

PATENT SPECIFICATION

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(54) WATER SWELLABLE POLYMERS AND THEIR METAL
COMPLEXES

(71) We, ASTRA LAKEMEDEL AKTIEBOLAG, a Swedish Body Corporate of, Kyrnbergagatan, 16, S-151 85 Sodertalje, Sweden, 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:—

This invention relates to water swellable or soluble polymers and their use.

In the treatment of iron deficiency in mammals including man, iron may be administered orally with subsequent absorption *via* the alimentary canal, or parenterally by intravenous or intramuscular injection of a solution containing iron. In such solutions for parenteral administration the iron must be present as ferric iron in a stabilised form in order to prevent gel formation and precipitation, for example precipitation of ferric hydrate, at physiological pH values. The iron must also be present in such a form that no toxic side reactions, whether of a local or of a general type, occur with injection of dosages containing at least 100 mg. of iron. Solutions of salts of iron cannot be used for parenteral administration mainly because of their relatively high toxicity.

Various substances have previously been used as stabilizing agents in iron preparations for parenteral administration. In order to prevent precipitation of ferric hydrate when an aqueous ferric salt solution is rendered alkaline, some kind of carbohydrate was previously used as stabilizing agent. Thus, one early preparation for parenteral administration consisted essentially of an aqueous solution of a saccharated oxide of iron. However, in order to prevent precipitation of ferric hydroxide, the pH of this iron preparation must be alkaline, and parenteral administration of the preparation often led to undesired side effects.

Other types of stabilizing agents hitherto used in preparations of iron for intramuscular injection are dextrans and dextrans. The use of dextrans and dextrans made it possible to prepare injection solutions with a physiological pH. However, preparations containing a complex of low molecular weight dextran and iron have proved to give undesired side effects such as local pain and discolouration of the skin surrounding the site of the injection, see Acta Medica Scandinavica Suppl. 342—T. Karlefors and Å Nordén "Studies on iron-dextran complex". Dextrin, a degraded starch, contains reducing groups which may reduce some ferric iron in the iron preparation to ferrous iron. The presence of ferrous iron in the preparations is undesirable; it is fairly toxic and may give rise to side effects when administered in high dosages.

Still another type of stabilizing agent used in the preparation of iron preparations for intramuscular administration is a combination of sorbitol, citric acid and dextrin, see Canadian Patent Specification No. 659,420. It was found that such a combination of sorbitol, citric acid and dextrin could be used to stabilize ferric iron so that an iron complex with an average molecular weight of about 5000 was obtained whereas the previously used iron-dextran and iron-dextrin complexes had average molecular weights exceeding 150,000. The acute toxicity, LD₅₀, for intraperitoneal administration to mice of this complex of iron was about 50 mg per kg bodyweight, which toxicity, although higher than the toxicity of the iron-dextrin and iron-dextran preparations, made administration to humans of dosages not exceeding 200 mg of iron possible. The iron in this preparation, sold under the trade name "Jectofer", is present in the form

of particles of such small size that they are rapidly absorbed via both the lymphatic vessels and the blood vessels. The small size of the particles and the comparatively low average molecular weight also mean, however, that about 30% of the administered iron is excreted *via* the kidneys. The remaining part of the administered iron is utilized to a high degree in the hematopoiesis. Thus, while many drawbacks experienced with iron-dextran and iron-dextrin were obviated by use of "Jectofer", there still remained some disadvantages, namely the relatively high losses of administered iron *via* the kidneys and the acute toxicity which, however, did not limit the usefulness of "Jectofer" when administered to humans in single dosages containing not more than 200 mg of iron but this made a large number of injections to a single patient necessary. The presence of reducing groups in the dextrin may convert part of the ferric iron to ferrous iron and may be the cause of undesired side effects on administration to patients in high single dosages.

As stated above, hitherto used stabilizing agents in iron preparations for intramuscular injection contain sugar or sugar polymers such as dextrin or dextran, which have a stabilizing effect on a ferric iron colloid at a neutral pH. These previously used stabilizing agents have in common that they contain reducing groups which to some degree convert ferric iron in the injection solution to ferrous iron. Ferrous iron is an undesired component in iron preparations for intramuscular injection due to its toxicity and may cause undesired side effects on administration of solutions to patients. The amount of ferrous iron present in the injection solution may limit because of its toxicity, the maximum dose of iron which may be administered to the patient at each injection.

This invention provides an iron preparation for intramuscular administration which contains as stabilizing agent a new polymer which

- (i) can stabilize ferric iron at a physiological pH,
- (ii) causes an insignificant reduction of ferric iron to ferrous iron in an injection solution,
- (iii) can yield a complex with ferric iron having a low toxicity and after intramuscular injection is absorbed to a high degree from an intramuscular depot while only a minor part is excreted *via* the kidneys.
- (iv) can yield a complex with ferric iron, which has such toxicity that a dose of more than 500 mg of iron may be administered without serious side effects.

Complexes of the polymer with iron are well absorbed and have a low toxicity which makes administration of unit dosages containing more than 500 mg iron possible without serious side effects.

Although the main use of the new polymer used as stabilizing agent is in the preparation of iron preparations for intramuscular administration, other fields of use will be apparent from the following discussion. Thus the new polymer can form complexes with ions of heavy metals such as iron, cobalt, nickel and aluminium. An especially valuable property of the polymer of the invention is its capability to stabilize ferric iron at physiological pH, thus yielding an iron complex which has advantageous therapeutical properties and may be used for intramuscular or intravenous injection to mammals including man in need of such treatment.

The invention provides a physiologically innocuous, water swellable or soluble polymer capable of forming a complex with a polyvalent metal cation, which comprises recurring units derived from

a) at least one hydroxy carboxylic acid component which is arabonic acid, gluconic acid or glucoheptonic acid or a salt or lactone derivable therefrom;

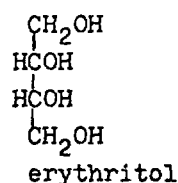
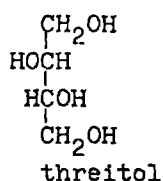
b) at least one polyhydric alcohol component, which is glycerol, a polyglycerol, tetritol, pentitol, hexitol, heptitol, or a partially etherified derivative of one of these alcohols with an alkyl group containing from 1 to 5 carbon atoms, or a partially etherified derivative of one of these alcohols with a hydroxyalkyl group containing from 1 to 5 carbon atoms; and

c) at least one polymerizing agent which is a dihalohydrin, as hereinafter defined, a monoepoxide as hereinafter defined or a diepoxide as hereinafter defined.

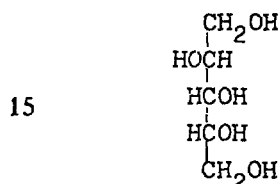
The hydroxycarboxylic acids referred to above may occur in various steric configurations and in racemic form as well as in the form of substantially pure optical isomers. The term "hydroxycarboxylic acids" as used herein refers to all such steric and optical isomers as well as mixtures thereof.

5 Besides polyhydric alcohols which solely contain non-etherified groups, poly-
hydric alcohols which are partially etherified may be used as a reactant in the poly-
merisation process. In such etherified alcohols, one or more but not all of the
alcoholic hydroxyl groups may be etherified with alkyl groups containing 1 to 5 carbon
atoms, or with hydroxyalkyl groups containing 1 to 5 carbon atoms in the alkyl moiety
10 of the hydroxyalkyl group. One suitable partially etherified alcohol is hydroxypropyl-
sorbitol. 10

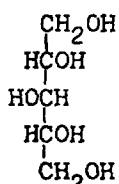
The tetritols are compounds with for example the structural formulae



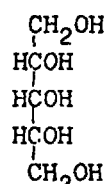
the pentitols are compounds with for example the structural formulae



arabitol (lyxitol)

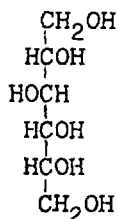


xylitol

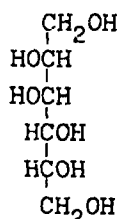


ribitol (adonitol)

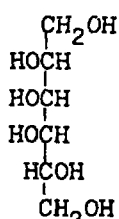
and the hexitols are compounds with for example the structural formulae



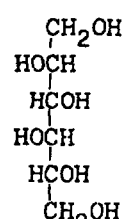
sorbitol



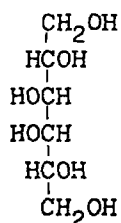
mannitol



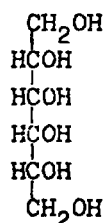
talitol



iditol

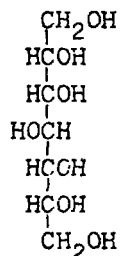


galactitol
(dulcitol)

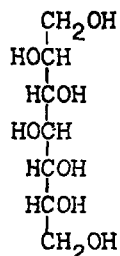


allitol

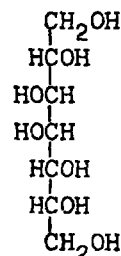
Examples of the heptitols are:



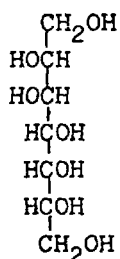
glycero-gulo-
heptitol
(α -Glucoheptitol)



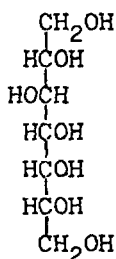
D-glycero-D-ido-
heptitol
(D- β -Glycohepti-
tol)



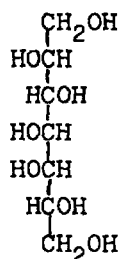
D-glycero-D-gala-
heptitol
(Perseitol)
(α -Mannoheptitol)



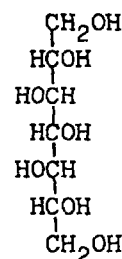
D-glycero-D-
manno
Heptitol
(Volemitol)
(D- β -Manno-
heptitol)
(α -Sedo-
heptitol)



D-glycero-D-
gluco
Heptitol
(β -Sedo-
heptitol)

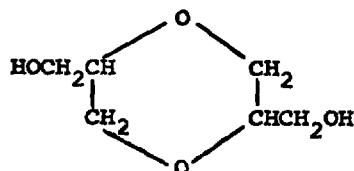


D-glycero-L-
gluco
Heptitol
(D- β -Gala-
heptitol)
(D- α -Gulo-
heptitol)



glycero-ido-
heptitol
(meso)

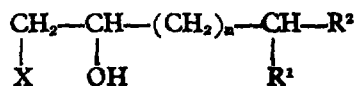
5 The polyhydric alcohol can also be a polyglycerol, that is a condensation product of glycerol in which molecules of glycerol have been condensed to give open-chain or cyclic ethers such as 5



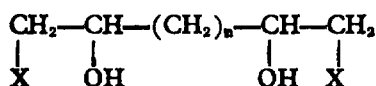
10 Still further examples of the polyhydric alcohols are the inositols or cyclohexanehexols. One further example of a tetritol is pentaerythritol. 10

Many of the polyhydric alcohols referred to above occur in various steric configurations and in racemic form as well as in the form of optical isomers. The term "polyhydric alcohol" refers to all such steric and optical isomers as well as mixtures thereof.

