching below the expected liquid level, is placed 420 parts (2 moles) of citric acid monohydrate and 2000 parts of water. The solution is stirred at room temperature while nitrogen is passed in, and when the air is displaced from the kettle (about 30 minutes) 111.7 parts (2 moles) of reduced powdered iron is added rapidly. The introduction of nitrogen is continued throughout the reaction and the mixture is stirred and heated to 80° C. during a period of two hours and maintained at that temperature for an additional two or three hours. When the reaction is completed, as indicated by the disappearance of unreacted iron particles, an additional 55.9 parts (1 mole) of reduced powdered iron is added and stirring is continued under nitrogen while maintaining the reaction temperature at 80° C. until the total reaction time is 24 hours.

At the end of this period, the mixture is suction-filtered while hot. The filtered cake is washed with water until free from chloride ion and then three times with an equal volume of isopropanol. The product is dried at 50° C. for six hours. The yield is 650 parts (90% calculated as the decahydrate) of white crystalline material.

The product so obtained is analyzed for carbon, hydrogen, and iron.

	Found, percent	Theory for the decahydrate, percent
Carbon	20.02	19.85
Hydrogen	4.15	4.17
Iron	23.16	23.08

The above analysis corresponds most closely to the decahydrate.

EXAMPLE II

Monoferrous acid citrate monohydrate

In a reaction kettle, similar to that described in Example I above, is placed 500 parts of water and 105 parts (0.5 mole) citric acid monohydrate. A slow stream of nitrogen is passed through the mixture during the entire reaction. Twenty-seven and nine-tenths parts (0.5 mole) of reduced iron powder is added to the citric acid solution and the mixture is heated to 75° C. and maintained at that temperature for 3.5 hours. At the end of this period the solid material is removed by filtration, washed with water, then with acetone, and air dried. One

hundred twenty-one parts of the dry product is recovered. The product so obtained is analyzed for carbon, hydrogen, and iron.

	Found, percent	Theory for the $FeH(C_6H_5O_7)\cdot H_2O$ percent
Carbon	27.01	27.30
Hydrogen	3.08	3.05
Iron	21.13	21.16

EXAMPLE III

Triferrous dicitrate decahydrate

One hundred seventeen and four-tenths parts (0.445 mole) of the monoferrous acid citrate monohydrate obtained from Example II above is added to 500 parts of water, and air is displaced from the reaction kettle with nitrogen as described above. To this suspension is added 12.4 parts (0.223 mole) of powdered iron and the mixture is stirred and heated at 85°–90° C. for 24 hours. The product is filtered off, washed with water, then with acetone, and air dried. One hundred twenty-nine parts of a crystalline product similar to the product obtained in Example I is recovered. The product so obtained had the final analysis:

	Found, percent	Theory for the decahydrate, percent
Carbon	19.97	19.85
Hydrogen	4.09	4.17
Iron	23.44	23.08
Fe^{+++}	0.017	0

In employing the ferrous citrate complex of the present invention for the provision of a source of iron in the diet, the complex may be uniformly distributed in a suitable vehicle and formed into a tablet. Inert diluents or fillers are chosen which are chemically compatible with the complex. Satisfactory diluents include lactose, dextrose, sucrose, sodium chloride, glycine, kaolin and starch. It is desirable that a binder such as acacia, zein, tragacanth, gelatin, sodium carboxymethylcellulose, or methylcellulose and also, in order that a tablet may be readily prepared, that a lubricant such as magnesium stearate, zinc stearate, mineral oil, stearic acid, stearyl alcohol or mono- and polyglycol esters also be intimately admixed with the filler and active agent. The above ingredients, including the complex, may be formed into a tablet by thoroughly mixing the ingredients in a moist condition, granulating and compressing the mixture into tablets by conventional methods. Additives such as tri-

calcium citrate may be used alone or with inert diluents if it is desired to supply calcium along with the iron in the tablet or formulation.

EXAMPLE IV

	Milligrams
$Fe_3(C_6H_5O_7)_2\cdot 10H_2O$	250
$Ca_3(C_6H_5O_7)_2$	50
Dipotassium phosphate	50
Acacia	50
Magnesium stearate	30
Lactose	70

EXAMPLE V

$Fe_3(C_6H_5O_7)_2\cdot 10H_2O$	200
$Ca_3(C_6H_5O_7)_2$	100
Dipotassium phosphate	100
Acacia	50
Magnesium stearate	30
Lactose	70

The novel ferrous citrate complex to which the present invention is directed, has been found to have value for the provision of a source of iron where the administration of this element in the diet is indicated and is particularly valuable for oral administration in the diet of anemic, pregnant, and aged individuals.

Since certain changes in carrying out the above process and certain modifications in the compositions which embody the invention may be made without departing from its scope, it is intended that all matter contained in the description shall be interpreted as illustrative and not in a limiting sense.

This application is a continuation-in-part of application Serial No. 617,943 filed October 24, 1956, now abandoned.

What is claimed is:

1. Triferrous dicitrate decahydrate.

2. A composition of matter in dosage unit form for oral administration effective as a source of iron in the diet which comprises a ferrous citrate complex having the formula $Fe_3(C_6H_5O_7)_2\cdot 10H_2O$ in intimate admixture with an inert solid diluent.

3. A process for the preparation of a triferrous dicitrate complex having associated therewith water of hydration; comprising the steps of adding powdered iron to a suspension of monoferrous acid citrate in water and heating the mixture whereby the complex is formed and precipitated, and removing the precipitated complex.

References Cited in the file of this patent

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