

PATENT SPECIFICATION

NO DRAWINGS

Inventors: RANULPH MICHAEL ALSOP and IAN BREMNER

1.183.940



Date of filing Complete Specification (under Section 3 (3) of the Patents Act 1949): 5 Oct., 1967.

Application Date: 22 Oct., 1966.

No. 47466/66.

Application Date: 21 Dec., 1966.

No. 57323/66.

Application Date: 16 Aug., 1967.

No. 37691/67.

Complete Specification Published: 11 March, 1970.

Index at acceptance: —C3 U(2AX, 2C5, 3B, 4L, 4X); A5 B(23Y, 23X, 231, 27Y, 271, 36Y, 361, 38Y, 382, 394, 40Y, 401, 402)

International Classification: —C 08 b 19/00

COMPLETE SPECIFICATION

Ferric Hydroxide Complexes

We, FISONS PHARMACEUTICALS LIMITED, a British Company, of 12 Derby Road, Loughborough, Leicestershire, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with improved therapeutically useful ferric hydroxide-carbohydrate complexes and to their preparation.

Iron dextran has been known for approximately thirteen years, and its development for the intramuscular administration of iron represented a substantial advance over previously available methods for the administration of iron. Iron dextran possesses many advantageous properties including comparatively low toxicity, comparatively low incidence of side reactions, and good absorption of iron. However iron dextran does suffer from the disadvantages that it is very difficult to prepare therapeutic compositions containing more than 10% iron, some side reactions do occur, the intramuscular administration has to be carried out over an extended period to correct low homoglobin levels, the intravenous toxicity is not as low as is optionally required, staining of the skin can occur, particularly where a faulty administration technique is employed, and absorption of iron may not be complete within a short period of days.

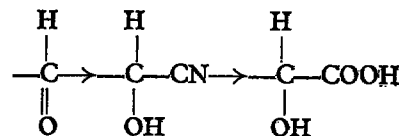
It has now been found that these disadvantages may be overcome with a new ferric hydroxide complex as hereinafter described.

Accordingly the present invention is for a complex of ferric hydroxide with at least one of the heptonic acids dextran heptonic acid

and dextrin heptonic acid. According to a preferred embodiment the invention is for a complex of ferric hydroxide with dextran heptonic acid.

Dextran and dextrin are polymeric glucose derivatives; in the case of dextran the anhydroglucose units are linked predominantly by alpha—1:6 linkages, and to a lesser extent by alpha—1:4 or alpha—1:3 linkages; in the case of dextrin the anhydroglucose units are linked predominantly by alpha—1:4 linkages and to a lesser extent by alpha—1:6 linkages. Dextran is formed *inter alia* by the controlled fermentation of sucrose with *Leuconostoc mesenteroides*; partially depolymerised dextran may be obtained *inter alia* by hydrolysis of native dextran, and fractions of different molecular weight may be obtained by solvent fractionation. Dextrin may be obtained by the hydrolysis of starch; fractions of different molecular weight may be obtained similarly by solvent fractionation.

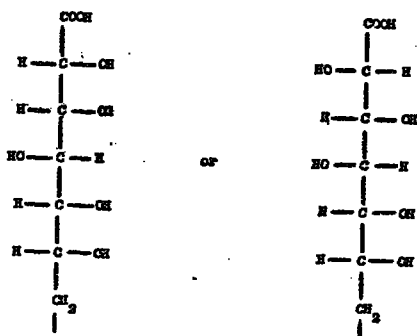
Dextran heptonic acid and dextrin heptonic acid are chemically different from dextran and dextrin and are prepared by the reaction of dextran or dextrin with cyanide ions, forming the corresponding cyanhydrin, which may then be hydrolysed to the corresponding heptonic acid. By this reaction the aldehyde group on the terminal anhydroglucose unit of the dextran or dextrin is converted to a glycolic group as follows:



Consequently the heptonic acid can be in the

[Price 5s. 0d.]

form of stereoisomers, which can be shown in the terminal C₇ part of the molecule as follows:



- 5 The terms dextran heptonic acid and dextrin heptonic acid used herein cover both stereoisomers.

10 The present invention is also for a process for the preparation of a ferric hydroxide complex with a heptonic acid selected from dextran heptonic acid and dextrin heptonic acid which comprises reacting together a suspension of ferric hydroxide and at least one of the compounds dextran heptonic acid and dextrin heptonic acid.