15 By the term "dihalohydrin" we mean a compound of the general formula 15

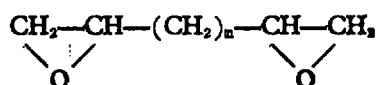


wherein n is 0 or an integer of 1, 2, 3 or 4; X is Cl, Br or I, R^1 is OH or X, and R^2 is H or CH_2X with the proviso that when R^1 is OH, R^2 is $-CH_2-X$, wherein X is as defined above. Examples of such dihalohydrins are those of general formula



II

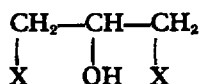
wherein n and X are as defined above, which compounds in alkaline solution are converted to a diepoxide of general formula



III

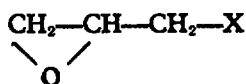
wherein n is as defined above; The term "diepoxide" is used in this specification to mean compounds of formula III.

Further examples of halohydrins which can be used are those of general formula



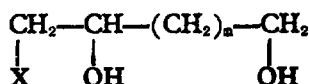
IV

wherein X is as defined above, which compounds in alkaline solution are converted to compounds of general formula



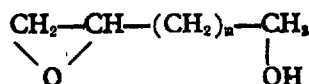
V

wherein X is as defined above; and compounds of general formula



VI

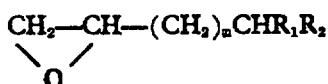
which compounds in alkaline solution are converted to compounds of general formula



VII

in which formulae n is as defined above.

The term "monoepoxide" is used in this specification to mean compounds of the general formula



where R_1 , R_2 and n are as defined above.

The epoxides of general formulae III, V and VII are further examples of the polymerising agents. It is a common feature of the polymerising agents of general formulae I—VII that they contain at least two reactive groups capable of participating in formation of ether linkages.

Preferred hydroxy carboxylic acids are gluconic acid and glucoheptonic acid.

Preferred polyhydric alcohols are the hexitols and the heptitols. Of the polymerising agents, the epihalohydrins, particularly epichlorohydrin, are preferred. The

5 preferred combination of reactants used for preparing the polymer is gluconic acid, sorbitol and epichlorohydrin. Other suitable combinations of reactants are gluconic acid lactone, sorbitol, and epichlorohydrin; arabonic acid, sorbitol, and epichlorohydrin; gluconic acid lactone, pentaerythritol, and epichlorohydrin; glycerol; gluconic acid lactone, and epichlorohydrin; mannitol, gluconic acid lactone, and epichlorohydrin; dulcitol, gluconic acid lactone, and epichlorohydrin; and hydroxypropylsorbitol, gluconic acid lactone, and epichlorohydrin. 5

The polymer of the invention can be prepared by reacting in solution

- 10 a) the hydroxy carboxylic acid component;
b) the polyhydric alcohol component and
c) the polymerising agent 10

whereafter if desired the reaction product is purified by precipitation and redissolution.

15 The polymerisation is preferably carried out in the presence of an alkali e.g. sodium hydroxide or potassium hydroxide. The alkali may be used either in the form of a solution or in the solid state, for example in the form of tablets. Alkaline earth metal hydroxides such as for example barium hydroxide may also be used as the alkali but are generally less useful. The preferred alkali is sodium hydroxide. 15

20 The use of a lactone of the hydroxy carboxylic acid as starting material is equivalent to the use of the hydroxy carboxylic acid *per se*, since the lactone in the alkaline solution wherein the polymerisation is carried out is converted to the acid or a salt thereof. 20

25 The reaction conditions may be varied to a considerable extent with regard to the relative proportions of the hydroxycarboxylic acid, the polyhydric alcohol and the polymerizing agent. Also the reaction temperature and the manner in which the reactants are brought together may be varied considerably. As examples of possible variations of the relative proportions of the reactants it may be mentioned that, per mole of the polyhydric alcohol 0.1 to 1.0 moles of hydroxycarboxylic acid and 0.05 to 5 moles of polymerizing agent may be used. In the preferred embodiment of the process of the invention, using gluconic acid or a salt or a lactone derived therefrom, sorbitol and epichlorohydrin, there may advantageously be used per mole sorbitol, 0.2 to 1.0 moles of gluconic acid or a suitable derivative thereof and 0.1 to 4 moles of epichlorohydrin. 25

30 It is usually advantageous to carry out the polymerisation by adding the alkali and the polymerizing agent separately in portions to an alkaline aqueous solution of the hydroxycarboxylic acid and the polyhydric alcohol. However, the addition of alkali and polymerizing agent may also be added continuously to the alkaline solution of hydroxycarboxylic acid and the polyhydric alcohol in the reaction vessel. The reaction temperature may be varied within wide limits but is advantageously held from 20°C up to the boiling point of the reaction mixture. The preferred reaction temperature is 75°C to 85°C. 30

35 The amount of alkali which should be present or added during the reaction will largely depend upon the amount of polymerizing agent which is added. In the preferred embodiment of the invention, that is when sorbitol and gluconic acid, or a salt or a lactone derived therefrom, are polymerized with epichlorohydrin, the total amount of hydroxyl ions present during the reaction is preferably 1.5 to 4.5 moles per mole of sorbitol. In this preferred embodiment, sodium hydroxide is used as alkali. 35

40 As is stated above, the preferred embodiment of the present invention relates to a polymer prepared by reacting sorbitol, epichlorohydrin and gluconic acid, or a salt or lactone derived from gluconic acid, in alkaline aqueous solution. In one method of carrying out this reaction, a solution gluconic acid, or the corresponding lactone, and sorbitol in the approximate relative amounts of 0.1 to 1.0, preferably substantially 0.5, moles of gluconic acid per mole sorbitol is prepared and made alkaline by adding sodium hydroxide. To this solution are separately added during the course of the reaction, epichlorohydrin and sodium hydroxide in the approximate relative amount of 0.1 to 4, preferably substantially 2 moles of epichlorohydrin, based on the amount of sorbitol. The temperature of the reaction mixture is raised successively during the reaction up to the desired temperature, i.e. 75°C to 85°C. After addition of the epichlorohydrin and the sodium hydroxide, the reaction solution is allowed to stand for some time, the temperature is then lowered to substantially 50°C and the pH of the reaction mixture is adjusted by adding a suitable acid such as HCl to 0.6 to 4, usually 0.65 to 1.0. 40

60 The sodium chloride which precipitates is removed by filtration and discarded, and the remaining reaction mixture is worked up. This working up of the reaction 60

- mixture is suitably carried out by repeated precipitation and redissolving of the polymer obtained. It is preferred to use ethanol as precipitating agent, but also other organic solvents such as dioxan, methanol, chloroform, acetone, *n*-propanol and *iso*-propanol may be used. The addition of ethanol results in the formation of a two-phase system, which in the aqueous phase contains the desired reaction product. The ethanol phase contains *inter alia* such reaction products of a low molecular weight which are not precipitated. The aqueous phase containing the desired reaction product is then again mixed with water and ethanol, and the resulting aqueous phase collected. This purification and fractionating procedure may be repeated several times, suitably at least five times; the final product is then diluted, with a suitable amount of water in order that a product that is easy to handle can be obtained.
- In the polymerization reaction of the present invention, a mixture of reaction products with widely varying molecular weights is obtained. It is not possible to ascribe a precise, unitary chemical structure to the reaction products. The working up of the immediate reaction product obtained after the polymerization process is completed also means, as indicated above, that the molecular weight distribution of the immediate reaction product is changed, in that low molecular weight components are removed. For characterizing the product, therefore, the methods described below have been used. The terms and methods defined and described below are also found in the Examples, where the particular reaction product in each Example is characterized. The expression "final product" used herebelow denotes the polymer product obtained after the working up procedure including such optional addition of water which is mentioned above.
- A. The *loss of weight on drying* is obtained by drying the final product at about 105°C until constant weight is obtained. The loss of weight is given in percent of weight calculated on the final product.
- B. The *water content* in the final product is determined by the Karl Fischer method which is described *inter alia* in Pharmacopoeia Nordica, volume 1, page 75. The water content is given in percent of weight calculated on the final product.
- C. The *sodium (Na⁺) content* in the final product is determined using a flame spectrophotometer and is given in percent by weight calculated on the final product in dried form.
- D. The *chloride ion (Cl⁻) content* is determined by potentiometric titration and is given in percent by weight calculated on the final product or on the final product in dried form. The amounts of Na⁺ and Cl⁻ which are given indicate the amount of salts present in the polymer preparation and do not mean that chloride ions are part of the polymer itself.
- E. The *organic dry substance content* in the final product is calculated as the weight of the final product excluding the loss of weight at drying and excluding the weight of Na⁺ and Cl⁻ and is given in grams or in percent by weight calculated on the final product.
- F. *Gel filtration.* The molecular weight distribution of the final product is estimated by gel filtration on Sephadex ("Sephadex" is a Registered Trade Mark) G:15, G:25 or G:50. A sample consisting of an amount of final product corresponding to substantially 100 mg of organic dry substance is dissolved in 4 ml of water, added to the column of Sephadex eluted with water. The eluate is analyzed for its organic dry substance content by measuring the extinction at 700 mμ of a mixture of 0.5 ml of eluate and 5 ml of a solution of 0.8 g of K₂Cr₂O₇ in 10 ml of H₂O and 200 ml of conc. H₂SO₄. The extinction measured is corrected against a blank and plotted against the volume of eluate. The diagram obtained is a measure of the molecular weight distribution. The eluate is also tested for contents of Cl⁻.
- G. The *carboxylic group content* in the final solution is determined in known manner.
- H. The *iron-complex-forming capacity* of the final product may be determined in the following way.
- The following solutions were used:

I	Distilled water	225 ml
	Lactic acid	90 ml (1.20 mole)
	Sodium hydroxide	148 ml (0.90 mole)
	Polymer (organic dry substance)	202.5 g
II	Sodium hydroxide	288 g (7.3 mole)
	Distilled water	1200 ml
III	Ferric chloride hexahydrate $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$	270 g (1.0 mole)
	Distilled water	405 ml
IV	Hydrochloric acid 6N	about 150 ml
V	Distilled water	about 2.2 l
VI	Ethanol 95.5% (volume percent)	about 14.8 l

Separate solutions of the ferric chloride, the sodium hydroxide and the polymer were prepared. The lactic acid (90 ml), $\frac{2}{3}$ of the volume of water (150 ml) and the sodium hydroxide (148 ml) were mixed separately before the polymer was added. The rest of the water (75 ml) was used for rinsing the vessels used and then it was added to the solution. Mixture I thus obtained was heated to 80°C under stirring. To Mixture I, were added alternately under vigorous stirring 9 × 90 ml portions of the sodium hydroxide solution (II), in all 4.86 mole NaOH, and 9 × 60 ml portions of the ferric chloride solution III, in all 1.0 mole. The addition was carried out dropwise over 1 minute for the sodium hydroxide and dropwise over 2 minutes for the ferric chloride solution. Between each addition, there was a delay of 2 minutes. 1 Minute after the final addition of ferric chloride solution, 167 ml (0.98 mole) of sodium hydroxide (II) were added. The temperature of the reaction mixture was then kept at 80°C for 35 minutes, and the mixture was then cooled to 25°C. The volume of the reaction mixture was adjusted to 2250 ml using distilled water and 5100 ml ethanol was added over 15—30 minutes while vigorously stirring. The stirring was then continued for 10 minutes more. The precipitate obtained was allowed to settle for 30—60 minutes, and the mother liquor was sucked off. The precipitate was filtered off and washed once with 900 ml diluted ethanol (2 volumes of ethanol + 1 volume of distilled water). The precipitate was dissolved by adding it while stirring to 1350 ml of distilled water heated to 40°C. After addition of the precipitate, the solution was heated to 80°C in substantially 30 minutes. The mixture was kept at 80°C while stirring for 30 minutes more. The solution was cooled to 25°C and neutralized using 6N hydrochloric acid, added dropwise under vigorous stirring over 20—25 minutes, until the pH of the mixture was 6.2. Usually 140—150 ml of hydrochloric acid was necessary. The reaction mixture was freed from undissolved matter and the volume was adjusted with distilled water to 2100 ml. A second precipitation was carried out by adding to the solution, under stirring, 4575 ml of ethanol over 15—20 minutes. Stirring was continued for 2 minutes more. The precipitate was allowed to settle overnight. The mother liquor was then sucked off and the solid was sucked off and washed three times using 900 ml of diluted ethanol (ethanol:water 2:1) and three times with undiluted ethanol (900 ml) and it was dried *in vacuo* at 40°C for 4—5 hours or overnight.

The following parameters were determined on the dried iron preparation:

1. Yield of dried iron preparation, measured in grams.
2. Yield of complex-bound iron, calculated in percent of the total amount of ferric iron added during the reaction.
3. Iron content of the dried iron preparation, in percent by weight calculated on the dried iron preparation.

I. *Absorption in rabbits* of intramuscularly administered injection solution prepared using the dried iron preparation obtained in H above.

The injection solution of the dried iron preparation obtained and described in H above was prepared according to the following method. 125 ml of distilled water was heated to 80°C in a 3-necked round-bottomed flask provided with a cooler, thermometer and stirrer. Dried iron preparation obtained as described above was added in small portions over 15 minutes under vigorous stirring. A dried preparation corresponding to 7.5 g of iron was added. The solution thus obtained was kept at 80°C for 50 minutes and it was cooled to 25°C. After dilution with distilled water to 150 ml, the solution obtained was filtered, filled into 10 ml ampoules and sterilized at 120°C for 20 minutes. The injection solution obtained had a total iron content of substantially 50 mg/ml.

The absorption tests on rabbits were carried out in the following way. The injection solution was injected in doses of 20 mg of Fe per kg bodyweight deep into the glutei of rabbits. Male albino rabbits weighing 2 to 3 kg were always used. The animals were killed at different time intervals after injection and the gluteal muscles were dissected away from the leg. Muscle and skin around the injection site were wet oxidized with sulphuric acid and nitric acid, and the iron content was then determined by a colourimetric rhodanide method. It was found that the iron was absorbed very rapidly. In most cases, more than 60% of the administered iron had been absorbed after 24 hours; more than 85% of the iron had been absorbed after 7 days; and more than 90% of the iron had been absorbed after 14 days. It was also found that the amount of iron which was excreted after 24 hours was usually less than 15%. Thus, it is clear that iron preparations for intramuscular injection prepared using the polymer of the present invention as stabilizing agent compare favourably with presently existing and marketed intramuscularly administrable iron preparations.

It can be concluded from the results of gel filtration on Sephadex G:15, G:25 and G:50 gels that the average molecular weight of the polymer as obtained is in the range 700 to 5000. It has also been established that polymers which according to gel filtration tests have an average molecular weight in the range of 1500 to 5000 give iron complexes which in the form of injection solutions give particularly advantageous responses with regard to desorption and excretion when tested on rabbits.

J. The *intrinsic viscosity* of the polymer was in many cases found to be 0.020 to 0.080 dl/g.

In the attached Drawings, Figures 1, 2 and 3 show the result of gel filtration on Sephadex G:15 of polymers according to the invention. G:15 is considered to separate components having a molecular weight up to about 1500. It is seen in Fig. 1 that the major part of the polymer, represented by the peak after about 80—90 ml of eluant, is not absorbed in the gel and so is eluted with the first portions of eluant collected. Fig. 2 shows the molecular weight distribution of a polymer which has a larger proportion of components which are retarded by the gel and thus molecular weights below 1500 may be ascribed thereto. The components in the polymer represented by Fig. 3 are to a large extent absorbed on the gel. The peak at about 130 ml of eluant indicates that the average molecular weight of the tested polymer is well below 1500.

In Figs. 1, 2 and 3, the Cl⁻ contents in the eluant have also been plotted.

Figure 4 gives the result of gel filtration on "Sephacrose" 6B of "Jectofer" and an iron preparation of the present invention.

The amount of carboxylic groups in the polymer used as stabilizing agent in this invention generally is 0.2 to 1.5 milliequivalents as calculated per g of organic dry substance determined as described under E above.

The polymerization may be carried out in a medium which is inert to the reactant solutions. Examples of such inert media are benzene and white spirit. However, an aqueous solution is the preferred medium.

In one modification of the process for preparing the polymer, a three-step procedure is used, which hereafter is described with respect to gluconic acid, sorbitol and epichlorohydrin as examples of the hydroxy carboxylic acid, polyhydric alcohol, and polymerizing agent respectively. In the first step, monoethers of epichlorohydrin and gluconic acid are prepared in acidic solution using sulphuric acid as a catalyst. In a second step, epichlorohydrin and sorbitol are polymerised in alkaline solution. In the third step, the monoethers obtained in step 1 are reacted in alkaline solution with the polymer obtained in step 2, and the reaction product is then worked up in a similar way as described above.

The carboxyl group content of the polymer of the present invention may be increased by reacting the polymer in alkaline solution with monochloroacetic acid. Hydroxyl groups in the polymer react with the monochloro acetic acid under formation of ether linkages according to the reaction scheme



In this reaction, highly viscous solutions are commonly used and the reaction may be carried out in a medium (e.g. benzene) which is inert to the reactant solutions.

10 In another four-step process for preparing a polymer which can be used as stabilizing agent for ferric iron, a polyhydric alcohol and a polymerizing agent as defined above, and saccharose are reacted and the process is the subject of Patent Application No. 11496/75 (Serial No. 1 411 267). 10

The acute intraperitoneal toxicity in mice of the polymer of the present invention has been found to be about 15 g organic dry substance per kg bodyweight. Thus the polymer is practically non-toxic.

15 The polymer of the present invention is a new composition of matter which 15

a) is soluble or swellable in water;

b) is physiologically innocuous;

20 c) has the capability of reacting with polyvalent metal cations such as Fe^{3+} , Al^{3+} , Cr^{3+} , Sb^{3+} , Bi^{3+} , Zr^{4+} , Sn^{4+} , Ti^{4+} , Bi^{2+} and Ca^{2+} , or mixtures thereof, by formation of a complex between the polymer and the metal cation; 20

d) has the capability of stabilizing ferric iron in aqueous solutions intended for intramuscular or intravenous injection to mammals including man.

The preferred embodiment of the invention, that is the polymer prepared from gluconic acid or a salt or a lactone thereof, sorbitol and epichlorohydrin, furthermore

25 e) contains 0.2 to 1.5 milliequivalents of carboxyl groups per gram organic dry substance; 25

f) has an average molecular weight, as estimated by gel filtration, of 700 to 5000;

30 The polymer of the present invention is a new composition of matter which stabilizing agent for iron preparations intended for intramuscular injection. The use of the polymer as such a stabilizing agent is an important aspect of the present invention. Examples of other fields where the polymer may be used are 30

a) as a viscosity — regulating agent in foodstuffs, pharmaceuticals, herbicides and similar preparations, or in washing agents;

35 b) as a substitute for blood plasma; 35

c) as a carrier substance for biologically active substances such as enzymes;

d) in the form of a polymer-metal ion complex as a soil improving material;

e) as a liquid cement or glue;

f) as a starting material in the preparation of plastic materials;

40 g) as a precipitation — or flocculation — inhibiting agent in the production of beer; 40

h) as an additive for electrolytes;

i) as a detoxifying agent;

45 j) in combination with suitable substances such as Ba^{2+} , as a X-ray contrast agent. 45

Iron preparations for intramuscular injection wherein the polymer of the present invention is used as a stabilizing agent are a further aspect of this invention. A dry iron-containing composition (from which can be obtained a preparation suitable for intramuscular injection in human and veterinary medicine) is prepared by reacting in alkaline aqueous solution

a) at least one water-soluble ferric salt, and

b) a physiologically innocuous, water swellable polymer of the invention and capable of forming complexes with ferric iron at an alkaline pH, the iron-containing complex is precipitated and the precipitate is purified and dried. The reaction between the ferric salt and the polymer can be carried out at a pH such that at the end of the reaction it can be adjusted to 10 to 14 by adding alkali.

