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IRON-SORBITOL, DEXTRIN AND CITRIC ACID COMPLEX

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Preparation containing complex of iron, sorbitol, dextrin and citric acid is described. Complex formation with sorbitol alone or in conjunction with citric acid is not satisfactory and dextrin is an essential component for its stability.

INTRODUCTION

Anaemia due to the deficiency of iron is very common in Pakistan and hence there is a great demand for efficacious but nonirritant iron preparations. Salts of iron such as ferrous sulphate, gluconate and fumarate are quite effective but being ionic in nature, are not free from side reactions. Their use in parenteral therapy has almost been discontined while in oral therapy it has been reported that approximately half of all patients given ionic iron by mouth have some complaints and 10–12% have severe gastrointestinal symptoms to interfere with the treatment.

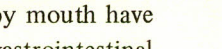
Iron saccharate was the first nonionic preparation introduced by Nissim [1] in 1947 for intravenous administration. It was followed by complexes of iron-dextrin [2]; dextran [3], cholin [4], citric acid, disodium - N - hydroxy ethyl [5], ethylenediamine triacetate and sorbitol [6], dextrin and citric acid. Among these iron–saccharate, iron–dextran and iron–sorbitol, dextrin and citric acid complex have achieved commercial importance. These preparations being nonionic and colloidal in nature are miscible with blood and show no or minimal pain at the injection site.

In developing countries like Pakistan parenteral therapy is beyond the reach of the majority of the population living in rural areas. In such a case the idea is, therefore, an oral preparation of iron which does not in any way irritate the stomach or the intestine nor cause vomiting or diarrhoea. Nonionic and colloidal preparations conform to a large extent to these specific cations. The formation of iron-saccharate, iron-dextrin, iron-glucose, maltose and lactose was studied [7] earlier by us for this purpose. Iron-saccharate proved an excellent oral preparation. In the present communication we have studied the formation of iron-sorbitol, dextrin and citric acid complex, as sufficient information on its preparation is not available in literature.

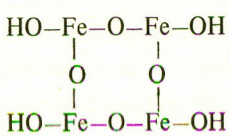
As an intramuscular preparation its pharmacology [9–10] has been thoroughly investigated, but clinical study on its oral use is lacking.

Methods and Characterization of the Preparation

Aqueous ferric chloride solution (24%, 20 ml) equivalent to 1 g elemental iron was warmed to 40° and 20% anhydrous sodium carbonate solution (16 ml) was added to it dropwise with vigorous stirring. Red precipitate of



γ-ferric hydroxide, HO–Fe–O–Fe–O–Fe–OH was obtained. When precipitation is effected in cold a yellow precipitate of α-ferric hydroxide (I) is obtained, which does not react



(I)

with sorbitol in forming a complex. The reddish ferric hydroxide was washed with distilled water by decantation to get rid of electrolytes. The wet ferric hydroxide was taken in a porcelain dish, required quantity of sorbitol, dextrin, sodium hydroxide and citric acid was admixed thoroughly and heated at different temperatures for the periods indicated in the Tables 1–3. A dark brown cake was obtained which gave clear solution when dissolved in water. The solution was centrifuged, anlaysed and made up to contain 5% elemental iron. Different ratios were tried to get the ideal complex, but only successful results have been recorded in the Tables. At low temperatures or when the time of heating is shorter, the solution of the final product looks brownish and turbid against reflected light. About 5% iron was transformed into oxide and its complete utilization in the formation of complex has never been observed. The formation of the complex with sorbitol alone or with sorbitol and citric acid is not satisfactory since its

Table 1. Complex with sorbitol isoelectric point 6.5–7.5; stable on long boiling; time 8 hr).