15 The dextran heptonic acid and dextrin heptonic acid are desirably of low molecular weight, and suitably have a molecular weight of 500 to 50,000 and preferably from 1,000 to 10,000. The dextran starting material is suitably partially depolymerised and fractionated to the appropriate molecular fraction; similarly the dextrin starting material is fractionated to the appropriate molecular fraction. The dextran heptonic acid and dextrin heptonic acid are suitably prepared by the reaction of dextran or dextrin of the appropriate molecular fraction, suitably having a molecular weight of 500 to 50,000 with cyanide ions in solution. The reaction is suitably effected with an alkali metal cyanide; it may also be carried out with hydrogen cyanide and ammonia. The reaction is preferably carried out in an aqueous medium; it may however be carried out in the medium of a highly polar organic solvent such as pyridine or dimethyl formamide. The reaction with cyanide is suitably carried out at a pH in the range 7—11, and preferably at about pH 9. The reaction may be carried out at various temperature, suitably in the range 20—50°C; the rate of reaction is increased with temperature, but at temperatures much in excess of 50°C. hydrolysis of the cyanide reactant takes place. When the formation of the cyanhydrin is complete or substantially complete, the cyanhydrin may be hydrolysed, suitably by heating the solution, for example to 90—100°C. The hydrolysis is assisted by the passage of gas, for example air or nitrogen,

through the solution to assist in the removal of the ammonia formed in the hydrolysis step. If desired the cyanhydrin product could be separated before the hydrolysis step; however this is not necessary, and the reaction product may be subjected to the hydrolysis step. The hydrolysis may be assisted if excess cyanide is removed from the reaction mixture before the hydrolysis step, for example by ion exchange. The product of the hydrolysis step is the heptonic acid which may be separated from the reaction mixture, if desired, for example by alcohol precipitation. However, it is not necessary for the heptonic acid to be separated, and the hydrolysis product may be used in the formation of the ferric hydroxide complex.

The suspension of ferric hydroxide is suitably a colloidal suspension and may be performed or formed *in situ* or both. The reaction may be carried out in various ways, but desirably the last stage of the reaction is effected at a pH between 5 and 7, preferably about 6, and the product is subjected to heating, for example to a temperature greater than 50°C. If desired an intermediate complex of ferric hydroxide with the heptonic acid may be precipitated, for example by the addition of alcohol, and the precipitate thereafter subjected to this heating step at a temperature greater than 50°C. at a pH of between 5 and 7.

The colloidal ferric hydroxide is generally prepared by a double decomposition reaction between a ferric salt and an alkali. Suitable ferric salts include ferric chloride, ferric nitrate, ferric perchlorate, ferric trichloroacetate, ferric ammonium acetate, ferric citrate, ferric ammonium citrate and ferric oxy salts. Suitable alkalis include sodium hydroxide, sodium carbonate, potassium hydroxide and ammonium carbonate.

Alternatively, the ferric hydroxide may be prepared by treatment of the ferric salt with an anion exchange resin, which may be strongly or weakly basic. A further process for the preparation of ferric hydroxide from a ferric salt is by dialysis against an aqueous solution containing an alkali or by electrodialysis (electrometathesis).

A preferred process for the complexing of the heptonic acid with ferric hydroxide includes partial preforming of the colloidal ferric hydroxide by slow partial neutralisation of the ferric salt with the alkali before reaction with the heptonic acid and subsequent completion of the formation of the ferric hydroxide in the presence of the heptonic acid, the slow neutralisation taking place over at least 30 minutes. This first part of the process for the formation of the complex suitably takes place without heating, for example at a temperature of about 30°C. The partially formed complex may then be heated

in solution to complete the reaction, suitably after adjustment of the pH to the range 5—7.

Where the complex is prepared using partial or complete formation of the ferric hydroxide *in situ* in the presence of the heptonic acid, the resultant aqueous solution of the complex will also contain a "salt" comprising the anion of the ferric salt and the cation of the alkali, except, of course, where the ferric hydroxide is prepared by the electrodialysis or ion exchange processes.

The complex may be freed from this impurity either by subjecting the solution to dialysis or by precipitating the complex by the addition of a suitable water-miscible solvent such as methyl or ethyl alcohol and subsequently redissolving the complex in distilled water.