The invention also provides liquid iron-containing compositions comprising an aqueous solution of the dry iron-containing composition obtained as described above. The compositions are readily soluble at physiological pH values and are sufficiently stable for the solutions to be sterilized by autoclaving.

The iron must be in the trivalent form since ferrous compounds do not give the desired stability. Suitable ferric compounds include ferric chloride (which is preferred), ferric nitrate, sulphate and acetate, and double salts, for example ferric ammonium sulphate.

The dried compositions may contain 5 to 40%, especially 20—35%, by weight, of iron and the injectible solutions may contain 5 to 100 mg of iron per ml, especially substantially 50 mg of iron per ml. It is generally desirable that the iron concentration in the injection solution should be as high as possible, in order that the injected volume may be small. In some cases, however, less concentrated preparations may be more suitable.

The dry iron preparation is prepared by reacting in aqueous solution a polymer of the invention with a water-soluble, ferric compound, preferably ferric chloride, the iron-containing complex thereby obtained is precipitated and the precipitate purified and, if desired, dried. The pH in the reaction mixture is adjusted so that at the end of the reaction it has been brought to 10 to 14. The amount of polymer used in the reaction may be 1 to 15 g, suitably 3 to 6 g, calculated as dried product, per gram of iron, depending on the particular polymer used. The reaction temperature suitably is 0°C to 100°C depending on the particular embodiment used. In the first embodiment described below, the temperature is preferably at substantially 80°C. The pH of the acidic reaction mixture is successively increased during the reaction to 10—14. As alkali, sodium hydroxide may advantageously be used. The precipitation of the iron complex from the reaction solution is effected using a non-solvent for the complex. Suitably, ethanol is used. If the solution of the iron complex is to be used directly, the complex is not precipitated after the final dissolution.

Instead of the easily water-soluble ferric compounds ferric compounds which are slightly or very slightly soluble in water may also be used; examples are freshly prepared ferric hydroxide, ferric carbonate and ferric lactate.

To purify the precipitate, redissolution is conveniently carried out by adding the precipitate to distilled water at substantially 40°C. The temperature is subsequently raised to substantially 80°C, and kept there for some time. The solution is then cooled to room temperature and the pH adjusted to 5.5 to 10, preferably 6 to 8, with a suitable acid such as HCl.

In one embodiment of the process for preparing the dry iron preparation, an alkaline aqueous solution of the polymer and, optionally, lactic acid is prepared. Lactic acid may be added in an amount up to 10 g per gram of iron. The mixture is heated to substantially 80°C and portions of the ferric compound in aqueous solution and portions of alkali in aqueous solution alternately added. In this way the pH of the reaction mixture is always kept on the alkaline side. The polymer is added in an amount corresponding to 1 to 15 g, calculated as dried substance, per gram of iron. Preferably 3 to 6 g polymer, calculated as dried product, is used per gram of iron. The reaction mixture may then be allowed to stand for some time and subsequently cooled to room temperature. The iron complex formed is precipitated using a non-solvent for the complex, suitably ethanol. The precipitate formed is separated and purified by repeated dissolution in water, precipitation and washing and is finally dried.

In another embodiment of the process for preparing the dry iron preparation, a first aqueous solution containing the polymer and the total amount of the ferric salt to be used is prepared. Per gram of iron, 1 to 15 g of polymer is used in the first

	aqueous solution. The preferred ratio is 3 to 6 g polymer per g of iron. To the acidic solution thus obtained to which lactic acid suitably is not added, alkali is added at a suitable temperature of 0°C to 60°C. When all the alkali has been added, the temperature of the reaction mixture is raised to substantially 80°C, kept there for some time, and subsequently lowered to substantially 25°C. The iron complex formed is worked up by precipitation and redissolution as described previously, with the exception that some further polymer in alkaline aqueous solution is suitably added at each redissolution. For example, if two precipitations and redissolutions are carried out, about one fourth of the amount of initially added polymer may be added at each redissolution.	
5	When preparing an injection solution of the dry iron preparation, the dry iron preparation is dissolved in water and sterilized by autoclaving. The dry iron preparation is added in portions, while stirring, to distilled water at substantially 80°C. When all the dry iron composition has been added, the temperature is kept at 80°C for some additional time, for example substantially 50 minutes, the solution is cooled to substantially 25°C, optionally diluted with distilled water, filtered, and filled into bottles which are autoclaved at substantially 120°C for substantially 20 minutes. A typical preparation thus obtained contains substantially 50 mg iron per ml.	5
10	As is evident from the following Examples, the iron preparations in the form of sterilized injection solutions are well absorbed when tested on rabbits while at the same time the excretion of iron, often less than 15%, 24 hours after the administration, is low. The cute intraperitoneal toxicity in mice of the injectable iron preparations has been found to be 300 to 500 mg per kg bodyweight. The acute intraperitoneal toxicity in mice of Jectofer as tested on the same strain of mice is substantially 50 mg per kg bodyweight. The low toxicity of the iron preparation according to the present invention in combination with its high absorption and low excretion makes it possible to administer unit dosages of the preparation which contain more than 500 mg iron. Two such dosages may be given to each patient at a single occasion.	10
15	The invention is further illustrated by the following Examples.	15
20	Example 1.	20
25	Preparation of polymer U:II 7—69 from gluconic acid lactone, sorbitol and epichlorohydrin.	25
30	To a 5 l flask provided with stirrer, charging vessel, cooler and thermometer were added	30
35	150 ml deionised water 60 g NaOH 150 g gluconic acid lactone 300 g sorbitol and in the charging vessel 200 ml epichlorohydrin	35
40	The temperature of the mixture in the 5 l flask was adjusted to 40°C. At 0, 15, 30, and 45 minutes after starting, 50 ml of epichlorohydrin were added over substantially 7 minutes. The temperature was raised so that after 30 minutes it was 60°C and this temperature was maintained during the subsequent polymerisation. At 60 minutes after starting 5.0 g of NaOH were added over substantially 2 minutes. At 90, 120, 150, 165 and 180 minutes after starting, 10.0 g NaOH were added. At 180 minutes after starting, 50 ml of epichlorohydrin were added over substantially 7 minutes. At 195, 210 and 225 minutes after starting, 10.0 g NaOH were added. At 240 and 255 minutes after starting, 14.0 ml of 50% NaOH were added and 270 minutes after starting 40.0 ml of epichlorohydrin were added. At 285, 300 and 315 minutes after starting, 14.0 ml of 50% NaOH was added. The polymerisation was allowed to proceed at 60°C to 415 minutes after starting, whereafter the temperature was lowered to 50°C and 50 ml of 4N HCl were added. During continued cooling, 160 ml of 6 M HCl were added giving a pH of 0.65 in the reaction mixture obtained. The reaction mixture was filtered in order to remove precipitated NaCl, which substance was washed with 100 ml of 50% ethanol.	40
45	The filtrate and the washing liquor were combined and stirred with 2220 ml of 95% ethanol and 65 ml of water; the polymer phase and alcohol phase were allowed to separate over night. The following day the ethanol phase was sucked off and the polymer phase filtered in order to remove precipitated NaCl, which was washed with 100 ml of 70% ethanol. The polymer phase was stirred with 1550 ml	45
50		50
55		55
60		60

of 95% ethanol and 10 ml of absolute ethanol. The phases were allowed to separate for 1 hour; the alcohol phase was sucked off and the polymer phase was stirred with 1550 ml of 95% ethanol and 10 ml of absolute ethanol. The phases were allowed to separate for 1 hour; the alcohol phase was sucked off and the polymer phase was stirred with 316 ml of 15% ethanol and 100 ml of water. After separation for 1 hour, the alcohol phase was sucked off and the polymer phase was washed twice with 316 ml of 95% ethanol followed by 5 washings using 300 ml acetone each. After addition of the final acetone, the mixture was allowed to stand overnight. The following day, the acetone was decanted and the polymer dried in a vacuum dryer at 40°C for 45 minutes.

Analysis:

Weight of polymer phase before drying: 519.1 g

Weight loss at drying: 26.2% w/w

Cl⁻ Content: 6.0% w/w

Na⁺ Content: 4.0% w/w

Organic dry substance: 346.1 g

Gel filtration curve, Sephadex G:15, is shown in Fig. 1.

Example 2.

Preparation of polymer U:II 53—69 from sorbitol, gluconic acid lactone and epichlorohydrin.

To a 5 l round-bottomed flask provided with stirrer, 2 dropping funnels, thermometer and cooler were added

300 ml deionised water

600 g sorbitol

67.4 g NaOH and

300 g gluconic acid lactone

In one dropping funnel, 299 g of NaOH were dissolved in 299 ml of water and to the other dropping funnel was added 580 ml of epichlorohydrin.

The temperature of the mixture was raised to 75°C; the sodium hydroxide and the epichlorohydrin were added continuously over 180 minutes. The reaction mixture was stirred for 30 minutes; the temperature was lowered to room temperature and pH adjusted with 6M hydrochloric acid to 0.7. The reaction mixture was filtered and 1025 ml of the filtrate were stirred with 2650 ml absolute ethanol; the phases in the resulting mixture were allowed to separate overnight. Next day the alcohol phase was sucked off and the polymer phase was filtered. The filtrate was stirred with 50 ml of water and 100 ml of absolute ethanol; the phases were allowed to separate for 2 hours. The alcohol phase was sucked off and the polymer phase stirred with 80 ml of water and 800 ml of absolute ethanol; the phases were allowed to separate for 1 hour. The alcohol phase was sucked off and the polymer phase stirred with 40 ml of water and 200 ml of absolute ethanol; the phases once more were allowed to separate for 1 hour. The alcohol phase was sucked off and the polymer phase was stirred twice with 150 ml absolute ethanol. After the second mixing with ethanol, the phases were allowed to separate overnight. Next day the alcohol phase was sucked off and the polymer phase was diluted with 20 ml of water.

Analysis:

Weight of polymer phase before drying: 342 g

Weight loss at drying: 29.3% w/w

Cl⁻ Content: 5.0% w/w

Na⁺ Content: 3.4% w/w

Organic dry substance: 221.7 g

Example 3.