Expt. No.	Ratio of NaOH	Iron	Sorbitol	Temp. (°C)	pH
Sorbitol-variable					
1	1	8	0.75	120–125°	11.3
2	1	4	0.75	120–125°	11.3
Alkali-variable					
3	1	8	0.4	125°	9.0
4	1	8	0.75	125°	11.0

Table 2. Complex with sorbitol and citric acid (Temp. 120–125°; time 8 hr; stable on long boiling; isoelectric point 5.6–6.6)

Expt. No.	Ratio of Iron	NaOH	Sorbitol	Citric acid	pH
1	1	8	0.75	1.25	9.7
2	1	8	0.75	2.0	6.2

Table 3. Complex with sorbitol, dextrin and citric acid (Temp. 120–125°; time 5 hr; isoelectric point 2.5–3.5; stable on long boiling)

Expt. No.	Ratio of Iron	Sorbitol	Dextrin	NaOH	Citric acid	pH
Sorbitol and dextrin-variable						
1	1	4	4	0.75	1.8	6.2
2	1	2	2	0.75	1.8	6.2
Citric acid-variable						
3	1	4	4	0.75	2.0	6.2
4	1	4	4	0.75	1.6	6.2
5	1	4	4	0.75	1.0	9.3

isoelectric point ranges between pH 6.5 – 7.5. Various ratios were tried, but only four are given in the table. Addition of dextrin gives a satisfactory final product.

Estimation. The complex (1 ml) was taken in a Kjeldahl flask, pure H_2SO_4 (5 ml), nitric acid (2 ml) were added and heated till organic matter carbonized. Ferric sulphate thus obtained was estimated volumetrically with potassium dichromate.

Stability. The aqueous solution of the complex containing 5% elemental iron was boiled for 1 hr at 100° or for 30 min at 115°. The solution remained clear.

Stability at Different pH. The pH of the preparation in aqueous solution was regulated within the range of 1–8 with 0.1 to 1.0*N* HCl, in accordance with the method of Nissim and Robson [8]. The iron concentration in all solution was 1 mg/ml. After the solution had been standing for 24 hr at room temperature, the precipitate was removed by centrifugation and Fe content and pH in supernatant determined. The results from these studies showed that the complex precipitated within the pH range of 2.6–3.6. There was no precipitation between pH 3.7–8.0.

Relative Viscosity, Density, pH *and Isoelectric Point.* The relative viscosity at 31°, density, pH and isoelectric point of the aqueous solution containing 5% elemental iron of the best sample (No. 4, Table 3) were 7.743; 1.173; 6.2 and 2.5–3.5 respectively (No. 4, Table 3).

Acute Toxicity. The acute toxicity tests were carried out on albino mice and rats. By intraperitoneal route the L.D. 50 comes to 100 mg iron per kg body wt.

DISCUSSION

The interaction of iron with sorbitol alone or in conjunction with citric acid took place smoothly as has been observed with other carbohydrates [7], in a ratio of iron 1, sorbitol 8, NaOH 0.7 (Table 1) and iron 1, sorbitol 8, NaOH 0.7 and citric acid 1.25 (Table 2) respectively. Both complexes did not show precipitation or gel formation on long boiling. This phenomenon is, however, a rough indicator of the stability. Their isoelectric point or the pH at which precipitation with HCl took place ranges between 6.5–7.5. The precipitation point is more reliable measure of the stability and lower is the pH of precipitation more stable would be the complex. This is due to the fact that these complexes are alkaline and binding of iron with sorbitol is more firm if the pH of precipitation is lower towards acidic side. We found in case of iron-saccharate [7] that a preparation with precipitation pH of 6.5–7.5 showed gel formation on keeping for a few days while that with a precipitation pH of 4.9–5.2 remained stable for years. The stability of such a preparation can be varied by changing time of heating, temperature, or the proportion of the ingredients, but in case of these complexes, pH of precipitation could not be lowered. Various ratios, change of temperature and time were tried without success. In conjunction with dextrin, however, the pH of precipitation dropped to 2.5–3.5 (Table 3). Dextrin [2,7] alone forms

very stable complexes with iron and its pH of precipitation ranges between 1.6–2.0.

However, this complex proved very painful on intramascular administration [7]. Iron–sorbitol, dextrin and citric acid complex, on the other hand, is not painful. The incorporation of dextrin is essential for the stability of the complex, since sorbitol alone does not form stable complex.

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