The complex of ferric hydroxide with the heptonic acid according to the present invention can be separated as a solid. For therapeutic use this is required as a solution, and therapeutically useful solutions may be obtained directly from the aqueous reaction product or by dissolving the separated solid complex.

The complex of ferric hydroxide with the heptonic acid according to the present invention forms a stable mobile solution suitable for parenteral administration. The complex is of extremely low intravenous toxicity, and may readily be obtained with a high content of iron suitable for parenteral administration. The intravenous toxicity (LD_{50}) is generally greater than about 4,000 mg. Fe. per Kg. body weight. It is possible to obtain without difficulty ferric hydroxide-heptonic acid complexes according to the present invention containing up to 43% by weight of elemental iron, and preferably containing 38—42% by weight of elemental iron. Similarly it is possible to obtain injectable compositions of the complex of ferric hydroxide with the heptonic acid according to the present invention containing up to 250 mg. of elemental iron per ml. of solution, and preferably containing 50—200 mg. of elemental iron per ml. of solution.

On account of the extremely low intravenous toxicity of the product, and the high iron concentrations obtainable, it is possible using the product of the invention to administer a patient's total requirement of iron in a single intravenous injection. This is a very substantial advance and obviates the need for repeated intramuscular injections. Thus, for example, a single 10 ml. injection containing 2 grams of iron (Fe) of the ferric hydroxide-dextran heptonic acid complex according to the present invention may be administered as an intravenous injection over a period of a few minutes. By way of contrast, if 2 grams of iron are to be administered by intramuscular injection of iron dextran as the standard 5% solution, no less than 20 injections would

be required with each injection being separated by at least 24 hours. In addition to being used intravenously, the products of the invention may also be used by intramuscular injection. The products of the invention are suitable for the treatment or prevention of iron deficiency anaemia in both man and animals. For veterinary use, the product will generally be administered by intramuscular injection, and the high concentrations of iron represent a substantial advantage, as the volume of the injection is correspondingly smaller. With the small volume required, it is possible to use multiple dose injection guns for the injection of numbers of animals, such as pigs.

The present invention is also for a pharmaceutical including veterinary composition containing the ferric hydroxide heptonic acid complexes according to the present invention. Such compositions suitably contain conventional components such as carriers; such compositions may also contain other pharmaceutically active components, such as Vitamin B12 and/or folic acid.

The pharmaceutical composition for injection generally requires to be of an average intrinsic viscosity in the range 0.025 to 0.25, and preferably 0.05 to 0.07, at 25°C. The viscosity of the preparation is related *inter alia* to the concentration of the complex in the solution and the molecular weight of the heptonic acid used in the preparation of the complex. In general the lower the molecular weight of the heptonic acid starting material the lower the viscosity of the product. The variables molecular weight of the starting material and concentration may be adjusted to produce a product of any desired viscosity. By operation in accordance with the present invention preparations containing in excess of 20% iron of a viscosity suitable for injection may be prepared.

The ferric hydroxide heptonic acid complexes according to the present invention are stable in storage and to sterilisation by autoclaving.

The following examples are given to illustrate the present invention.

EXAMPLE 1

10 Grams of potassium cyanide were added to a solution of 200 grams of low molecular weight dextran (having an average molecular weight of about 5,000) in 1,500 ml. of water. The reaction mixture was left overnight at 40°C. and then the temperature of the mixture was raised to 90—100°C. to hydrolyse the cyanhydrin and excess potassium cyanide; air was passed through the solution to assist removal of ammonia. The pH of the solution was then adjusted to pH 7.0 by the addition of hydrochloric acid and the solution concentrated by evaporation. The liquid concentrate was an aqueous solution of dextran heptonic acid which could, if de-

sired, be precipitated by the addition of ethyl alcohol.

5 A solution of 36 grams of sodium carbonate in 150 ml. of water was added slowly over a period of 2 hours, to a solution of 75 grams of ferric chloride hexahydrate in 160 ml. of water, at a temperature of 30°C. A solution of 16 grams of dextran heptonic acid prepared as described above in 100 ml. of water was then added over a period of 15 minutes and the pH of the solution adjusted to pH 4.3 by the careful addition of 16% aqueous sodium carbonate solution.