Preparation of polymer U:II 38—69 from sorbitol, gluconic acid lactone and epichlorohydrin.

The polymerisation up to the filtration of the reaction mixture was carried out analogously with the polymerisation according to Example 1 and at a temperature of 80°C. The filtered polymer solution and the liquid used for washing after the filtering step were combined and stirred with 2560 ml of absolute ethanol and 80 ml of water; the polymer phase and the alcohol phase were allowed to separate overnight. The following day the alcohol phase was sucked off and the polymer phase filtrated in

order to remove precipitated NaCl. The precipitated NaCl was washed with 100 ml 70% ethanol. The filtrate and the washing liquid were combined and stirred with 1200 ml of absolute ethanol and 60 ml of water. The phases were allowed to separate for 2 hours; the alcohol phase was sucked off and the polymer phase stirred with 700 ml absolute ethanol and 70 ml of water. The phases were allowed to separate for 1 hour; the alcohol phase was sucked off. The polymer phase was stirred with 175 ml of absolute ethanol and 35 ml of water. The phases were allowed to separate for 1 hour; the alcohol phase was sucked off and the polymer phase was stirred with 175 ml of acetone. The mixture obtained after the final addition of acetone was allowed to stand overnight. The following day, the acetone was sucked off and the polymer dried at 40°C in a vacuum dryer over 45 minutes.

Analysis:

Weight of polymer phase before drying: 212.7 g
Weight loss at drying: 16.9% w/w
Cl⁻ Content: 6.5% w/w
Na⁺ Content: 4.3% w/w
Organic dry substance: 189.9 g.

Example 4.

Preparation of polymer U:II 6—69 from sorbitol, gluconic acid lactone and epichlorohydrin.

The polymerisation up to the filtration of the reaction mixture was carried out analogously with the polymerisation according to Example 1 and at a temperature of 75°C. The filtered polymer solution and the washing liquid from the filtering step were combined and stirred with 2500 ml of 95% ethanol and 55 ml of water; the polymer phase and the alcohol phase were allowed to separate overnight. The following day the ethanol phase was sucked off and the polymer phase filtered in order to remove precipitated NaCl. The filtered NaCl was washed with 100 ml of 70% ethanol. The polymer phase and the washing liquid were combined and stirred with 1320 ml of 95% ethanol. The phases were allowed to separate for 1 hour; the alcohol phase was sucked off and the polymer phase stirred with 870 ml of 95% ethanol. The phases were allowed to separate for 2 hours whereafter the alcohol phase was sucked off and the polymer phase stirred with 158 ml of 95% ethanol and 22 ml of water. After 30 minutes, the alcohol phase was sucked off and the polymer phase washed twice with 150 ml absolute ethanol and 5 times with acetone each time using 150 ml of acetone. The mixture obtained after the final washing with acetone was allowed to stand overnight. The following day the acetone was sucked off and the polymer was dried at 40°C in a vacuum dryer over 55 minutes.

Analysis:

Weight of polymer phase before drying: 281.2 g
Weight loss at drying: 15.8% w/w
Cl⁻ Content: 6.6% w/w
Na⁺ Content: 4.2% w/w
Organic dry substance: 211.5 g.

Example 5.

Preparation of polymer U:II 38—70 from sorbitol, gluconic acid lactone, and epichlorohydrin.

To a 100 l acid resistant boiler provided with stirrer, charging vessel, cooler and thermometer were added

2000 ml water
1200 g NaOH
3000 g gluconic acid lactone
6000 g sorbitol and in the charging vessel
4000 ml epichlorohydrin

The temperature of the mixture in the boiler was adjusted to 40°C and the epichlorohydrin was then added over 60 minutes. The temperature was raised so that after 30 minutes it was 80°C and was kept thereat during the remainder of the polymerisation. From 30 minutes to 60 minutes after starting, 1200 ml 50% NaOH were added. From 180 minutes after starting, simultaneous addition of 1600 ml 50% NaOH and 1000 ml epichlorohydrin was started. The epichlorohydrin was added from 180

minutes to 195 minutes after starting and the NaOH from 180 minutes to 270 minutes after starting. From 270 to 285 minutes after starting 800 ml of epichlorohydrin were added and from 285 to 315 minutes after starting 800 ml of 50% NaOH were added. The polymerisation was then allowed to proceed without addition of reactants until 345 minutes after starting; the temperature was then lowered by cooling. When the temperature of the reaction mixture was 50°C, 1000 ml 4M HCl were added and during continued cooling further 6M HCl was added until the pH reached 0.75. 60 L of 95% ethanol were added to the reaction mixture. The boiler containing the resulting mixture was allowed to stand without stirring overnight. Next day the alcohol phase was sucked off and the polymer phase was filtered in order to remove precipitated NaCl. The NaCl was washed with 2 litres of 70% ethanol. The polymer phase was stirred with 14.7 litres of 95% ethanol; the phases were allowed to separate for 2 hours. The alcohol phase was removed and the polymer phase stirred with 9.1 litre of 95% ethanol and 405 ml of water; the phases were allowed to separate for 1 hour. The alcohol phase was removed and polymer phase stirred twice, each time with 1600 ml absolute ethanol. The final separation of the phases was allowed to continue overnight. The alcohol phase was then removed and the polymer phase diluted with 300 ml of water.

Analysis:
 Weight of polymer phase before drying: 3667 g
 Weight loss at drying: 26.3% w/w
 Cl⁻ Content: 6.2% w/w
 Na⁺ Content: 3.9% w/w
 Organic dry substance: 2429.6 g
 Gel filtration curve, Sephadex G:15, is shown in Fig. 2.

Example 6.

Preparation of polymer U:II 41—70 from sorbitol, sodium gluconate and epichlorohydrin.

The polymerisation was carried out analogously as described in Example 5, using 3760 g of sodium gluconate instead of the gluconic acid lactone. The amount of NaOH present before addition of epichlorohydrin started was reduced from 1200 g to 526 g.

Analysis:
 Weight of polymer phase before drying: 4458 g
 Weight loss at drying: 25.7% w/w
 Cl⁻ Content: 6.1% w/w
 Na⁺ Content: 4.0% w/w
 Organic dry substance: 2976.6 g.

Example 7.

Preparation of polymer P 13—8—70 from sorbitol, glucoheptonic acid lactone and epichlorohydrin.

To a 5 l round-bottomed flask provided with stirrer, dropping funnel, thermometer and cooler were added at 45°C

150 ml distilled water
 60 g NaOH
 150 g glucoheptonic acid lactone
 300 g sorbitol

250 ml of epichlorohydrin were added continuously over 51 minutes. The temperature was raised to 75°C during 20 minutes and kept there until 165 minutes after starting. The temperature was raised to 85°C. At 315 minutes after starting, the temperature was lowered to 75°C. The time is counted from the start of the addition of epichlorohydrin. The reaction is carried out with efficient stirring.

Besides the above mentioned components the following amounts of NaOH and epichlorohydrin were added:

110 g NaOH in solid form
 50 g NaOH dissolved in 55 ml distilled water to a volume of about 70 ml
 90 ml epichlorohydrin

The addition of these further reactants was carried out in portions according to the following table:

Time (minutes after starting of addition of first portion of epichlorohydrin)	Epichlorohydrin (ml)	NaOH solid form (g)	NaOH solution (ml)
60		5	
75		5	
90		10	
105		10	
120		10	
135		10	
150		10	
165		10	
180	50	10	
195		10	
210		10	
225		10	
240			14 (10 g NaOH)
255			14
270	40		
285			14
300			14
315			14

5	At 415 minutes after the start of addition of the first portion of epichlorohydrin the reaction mixture was cooled to 60°C. 50 ml of 4M HCl were added slowly under continued cooling and stirring. 6M HCl was added until the pH was 0.8. The acidified reaction mixture was filtered and the solid residue on the filter was washed twice with ethanol, first with 25 ml and then with 50 ml of ethanol diluted with one volume of water. The filtrate was diluted and combined with the washing liquid giving a volume of 1025 ml excluding the ethanol in the washing liquid. 2560 ml of 99.5% ethanol were then added while stirring; the mixture was allowed to stand overnight. The alcohol phase was decanted and the polymer phase, containing crystals of NaCl, was filtered. The solid residue on the filter was washed twice with 50 ml of ethanol, diluted to the same concentration as the alcohol phase. The filtrate and the washing liquid were combined, giving a volume of 860 ml. 152 ml of distilled water and 1520 ml of 99.5% ethanol were added and the mixture was allowed to stand for 90 minutes. The ethanol phase was then decanted and the polymer phase, volume 550 ml, was mixed with 110 ml of distilled water. To the resulting mixture, 1100 ml of 99.5% ethanol were added. The mixture was allowed to stand for 30 minutes. The ethanol phase was decanted and the polymer phase, volume 450 ml, was mixed with 90 ml of distilled water and with 900 ml of 99.5% ethanol. The ethanol phase was decanted after 30 minutes. The polymer phase, volume 410 ml, was mixed with 41 ml of distilled water and with 205 ml of 99.5% ethanol. After 30 minutes, the ethanol phase was decanted and the polymer phase washed twice with 205 ml of 99.5% ethanol and 5 times with 205 ml of acetone. The washed polymer was dried in vacuum in	5
10		10
15		15
20		20
25		25

order to remove traces of acetone. The polymer obtained was weighed and mixed with about 1/10 w/w of distilled water in order to give the product a suitable consistency.

Analysis:

Weight of polymer phase before drying: 390 g

Weight loss at drying: 18.7% w/w

Cl⁻ Content: 4.8% w/w

Na⁺ Content: 3.3% w/w

Example 8.

Preparation of polymer U:II 31—69 from sorbitol, gluconic acid lactone and epichlorohydrin.

The polymerisation up to the filtration of the reaction mixture was carried out in an analogous way with the polymerisation according to Example 1, at a temperature of 85°C.