15 The ferric hydroxide dextran heptonic acid complex was precipitated by the addition of ethanol and the precipitate was washed twice with 60% aqueous ethanol. The precipitate was redissolved in 100 ml. of water, the solution heated to a temperature of 70–80°C., and the pH of the solution adjusted to 6.0 by the addition of 10% aqueous sodium hydroxide solution. The last traces of alcohol were boiled off and the solution was then autoclaved at 10 p.s.i. for 30 minutes. The solution was then concentrated to 100 ml. filtered and the filtrate autoclaved at 10 p.s.i. for 30 minutes.

25 The solution had an elemental iron content of 153 mg. Fe./ml. and demonstrated at LD₅₀, on intravenous administration to mice, of greater than 3,800 mg. Fe. per Kg. body weight.

30 On injection into the hind leg of a rabbit at a dosage of 40 mg. Fe./Kg. body weight an average of 14% of iron was retained at the injection site seven days after injection.

EXAMPLE 2

40 A solution of 7.2 Kg. of anhydrous sodium carbonate in 24 litres of water was added slowly, over a period of 2 hours, to 16.8 litres of liquor ferriperchloride (containing 20% w/v elemental iron) which had been previously diluted to 32 litres. 3.75 Kg. of dextran heptonic acid (average molecular weight 5,000) in 14 litres of aqueous solution was then added, maintaining the temperature at 30 to 40°C. On completion of this addition and maintaining the temperature above 30°C. a further quantity of 16% w/v sodium carbonate was added slowly to bring the pH to 6.0. The solution was heated to 90°C. for 2 hours and then the volume was reduced to about 20 litres by heating in vacuo at 55°C.

55 Salt was removed by dialysis against distilled water and the volume was again reduced to about 20 litres (i.e. to a concentration of 15% ferric hydroxide dextran heptonic acid complex). The salt concentration was adjusted to 0.9% w/v and phenol was added to a concentration of 0.5%. Particulate matter was removed by passing the solution through a No. 3 sintered glass filter and after being sealed into ampoules the solution was autoclaved at 15 lb./sq. in. for 1 hour.

65 The autoclaved solution had an iron content of 153.2 mg. Fe./ml. and demonstrated an LD₅₀ on intravenous administration to mice of 4,600 mg. Fe./Kg. body weight. The viscosity of the solution was 16.8 centistokes at 25°C. and the pH was 6.50.

70 On injection into the hind leg of a rabbit at a dosage of 40 mg. Fe./Kg. body weight an average of 15% of iron was retained at the injection site seven days after injection.

EXAMPLE 3

75 A solution of 360 grams of anhydrous sodium carbonate in 1.2 litres of water was added slowly with vigorous stirring to 840 ml. of liquor ferriperchloride containing 20% w/v elemental iron which had been previously diluted to 1.6 litres, 187.5 Grams dextran heptonic acid (average molecular weight 5,000) in 700 ml. water was then added, maintaining the temperature above 30°C. Still maintaining the temperature between 30°C. and 40°C. a further quantity of 16% sodium carbonate solution was added to bring the pH to 4.3. Ethyl alcohol was added to a concentration of 60% and the precipitated complex was filtered off and washed three times with 60% alcohol. The precipitate was redissolved in water and heated to 75°C. to remove alcohol. The pH was adjusted to 6.0 with 2.5N sodium hydroxide and the solution was heated to 90°C. for 2 hours. The volume was reduced to about 1 litre (15% iron) and the solution was filtered, filled into ampoules and sterilised by autoclaving at 15 lb./sq.in. for 1 hour.

100 The autoclaved solution of ferric hydroxide dextran heptonic acid complex had an iron content of 158.3 mg. Fe./ml. and demonstrated an LD₅₀ on intravenous administration to mice, in excess of 4,000 m. Fe./Kg. body weight.

105 On injection to the hind leg of a rabbit at a dosage of 40 mg. Fe./Kg. body weight an average of 14% of the iron was retained at the injection site seven days after injection.

EXAMPLE 4

110 The procedure of Example 3 was followed with the modification that the weight ratio of iron to carbohydrate in the starting materials was adjusted to 1:0.75. The final solution was concentrated to a volume containing approximately 20% w/v of elemental iron prior to the ultimate ampouling and sterilisation steps.

115 The autoclaved solution of ferric hydroxide dextran heptonic acid complex had an iron content of 186.0 mg. Fe./ml. and demonstrated an LD₅₀ on intravenous administration to mice of greater than 4,700 mg. Fe./Kg. body weight. The viscosity of the solution was 29.7 centistokes at 25°C. and the pH was 5.6.

125 On injection into the hind leg of a rabbit at

a dosage of 40 mg. Fe./Kg. body weight an average of 17.0% of iron was retained at the injection site seven days after injection.

EXAMPLE 5

5 840 ml. of liquor ferriperchloride (containing 20% w/v elemental iron) was diluted to 1.6 litres and added to 900 ml. of a 20% w/v aqueous solution of dextran heptonic acid (average molecular weight 5,000). The combined solutions were repeatedly passed through a column of an anion exchange resin (De-Acidite FF (Trade Mark)) until the pH of the eluate was 6.0. The column was regenerated after each pass by first washing with N hydrochloric acid to remove residual traces of iron, followed by N sodium hydroxide and then distilled water.

10 The eluate was heated to 90°C. for 2 hours and then dialysed against distilled water to remove residual chloride and the volume was then reduced to 1.0 litre by rotary evaporation *in vacuo*. After filtration through a No. 3 sintered glass funnel the solution of the ferric hydroxide dextran heptonic acid complex was filled into ampoules and autoclaved at 10 lbs. per sq. in. for 30 minutes.

EXAMPLE 6

30 84 ml. of liquor ferriperchloride (containing 20% w/v elemental iron) was diluted to 160 ml. with water and added to 19.0 gm. of dextran heptonic acid (average molecular weight 5,000) in 70 ml. of aqueous solution. The combined solution was dialysed against 10 litres of distilled water containing 100 ml. of 0.880 ammonia, for a period of 24 hours. The ammonia dialysis solution was replaced with a further 10 litres of distilled water and 50 ml. of 0.880 ammonia and dialysis was continued for a further 24 hours by which time the iron solution in the dialysis sac had been neutralised to pH 8.0. The ammonia dialysis solution was replaced by distilled water and dialysis for a further 24 hours reduced the pH to 6.5.

45 The solution of the ferric hydroxide dextran heptonic acid complex was heated in an autoclave at 15 lbs./sq. in. for 2 hours reduced to 100 ml. volume, filtered, ampouled and sterilised for 1 hour at 15 lbs./sq. in.

50 This autoclaved solution containing 117 mg. Fe./ml.; the viscosity of the solution was 6.6 centistokes at 25°C. and the pH was 6.2. On injection into the hind leg of a rabbit at a dosage of 40 mg. Fe./Kg. body weight an average of 12.5% of iron was retained at the injection site seven days after injection.

EXAMPLE 7

60 10 Grams of potassium cyanide are added to a solution of 200 grams of low molecular weight dextran (having an average molecular weight of about 5,000) in 1.5 litres of water. The reaction mixture is allowed to stand over-

night at 40°C. and the temperature is then raised to 90—100°C. and the solution aerated to hydrolyse the cyanhydrin and excess potassium cyanide. The pH of the solution is then adjusted to pH 7.0 by the addition of hydrochloric acid and the solution concentrated by evaporation. The liquid concentrate was an aqueous solution of dextran heptonic acid, which could, if desired, be precipitated by the addition of ethanol.

75 A solution of 24 grams of sodium carbonate in 100 ml. of water is added slowly over a period of 20 minutes, with stirring, to a solution of 46.4 grams of ferric chloride hexahydrate in 160 ml. of water. Then a solution of 24 grams of dextran heptonic acid prepared as described above in 100 ml. of water is added over a period of 15 minutes and the mixture brought to pH 4.3 by the addition of 16% aqueous sodium carbonate solution. The reaction mixture is maintained at a temperature of 30°C. throughout.

85 The resultant ferric hydroxide dextran heptonic acid complex is then precipitated by the addition of ethanol and the precipitate washed three times with 60% aqueous ethanol. The precipitate is then redissolved in 100 ml. of water.

90 The resultant solution is then heated to a temperature in the range 70—80°C. and the pH of the solution adjusted to pH 6.0 by the addition of 10% aqueous sodium hydroxide solution. The solution is then maintained at a temperature of 90°C. for a period of 2.25 hours, the pH of the solution being kept at 6.0 throughout this period.

95 The solution is then filtered, the volume adjusted to 95 ml. and finally the solution is autoclaved at 10 p.s.i.g. for 30 minutes to yield a final solution containing about 100 mg. Fe./ml.