The reaction mixture was filtered and the crystals of NaCl were washed with 100 ml of 50% acetone. The filtered polymer solution and the washing liquid were stirred with 2560 ml of acetone. The phases were allowed to separate overnight. The following day the acetone phase was sucked off and the polymer phase was filtered. Precipitated NaCl was washed with 100 ml of 70% acetone. The polymer phase and the acetone used for washing were combined and stirred with 100 ml of water and 2000 ml of acetone; the phases were allowed to separate for 1 hour. The acetone phase was sucked off and the polymer phase stirred with 200 ml of water and 2000 ml of acetone. The phases were allowed to separate for 1 hour; the acetone phase was sucked off and the polymer phase stirred with 100 ml of water and 500 ml of acetone. The phases were allowed to separate for 1 hour; the acetone phase was sucked off and the polymer phase stirred with acetone four times, 500 ml acetone each time. After the fourth stirring with acetone, the polymer phase was filtered. The filtered polymer phase was dried in a vacuum drier at 40°C for 1 hour and 30 minutes.

Analysis:

Weight of polymer before drying: 857 g

Weight loss at drying: 30.9%

Na⁺ Content: 10.3% w/w

Cl⁻ Content: 6.8% w/w

Organic dry substance: 491.7 g

Gel filtration curve, Sephadex G:15, is shown in Fig. 3.

Example 9.

Preparation of polymer U:II 19—69 from sorbitol, gluconic acid lactone and epichlorohydrin.

The polymerisation was carried out at 85°C but otherwise the methods and amounts of reactants described in Example 1 up to precipitation of the polymer with ethanol were used.

The filtered polymer solution and the washing liquid from the filtering step were combined and stirred with 2680 ml of 95% ethanol; the polymer phase and the alcoholic phase were allowed to separate overnight. Next day the ethanol phase was sucked off and the polymer phase filtered in order to remove precipitated NaCl. The precipitated crystals of NaCl were washed with 100 ml of 70% ethanol. The polymer phase and the washing liquid were combined and stirred with 657 ml of 95% ethanol and 5 ml of water. The phases were allowed to separate for 1 hour; the alcohol phase was sucked off and the polymer phase stirred with 333 ml of 95% ethanol and 20 ml of water. The phases were allowed to separate for 1 hour; the alcohol phase was sucked off. The polymer phase was stirred with 50 ml absolute ethanol and 10 ml water. The phases were allowed to separate for 30 minutes; the alcohol phase was sucked off and the polymer phase treated twice with 50 ml of absolute ethanol and treated 5 times with 50 ml of acetone. The final mixture of acetone and polymer was allowed to stand overnight. The following day the acetone was sucked off and the polymer dried at 40°C for 1 hour.

Analysis:

Weight of polymer phase before drying: 90.1 g

Weight loss at drying: 12.1% w/w

Cl⁻ Content: 6.7% w/w

Na⁺ Content: 4.7% w/w

Organic dry substance: 70.6 g.

Example 10.

Preparation of polymer U:II 23a—69 from sorbitol, gluconic acid lactone and epichlorohydrin.

5 The polymerisation was carried out at 85°C but otherwise the method and amounts of reactants as described in Example 1 up to precipitation of the polymer with ethanol were used. One third of the filtered polymer solution was stirred with 600 ml absolute isopropanol and 42 ml of water. The phases were allowed to separate overnight. The following day the isopropanol phase was sucked off and the polymer phase filtered. The filtrate was stirred with 540 ml of isopropanol and 27 ml of water. 10 The phases were allowed to separate for 2 hours; the isopropanol phase was sucked off and the polymer phase stirred with 440 ml of isopropanol and 40 ml of water. The phases were allowed to separate for 1 hour. The isopropanol phase was sucked off and the polymer phase stirred with 110 ml of isopropanol and 22 ml of water. The phases were allowed to separate for 1 hour. The isopropanol phase was sucked off and the polymer phase stirred twice with 110 ml of isopropanol. After the second treatment with isopropanol, the polymer was filtered; it was treated 5 times with acetone (80 ml of acetone each time). After the final treatment with acetone the polymer was dried in a vacuum drier for 1 hour at 40°C. 15

Analysis:

20 Weight of polymer phase before drying: 155.4 g
Weight loss at drying: 19.6%
Cl⁻ Content: 5.6% w/w
Na⁺ Content: 8.2% w/w
Organic dry substance: 108.1 g. 20

Example 11.

25 Preparation of polymer U:II—26—70 from sorbitol, sodium gluconate and epichlorohydrin. 25

To a 5 l round-bottomed flask provided with stirrer, dropping funnel and cooler were added

30 300 g sorbitol
94 g sodium gluconate
121.4 g water
22.4 g NaOH 30

35 The temperature of the mixture was adjusted to 40°C and the addition of 200 ml of epichlorohydrin started. The reaction temperature was raised so that after 30 minutes the temperature was 80°C. 60 Minutes after starting all the epichlorohydrin had been added and the addition of 45 g of NaOH dissolved in 45 ml of water was started. At 175 minutes after starting sodium gluconate (94 g) and 3.9 g of NaOH dissolved in 28.6 g of water were added. At 180 minutes after starting, the addition of 50 ml of epichlorohydrin was started simultaneously with the addition of 60 g of NaOH in 60 ml water. From 195 minutes to 270 minutes after starting only NaOH solution was added. From 270 to 285 minutes after starting, 40 ml of epichlorohydrin were added. From 285 to 315 minutes after starting 30 g NaOH dissolved in 30 ml water were added. At 345 minutes after starting, the polymer solution was cooled. 45 When its temperature was 50°C, the addition of 50 ml of 4 M HCl was started followed by 150 ml of 6 M HCl giving a pH in the polymer solution of 0.7. To the suspension of polymer and precipitated sodium chloride were added under stirring 2560 ml of absolute ethanol. After stirring for 10 minutes, the phases were allowed to separate overnight. The following day the alcohol phase was sucked off and the polymer phase filtered. The NaCl crystals were washed with 100 ml of 70% ethanol. 50 The filtrate and the washing liquid were combined and stirred with 52 ml of deionised water and 1040 ml absolute of ethanol; the phases were allowed to separate for 2 hours. The alcohol phase was sucked off and the polymer phase stirred with 66 ml of water and 660 ml of absolute ethanol; the phases were allowed to separate for 1 hour. The alcohol phase was sucked off and the polymer phase stirred with 26 ml of water and 130 ml absolute ethanol; the phases were allowed to separate for 1 hour. 55 The alcohol phase was sucked off and the polymer phase stirred twice with 120 ml absolute ethanol. After the second stirring with ethanol, the phases were allowed to

separate overnight. The following day the alcohol phase was sucked off and the polymer phase diluted with 21 ml of water.

Analysis:

Weight of polymer phase before drying: 301 g

Weight loss at drying: 26.5% w/w

Cl⁻ Content: 5.5% w/w

Na⁺ Content: 3.8% w/w

Organic dry substance: 200.6 g

Iron preparations using polymers prepared according to some of the foregoing Examples were prepared as described under H above. The following results were obtained.

Example	Yield of dry iron preparation g	Yield of complex-bound iron %	Content of iron in dry iron preparation %	Absorption after		Excretion after 24 h %
				24 h	7 days 14 days	
2	19	40.3	26.3	61	86	7.2
3	35.4	84.0	29.4	67	90 93	12
4	17.4	37.2	26.5	42	80	9
6	80.5	66.0	22.9	68	86	19
5	75.4	63.0	23.5	57	83/87	11
7	26.6	56.6	26.4	70	82 93	9
8	28.4	72.5	31.7	18	51	6
9	33.9	77.0	28.9	43	41 59	11
10	27.6	70	31.5	11.	26 41	12

Example 12.

Preparation of polymer P 21—12—70 from sorbitol, gluconic acid lactone and epichlorohydrin in three steps.

Step 1.

5 To a two litre round-bottomed flask provided with stirrer, dropping funnel, thermometer, and cooler, were added 5

360 ml distilled water

360 g gluconic acid lactone, about 2 moles.

10 The mixture was heated to 60°C.

3 Ml concentrated sulphuric acid was added as catalyst.

15 190 G epichlorohydrin corresponding to substantially 162 ml and 2.05 moles were added dropwise over 100 min. The temperature was kept at 60—65°C by effective stirring while the epichlorohydrin is mixed with the water phase. The heating and stirring was continued for 180 minutes calculated from the start of addition of epichlorohydrin. The reaction mixture was cooled to room temperature and was allowed to stand overnight. 15

Volume: 700 ml

Step 2.

20 To a 5 l round-bottomed flask provided with stirrer, dropping funnel, thermometer, and cooler were added at 45°C 20

150 ml of distilled water,

450 g sorbitol and

26.3 g NaOH

25 250 Ml of epichlorohydrin were added continuously over 60 minutes. The temperature was raised to 75°C over 20 minutes calculated from the start of addition of epichlorohydrin. This temperature was then maintained during the polymerisation which was carried out while stirring effectively. 25

30 125 G of NaOH were added in the form of tablets according to the following scheme: 5 g after 75 minutes, 15 g after 105, 135, 165, 195, 225, 255, 285 and 315 minutes. After 345 minutes, the reaction mixture was cooled to room temperature and was allowed to stand overnight. 30

Step 3.

35 The reaction product from step 2 was heated to 60°C; the reaction product obtained in step 1 was added in portions of 100 ml. Every addition was made over 10 minutes and, after each such addition, NaOH in the form of tablets was added to the mixture. The times and amounts of the various additions are given in the following table. 35

Time minutes	Product from step 1 ml	NaOH g
0	100	
15		10
25		10
35		10
45		10
50	100	
60		10
65		10
70		10
75	100	
85		10
90		10
95	100	
105		10
110	100	
120		10
125	100	
135		10
140		10
145	100	
155		10
160		10
165		10
170		10
175		10
180		10
190		10
200		10

After having kept the temperature at 60°C over 300 minutes, the mixture was cooled to 40°C; 620 ml of 6 HCl were added under continued cooling over 30 minutes. After the addition of HCl, the pH was about 0.8.