EXAMPLE 8

105 Nine day old piglets were each given an intramuscular injection of a 15% ferric hydroxide dextran heptonic acid complex prepared as in Example 2 containing 200 mg. of elementary iron. Blood samples were taken every seven days thereafter and the piglets were weighed at regular intervals.

110 A group of control animals were similarly studied, these animals receiving exactly the same treatment as the experimental animals with regard to diet, husbandry etc., but not receiving the ferric hydroxide dextran heptonic acid complex injection.

115 The average weight in the animals at the start of the experiment was 1.6 Kg. and the haemoglobin level of the blood was 7.1 gms./100 ml. After six weeks the treated animals had an average weight of 8.9 Kg. and a haemoglobin level of 10.5 gm./100 ml. blood whereas the untreated animals had an average weight of 6.8 Kg. and a haemoglobin level of 7.7 gms./100 ml. blood.

EXAMPLE 9

Two adult female patients suffering from hypochromic anaemia were each given a single intravenous injection of ferric hydroxide dextran heptonic acid complex prepared as in Example 4 containing 2 grams of Fe. in 10 millilitres. Both patients showed a satisfactory rise in blood haemoglobin with a complete absence of side effects.

EXAMPLE 10

A solution of 2.88 kgm. of anhydrous sodium carbonate in 9 litres of water was added slowly over a period of two hours to 6.72 litres of liquor ferriperchloride (containing 20% w/v elemental iron) which had previously been diluted to 24 litres.

1.39 kgm. of dextran heptonic acid (average molecular weight 5,000) in 7 litres of aqueous solution was then added, maintaining the temperature at 30—40°C. On completing this addition, and maintaining the temperature above 30°C., 16% w/v sodium carbonate was added slowly to bring the pH to 5.0.

Salt was removed by electrodialysis and the pH adjusted to 6.0 by the addition of 10% sodium hydroxide. The resulting solution was heated in an autoclave at 15 lbs./sq. in. for one hour, and the volume then reduced to about 4.5 litres in a rotary evaporator. Particulate matter was removed by passing the solution through a No. 3 sintered glass filter and, after being sealed into ampules the solution was autoclaved at 10 lbs./sq. in. for 30 minutes.

The autoclaved solution of ferric hydroxide dextran heptonate complex had an iron content of 223 mgm./ml.

WHAT WE CLAIM IS:—

1. A complex of ferric hydroxide with at least one of the heptonic acids dextran heptonic acid and dextrin heptonic acid.

2. A complex of ferric hydroxide with dextran heptonic acid.

3. A complex of ferric hydroxide with dextrin heptonic acid.

4. A complex as claimed in any of claims 1—3 in which the heptonic acid has an average molecular weight of 500—50,000.

5. A complex as claimed in Claim 4 in which the heptonic acid has an average molecular weight of 1000—10,000.

6. A complex as claimed in any of the preceding claims which contains up to 43% by weight of elemental iron.

7. A complex as claimed in claim 6 which contains 38—42% by weight of elemental iron.

8. A complex as claimed in any of the preceding claims wherein the LD₅₀ on intravenous administration is greater than about 4000 mg Fe per KG body weight.

9. A complex of ferric hydroxide with a

heptonic acid substantially as hereinbefore described.

10. A process for the preparation of a ferric hydroxide complex with a heptonic acid selected from dextran heptonic acid and dextrin heptonic acid which comprises reacting together a suspension of ferric hydroxide and dextran heptonic acid or dextrin heptonic acid respectively.

11. A process as claimed in claim 10 wherein the ferric hydroxide is preformed.

12. A process as claimed in claim 10 wherein the ferric hydroxide is formed *in situ* in the reaction.

13. A process as claimed in claim 10 wherein the ferric hydroxide is partially preformed and partially formed *in situ*.

14. A process as claimed in any of claims 10—13 wherein the last stage of the process, either as a part of the process or a separate step, comprises heating to a temperature in excess of 50°C at a pH between 5 and 7.

15. A process as claimed in claim 14 wherein an intermediate product is precipitated and subjected to this heating step.

16. A process as claimed in any of the preceding claims 10—15 wherein the ferric hydroxide is formed by a double decomposition reaction between a ferric salt and an alkali.

17. A process as claimed in claim 16 wherein the ferric hydroxide is formed by a double decomposition reaction between a ferric chloride and sodium carbonate.

18. A process as claimed in any of the preceding claims 10—15 wherein the ferric hydroxide is formed by treatment of a ferric salt with an anion exchange resin.

19. A process as claimed in any of the preceding claims 10—15 wherein the ferric hydroxide is formed by dialysis of a ferric salt against an alkali.

20. A process as claimed in any of the preceding claims 10—15 wherein the ferric hydroxide is formed by electrodialysis.

21. A process as claimed in any of claims 10—20 wherein the heptonic acid is prepared by reacting dextran or dextrin with an alkali metal cyanide to form a cyanhydrin which is then hydrolysed to form the heptonic acid.

22. A process as claimed in claim 21 wherein there is used a partially depolymerised dextran having a weight average molecular weight of 500—50,000.

23. A process as claimed in claim 22 wherein there is used a partially depolymerised dextran having a weight average molecular weight of 1,000—10,000.

24. A process as claimed in claim 21 wherein there is used dextrin having a weight average molecular weight of 500—50,000.

25. A process as claimed in any of claims 21—24 wherein the hydrolysis takes place in the reaction liquor in which the cyanhydrin is formed.

EXAMPLE 9

Two adult female patients suffering from hypochromic anaemia were each given a single intravenous injection of ferric hydroxide dextran heptonic acid complex prepared as in Example 4 containing 2 grams of Fe. in 10 millilitres. Both patients showed a satisfactory rise in blood haemoglobin with a complete absence of side effects.

EXAMPLE 10

A solution of 2.88 kgm. of anhydrous sodium carbonate in 9 litres of water was added slowly over a period of two hours to 6.72 litres of liquor ferriperchloride (containing 20% w/v elemental iron) which had previously been diluted to 24 litres.

1.39 kgm. of dextran heptonic acid (average molecular weight 5,000) in 7 litres of aqueous solution was then added, maintaining the temperature at 30—40°C. On completing this addition, and maintaining the temperature above 30°C., 16% w/v sodium carbonate was added slowly to bring the pH to 5.0.

Salt was removed by electrodialysis and the pH adjusted to 6.0 by the addition of 10% sodium hydroxide. The resulting solution was heated in an autoclave at 15 lbs./sq. in. for one hour, and the volume then reduced to about 4.5 litres in a rotary evaporator. Particulate matter was removed by passing the solution through a No. 3 sintered glass filter and, after being sealed into ampules the solution was autoclaved at 10 lbs./sq. in. for 30 minutes.

The autoclaved solution of ferric hydroxide dextran heptonate complex had an iron content of 223 mgm./ml.

WHAT WE CLAIM IS:—

1. A complex of ferric hydroxide with at least one of the heptonic acids dextran heptonic acid and dextrin heptonic acid.

2. A complex of ferric hydroxide with dextran heptonic acid.

3. A complex of ferric hydroxide with dextrin heptonic acid.

4. A complex as claimed in any of claims 1—3 in which the heptonic acid has an average molecular weight of 500—50,000.

5. A complex as claimed in Claim 4 in which the heptonic acid has an average molecular weight of 1000—10,000.

6. A complex as claimed in any of the preceding claims which contains up to 43% by weight of elemental iron.

7. A complex as claimed in claim 6 which contains 38—42% by weight of elemental iron.

8. A complex as claimed in any of the preceding claims wherein the LD₅₀ on intravenous administration is greater than about 4000 mg Fe per KG body weight.

9. A complex of ferric hydroxide with a

heptonic acid substantially as hereinbefore described.

10. A process for the preparation of a ferric hydroxide complex with a heptonic acid selected from dextran heptonic acid and dextrin heptonic acid which comprises reacting together a suspension of ferric hydroxide and dextran heptonic acid or dextrin heptonic acid respectively.

11. A process as claimed in claim 10 wherein the ferric hydroxide is preformed.

12. A process as claimed in claim 10 wherein the ferric hydroxide is formed *in situ* in the reaction.

13. A process as claimed in claim 10 wherein the ferric hydroxide is partially preformed and partially formed *in situ*.

14. A process as claimed in any of claims 10—13 wherein the last stage of the process, either as a part of the process or a separate step, comprises heating to a temperature in excess of 50°C at a pH between 5 and 7.

15. A process as claimed in claim 14 wherein an intermediate product is precipitated and subjected to this heating step.

16. A process as claimed in any of the preceding claims 10—15 wherein the ferric hydroxide is formed by a double decomposition reaction between a ferric salt and an alkali.