5 *Working up of the product.*

The reaction mixture from step 3 was filtered. The residue on the filter was washed with 50 ml of ethanol diluted with 1 volume of distilled water. The washing liquid was mixed with the filtrate and diluted to 2100 ml with distilled water. 5250 Ml (2.5 volumes) of 99.5% ethanol were added while stirring. The mixture was allowed to stand for 40 minutes whereby two phases became apparent. The ethanol phase was decanted off and the remaining phase was allowed to stand overnight. Precipitated NaCl was filtered off and washed three times with 25 ml ethanol diluted to the same concentration at the mother liquor. The washing liquid was mixed with the filtrate giving a total volume of 920 ml. 184 Ml of distilled water were added followed by 1840 ml of 99.5% ethanol. The mixture was allowed to stand for 60

5

10

15

15

minutes; the mother liquor was decanted off. The remaining phase, volume 750 ml, was mixed with 150 ml of distilled water; 1500 ml of 99.5% ethanol were added while stirring. The mixture was allowed to stand for 10 minutes; the major part of the mother liquor could then be decanted. The very viscous phase remaining was allowed to stand overnight in order to achieve a better separation of the mother liquor. The remaining phase, volume 440 ml, was mixed with 44 ml of distilled water and 220 ml of 99.5% ethanol. After 60 minutes, the mother liquid was decanted off and the remaining phase washed twice with 220 ml of 99.5% ethanol and five times with 220 ml of acetone. The washed product was dried in vacuum during two hours at 50°C giving 562 g of product. 56 ml of distilled water was added in order to obtain a more handleable product. Yield after addition and mixture with water was 607.7 g.

Analysis:

Weight loss at drying: 24.8%

Cl⁻ Content: 4.9%

Na⁺ Content: 3.5%

Example 13.

Preparation of the carboxymethyl ether derivative of polymer P 25—5—70.

A polymer (P 25—5—70) was prepared from sorbitol, gluconic acid lactone and epichlorohydrin in the same way as described for polymer U:II 6—69 in Example 4.

To a round-bottomed flask, volume 2 l provided with stirrer, dropping funnel, thermometer, and cooler were added

82.0 g polymer, calculated organic dry substance

20 ml distilled water

400 ml benzene

90 g of NaOH dissolved in 80 ml of distilled water were dropped into the above mixture. 112 G monochloroacetic acid were added over 10 minutes and while stirring vigorously. The temperature was kept at substantially 50°C for 300 minutes calculated from the start of addition of the monochloroacetic acid. The mixture was cooled to room temperature and was allowed to stand for 30 minutes whereby the benzene phase is separated from the water phase. The benzene phase was sucked off and the water phase mixed with 200 ml of 6 M HCl giving a pH of 1.25. With the addition of acid, further benzene separated and was sucked off. The volume of the water phase was 500 ml. 1000 ml of 99.5% ethanol were added while stirring. The mixture was allowed to stand for 30 minutes yielding a water phase and a solid crystalline phase. The water phase was filtered off and concentrated *in vacuo* to about 250 ml. The pH was adjusted to 1.2 using substantially 3 g. of NaHCO₃. The evaporation was thereafter continued until the volume was about 180 ml. 450 ml of 99.5% ethanol were added while stirring whereafter the mixture was allowed to stand overnight. The crystalline precipitate which had formed was filtered off and the filtrate evaporated *in vacuo* to about 160 ml, pH 1.4. The remainder after the evaporation was washed five times with 160 ml acetone and then dried *in vacuo* over 3 hours at 40°C. 134 G of product were obtained, which product was diluted to 150 g with distilled water in order that a more easily handleable product would be obtained:

Analysis:

Weight loss at drying: 15.4%

Cl⁻ Content: 6.9%

Na⁺ Content: 5.9%

The carboxylic acid content in the high-molecular weight fractions increased from 0.319 milliequivalents per gram organic dry substance in the starting material to 2.479 milliequivalents per gram organic dry substance in the end product.

Example 14.

Variations of the relative amounts of epichlorohydrin and gluconic acid in preparation of polymers.

Polymers of sorbitol, epichlorohydrin and gluconic acid were prepared using varying amounts of epichlorohydrin and gluconic acid lactone. The variations were made with the following procedure as a basis:

To a mixture, temperature 45°C, of

300 ml distilled water

120 g NaOH

300 g gluconic acid lactone

600 g sorbitol

were added 400 ml of epichlorohydrin over substantially 50 minutes. The temperature was successively raised to 80°C under effective stirring. Over 270 minutes were added a further 180 ml of epichlorohydrin, one portion of 100 ml 180 minutes after the start of the addition of the first 400 ml epichlorohydrin, and one portion of 80 ml 270 minutes after the start of the addition of the first 400 ml of epichlorohydrin and 271 g of NaOH in 12 portions of substantially 20 g and 3 portions of substantially 10 g. The reaction product was worked up using precipitation with ethanol as described previously. The total amounts of sorbitol, epichlorohydrin and gluconic acid which had been added were accordingly 600 g, 580 ml and 300 g, respectively. Polymers were prepared using relative amounts of the reactants according to the following Table.

Sorbitol g	Used amount of epichlorohydrin g	gluconic acid g	Yield of dry organic substance g
600	25	300	228
600	580	300	332
600	880	300	527
600	980	300	493
600	1080	300	317
728	580	150	656
684	580	200	556
472	580	450	202

When the amount of epichlorohydrin and gluconic acid lactone was varied, corresponding adjustments to the total amount of NaOH were made.

Also the total amount of NaOH used in the above mentioned "standard" reaction was varied. In the process used as basis, in all 391 g of NaOH were added. Polymers were obtained using a total amount of 210, 290, 471, and 551 g NaOH in the "standard" procedure described above. The additions of 210 and 290 g of NaOH were carried out with addition of smaller amounts than in the "standard" process mainly during the latter part of the polymerisation. The processes with increased amounts of NaOH were carried out with addition of various amounts in the first part as well as in the latter part of the polymerisation process.

Example 15.

Preparation of dry iron composition FeU 127—70.

In 113 ml of distilled water were dissolved 154 g of a polymer (final product) prepared from sorbitol, gluconic acid lactone and epichlorohydrin in the same way as described for polymer U:II—41—70 in Example 6 and 45 ml lactic acid. A separate solution of 144 g NaOH in 600 ml distilled water was prepared. Of this NaOH solution, 75 ml was added to the mixture of polymer and lactic acid. After heating the mixture thus obtained to 80°C under stirring in a closed 2 l round-bottomed flask provided with baffles, 9 portions of 45 ml each of the NaOH solution were added. After the addition of each such portion, 30 ml of 1.88 M ferric chloride were added. The additions were made dropwise over 1 minute for the sodium hydroxide solution and over 2 minutes for the ferric chloride solution. The additions of NaOH and ferric chloride solutions were made with 2 minutes interval. After addition of the 9th portion of ferric chloride solution, 83 ml of the NaOH-solution was added. The temperature of the reaction mixture was then kept at 80°C for 35 minutes under stirring; the reaction mixture was cooled to 25°C. The solution was diluted to 1125 ml. To the

diluted solution were added 2550 ml of 95% ethanol over 20 minutes under stirring. The stirring was continued for 10 minutes. After 60 minutes, the mother liquor was sucked off from the deposited precipitate and the precipitate was washed with 450 ml of 63% ethanol. The precipitate was dissolved in 675 ml of distilled water at 40°C in a closed 1 l flask under stirring. The temperature was raised to 80°C over 30 minutes; the mixture was heated under stirring at 80°C for 30 minutes. The solution was cooled to 25°C and pH adjusted to 6.8 using 6 N HCl. The insoluble precipitate formed during the reaction was separated by centrifuging for 2 minutes. This precipitate weighed 30 g in dry state. The solution was filtered through Seitz filter 3/1250. The filtrate was diluted to 1050 ml with distilled water and 2300 ml 95% ethanol were added dropwise during 20 minutes under stirring; the stirring was continued for 2 minutes. The precipitate obtained was allowed to stand for 15 hours; the mother liquor was sucked off from the deposited precipitate and the precipitate was washed 3 times with 450 ml of 63% ethanol and 3 times with 450 ml of 95% ethanol. The precipitate was dried in vacuo at 40°C to give 72.8 g of a dried preparation with an iron content of 24.3% by weight, calculated on the dried preparation.

Example 16.

Preparation of an injection solution.

41.2 G of the dried preparation obtained in Example 15 was added in portions over 15 minutes to 170 ml of distilled water at 80°C in a closed 250 ml round-bottomed flask under stirring. The temperature was then kept at 80°C for a further 50 minutes; the solution was cooled to 25°C. The solution was diluted to 200 ml. After filtration through Seitz filter No. 3/1250 and 0.65 μ membrane filter, the solution was filled into 10 ml injection bottles which were sterilized at 120°C for 20 minutes. The iron solution obtained had a total content of iron of 48.8 mg/ml; a ferrous iron content of 0.70 mg/ml; a viscosity of 5.4 cps and a pH of 7.47. The absorption of the iron in rabbits after injection of 20 mg of iron per kg bodyweight was 63% after 24 hours and 88% after 7 days. After 24 hours, 16% of the iron had been excreted.

Example 17.

Preparation of iron composition FeU 146—70.

A dry iron composition was prepared in the same way as described in Example 15 using a polymer prepared from sorbitol, gluconic acid lactone and epichlorohydrin in the same way as described for polymer U:II—38—70 in Example 5 with the exception that only 6 portions of the ferric chloride and sodium hydroxide solutions were added. Furthermore, the final addition of 83ml of NaOH-solution was omitted. The ratio of grams of polymer organic dry substance to grams of iron was therefore 5.44 instead of 3.61. Only 0.3 g of precipitate was formed during the reaction, and centrifugation of the solution was omitted. 79.1 G of a dried iron preparation were obtained. The iron content was 22.1% by weight calculated on the dried iron preparation.

Of the dried iron preparation obtained an injection solution was prepared analogously as described in Example 16. The total iron content on the injection solution obtained was 51.8 mg/ml; the ferrous iron content was 0.36 mg/ml; the viscosity was 7.82 cps; and the pH was 7.62.

The absorption in rabbits after injection of 20 mg of iron per kg bodyweight was 68% after 24 hours and 89% after 7 days. After 24 hours, 21% of the administered iron had been excreted.

Example 18.

Preparation of dry iron composition FeU 27—71.