17. A process as claimed in claim 16 wherein the ferric hydroxide is formed by a double decomposition reaction between a ferric chloride and sodium carbonate.

18. A process as claimed in any of the preceding claims 10—15 wherein the ferric hydroxide is formed by treatment of a ferric salt with an anion exchange resin.

19. A process as claimed in any of the preceding claims 10—15 wherein the ferric hydroxide is formed by dialysis of a ferric salt against an alkali.

20. A process as claimed in any of the preceding claims 10—15 wherein the ferric hydroxide is formed by electrodialysis.

21. A process as claimed in any of claims 10—20 wherein the heptonic acid is prepared by reacting dextran or dextrin with an alkali metal cyanide to form a cyanhydrin which is then hydrolysed to form the heptonic acid.

22. A process as claimed in claim 21 wherein there is used a partially depolymerised dextran having a weight average molecular weight of 500—50,000.

23. A process as claimed in claim 22 wherein there is used a partially depolymerised dextran having a weight average molecular weight of 1,000—10,000.

24. A process as claimed in claim 21 wherein there is used dextrin having a weight average molecular weight of 500—50,000.

25. A process as claimed in any of claims 21—24 wherein the hydrolysis takes place in the reaction liquor in which the cyanhydrin is formed.

26. A process as claimed in claim 25 in which the hydrolysis is assisted by passing a gas such as air through the solution of the cyanhydrin.
- 5 27. Processes for the preparation of a ferric hydroxide complex with a heptonic acid selected from dextran heptonic acid and dextrin heptonic acid substantially as hereinbefore described.
- 10 28. Processes for the preparation of a ferric hydroxide complex with dextran heptonic acid substantially as hereinbefore described and illustrated in Examples 1—6, and 10.
- 15 29. Process for the preparation of a ferric hydroxide complex with dextrin heptonic acid substantially as hereinbefore described and illustrated in Example 7.
- 20 30. Complexes of ferric hydroxide with dextran heptonic acid when prepared by the process claimed in any of claims 10—28.
- 25 31. Complexes of ferric hydroxide with dextrin heptonic acid when prepared by the process claimed in any of claims 10—27 and 29.
- 30 32. A pharmaceutical or veterinary composition for the treatment of iron deficiency by parenteral administration which comprises an aqueous colloid solution of a complex of ferric hydroxide with dextran heptonic acid or dextrin heptonic acid.
- 35 33. A pharmaceutical or veterinary composition as claimed in claim 32 wherein the complex is a complex of ferric hydroxide with dextran heptonic acid.
- 40 34. A pharmaceutical or veterinary composition as claimed in claim 33 wherein the complex of ferric hydroxide with dextran heptonic acid is as claimed in claim 30.
35. A pharmaceutical or veterinary composition as claimed in any of claims 32—34 wherein the complex of ferric hydroxide with dextran heptonic acid or dextrin heptonic acid contains up to 43% by weight of elemental iron.
36. A pharmaceutical or veterinary composition as claimed in claim 35 wherein the complex of ferric hydroxide with dextran heptonic acid or dextrin heptonic acid contains 38—42% by weight of elemental iron.
- 50 37. A pharmaceutical or veterinary composition as claimed in any of claims 32—36 which contains up to 250 mg of elemental iron per ml. of solution.
- 55 38. A pharmaceutical or veterinary composition as claimed in claim 37 which contains 50—200 mg of elemental iron per ml. of solution.
- 60 39. A pharmaceutical or veterinary composition as claimed in any of claims 32—38 which contains one or more additional pharmaceutically active components.
- 65 40. A pharmaceutical or veterinary composition as claimed in claim 39 in which the additional pharmaceutically active components are selected from vitamin B12 and folic acid.
- 70 41. Pharmaceutical or veterinary compositions substantially as hereinbefore described.
- 75 42. A process for the treatment of iron deficiency in animals which comprises administering parenterally a solution of a complex of ferric hydroxide and dextran heptonic acid.
43. A process for the treatment of iron deficiency in animals which comprises administering parenterally a solution of a complex of ferric hydroxide and dextrin heptonic acid.
44. A process as claimed in claim 42 wherein the complex is as claimed in claim 30.

F. MURPHY,
Agent for the Applicants,
Chartered Patent Agent,
Fisons Limited,
Harvest House,
Felixstowe,
Suffolk.