1.52 Kg of polymer (final product) using a polymer prepared from sorbitol, gluconic acid lactone and epichlorohydrin in the same way as described for polymer U:II—38—70 in Example 5 and 0.45 l of lactic acid were dissolved in 1.125 l of distilled water. A separate solution of NaOH was prepared by dissolving 1.15 kg NaOH in 4.8 l distilled water. 0.745 L of the NaOH-solution was added to the solution of the polymer and lactic acid. The mixture obtained was heated to 80°C while stirring in a 30 l acid resistant boiler provided with baffles; 6 portions of 0.45 l each of the NaOH-solution were added. After each addition of NaOH, 0.3 l of a 1.88 M solution of ferric chloride was added. The additions were carried out dropwise over 1 minute for the sodium hydroxide and over 2 minutes for the ferric chloride solution. The additions of NaOH-solution and of ferric chloride solution were made with 2 minutes interval. 1 Minute after addition of the final portion of ferric chloride, 0.95 l of the NaOH-solution was added. The temperature of the reaction mixture was

then kept at 80°C for 35 minutes, still under stirring, the reaction mixture was cooled to 25°C and diluted to 9.2 l with distilled water. To the diluted solution, 21 l of 95% ethanol were added over 20 minutes under vigorous stirring; the stirring was then continued for 10 minutes. After 60 minutes, the mother liquor was sucked off from the deposited precipitate, which was washed with 4.5 l of 63% ethanol. The washed precipitate was added to 4.20 l of distilled water at 40°C in the reaction vessel; the temperature was raised to 80°C over 30 minutes. The temperature was kept at 80°C for a further 30 minutes. During all of the dissolution process the rate of stirring was 235 rpm. After cooling to 25°C, the pH was adjusted to 6.8 using 6 N HCl, and the solution was filtered through Seitz 3/1250 and diluted to 6.48 l. To this solution, 14.1 l 95% ethanol were added under stirring over 20 minutes. After stirring for a further 2 minutes, the precipitate was allowed to stand for 15 hours. The precipitate was washed 3 times with 4.5 l of 63% ethanol and 3 times with 4.5 l of 95% ethanol; it was dried in vacuum at 45°C yielding 730 g of dried iron preparation with an iron content of 19.9% by weight calculated on the dried preparation.

From the dried preparation, an injection solution was prepared in the same way as described in Example 15. The total iron content of the injection solution obtained was 56.0 mg/ml; the ferrous iron content was 1.92 mg/ml; the viscosity of the injection solution was 6.45 cps and the pH was 7.45. The absorption in rabbit after injection of 20 mg iron per kg bodyweight was 72% after 24 hours and 93% after 7 days. After 24 hours 24% of the administered iron had been excreted.

Example 19.

Preparation of dry iron composition SEM 19/70.

67.2 G of the polymer (final product) prepared from sorbitol, gluconic acid and epichlorohydrin in the same way as described for polymer U:II 38—70 in Example 5 and 20 ml of lactic acid were dissolved in 50 ml of distilled water. A separate solution of 80 g of NaOH in 400 ml of distilled water was prepared. Of this NaOH solution, 40 ml was added to the solution of polymer and lactic acid. The mixture obtained was heated to 80°C under stirring, and then 9 portions of 24 ml each of the NaOH solution were added. After each addition of NaOH solution, 14 ml of the ferric chloride solution prepared by dissolving 60 g of FeCl₃ · 6 H₂O in 90 ml distilled water were added. The 18 portions of NaOH and ferric chloride solutions were added over 25 minutes. 5 minutes later 45 ml of the NaOH solution were added; the temperature was kept at 80°C for a further 35 minutes under continued stirring. The mixture was cooled to 25°C and diluted to 550 ml with distilled water. To the diluted solution, 1100 ml 99.5% ethanol were added. After 30 minutes, the mother liquor was sucked off from the deposited precipitate which had formed, and the precipitate was washed with 200 ml diluted ethanol (ethanol and water in the proportions 2:1). The washed precipitate was added in portions during 15 minutes and under vigorous stirring to 300 ml of distilled water of temperature 80°C. The temperature was kept at 80°C for a further 30 minutes under stirring. The solution was cooled to 25°C and the pH of the solution was adjusted to 6.2 using 96 ml of 2 N HCl. The neutralized solution was filtered through Seitz filter plate No. Ko2. The solution was diluted to 450 ml with distilled water. To the diluted filtrate 900 ml of 99.5% ethanol were added under vigorous stirring. After 30 minutes, the mother liquor was sucked off from the precipitate obtained. The precipitate was allowed to stand for 15 hours. The precipitate was dissolved in distilled water in the same way as described above. After cooling and filtering through Seitz 3/1250, the solution was diluted to 350 ml with distilled water and 700 ml of 99.5% ethanol was added under stirring. After 30 minutes, the mother liquor was sucked off from the deposited precipitate, and the precipitate was washed 3 times with 200 ml of ethanol and water (in proportions 2:1) and 3 times with 99.5% ethanol. The precipitate obtained was dried *in vacuo* yielding 27.4 g of a dried preparation with an iron content of 27.6% by weight calculated on the dried preparation.

Example 20.

Preparation of an injection solution.

25.4 G of the dried iron preparation obtained in Example 19 were added in portions to 130 ml of distilled water at 80°C over 15 minutes and stirring. The temperature was kept at 80°C for further 50 minutes; the solution was cooled to 25°C. The solution was diluted to 140 ml. After filtering through Seitz filter No. 3/1250 and 0.65 μ membrane filter, the solution was filled into 10 ml injection flasks which were sterilized at 120°C for 20 minutes. The iron solution obtained had a total iron content of 49.7 mg/ml; a ferrous iron content of 0.9 mg/ml; a viscosity of 6.1 cps; a

freezing point depression of 0.3°C and a pH of 7.13. The absorption in rabbit after injection of 20 mg of iron per kg bodyweight was 56% after 24 hours and 93% after 7 days. The excretion after 24 hours was 9%.

Example 21.

5 Preparation of dry iron composition P 7—6—71 in a diluted reaction mixture and without lactic acid. 5

An amount of polymer prepared from sorbitol, gluconic acid and epichlorohydrin in the same way as described for polymer U:II—38—70 in Example 5 and corresponding to 40 g of organic dry substance, was dissolved in 300 ml of distilled water at room temperature. A solution consisting of 60 g of FeCl₃; 6 H₂O dissolved in 100 ml distilled water was mixed with the polymer solution at room temperature. To the mixture thus obtained were added under vigorous stirring 960 ml of 1M NaOH solution, with the temperature of the reaction solution must not exceed 30°C. After 10 45 minutes at room temperature, the temperature of the mixture was raised to 80°C. The mixture was kept at this temperature over 20 minutes whereupon it was cooled to room temperature and filtered through a Seitz filter plate No. Ko2. The filtrate was diluted to 1500 ml with distilled water; 3000 ml of 99.5% ethanol were added under vigorous stirring. After 20 minutes, the precipitate formed was filtered and dissolved in a mixture of 600 ml of distilled water, 10 g of polymer, calculated as organic dry substance, and 20 ml of 1 M NaOH. The temperature was raised to 80°C and kept there over 25 minutes; the solution was cooled to room temperature. After cooling, the solution was filtered through Seitz finger plate EKS. The filtrate was diluted to 1000 ml with distilled water and 2000 ml of 99.5% ethanol was then added under vigorous stirring. After 90 minutes, the precipitate was filtered and redissolved, heated and cooled in the same way once more. To the cooled solution thus obtained, 1 M HCl was added slowly and under stirring until pH of the solution was 7.0; the solution was then diluted with distilled water to 1000 ml. 2000 ml of 99.5% ethanol was added under stirring. After 60 minutes, the precipitate obtained was filtered and washed, first with 100 ml ethanol of the same concentration as the mother liquor and then with 100 ml of 75% ethanol. The precipitate was then washed 3 times with 150 ml of 99.5% ethanol; it was dried *in vacuo* at 50°C over 3 hours. Yield: 35.6 g of a dried preparation containing a total amount of 28.8% by weight of iron calculated on the dried iron preparation. 15 20 25 30

Example 22.

35 Preparation of injection solution. 35

To a round-bottomed 500 ml flask provided with stirrer, cooler and thermometer 130 ml of distilled water were added and heated to 80°C. 26.0 G of the dried preparation obtained as described in Example 21 were added to the distilled water over 10 minutes under stirring. The mixture obtained was kept at 80°C over 60 minutes calculated from the start of the addition of the dry preparation. The solution was then cooled to room temperature and the pH was adjusted to substantially 7.7 with 1M HCl. The volume of the solution was adjusted to 150 ml with distilled water; the solution was filtered through a Seitz filter plate No. 3/1250 and through 0.6 μ membrane filter Millipore ("Millipore" is a Registered Trade Mark). The filtered solution was filled into ampoules which were sterilized at 120°C over 20 minutes. The injection solution obtained had a total iron content of 51.4 mg/ml; a ferrous iron content of 0.57 mg/ml; a viscosity of 2.87 cps and a pH of 7.84. Absorption of iron in rabbit muscle after 7 days was 91%. After 24 hours 12% of administered iron had been excreted in the urine. 40 45

Example 23.

50 Preparation at room temperature of dry iron composition FeU 37—72. 50

80 g (organic dry substance) of a polymer (U:II 12—71), synthesized analogously and from the same ingredient as polymer U:II 38—70 described in Example 5, were dissolved 600 ml of distilled water. A mixture of 236 ml of 1.88 M FeCl₃ solution and 24 ml distilled water was added 1440 ml of 2N NaOH were added over 60 minutes under vigorous stirring at room temperature. After the NaOH solution had been added, the solution was kept at room temperature for another 90 minutes under stirring. The solution was filtered through Seitz filter plate No. 3/1250. The filtrate was diluted to 2400 ml, 5600 ml of 95% ethanol were added during 20 minutes under vigorous stirring; the slurry was kept under stirring for 10 minutes. After 80 minutes, the precipitate was filtered and dissolved in a mixture of 1200 ml of distilled water and 20 g of polymer U:II 12—71 calculated as organic dry substance and 40 ml 1N 55 60

NaOH under stirring. The solution was kept at room temperature under stirring for 90 minutes. 1M HCl was slowly added to the solution under stirring until the pH of the solution was 6.8. The solution was filtered through Seitz filter plate EKS. The filtrate was diluted to 2000 ml with distilled water; 4460 ml of 95% by volume ethanol was added over 20 minutes and vigorous stirring. The slurry was stirred for 2 minutes. After 16 hours, the precipitate was filtered and washed first with 200 ml of 63% by volume ethanol and then with 200 ml of 71% by volume ethanol. The precipitate was then washed 3 times with 300 ml of 95% by volume ethanol, and it was dried *in vacuo* at 40°C for 12 hours:

Yield: 65.2 g of dry substance containing a total amount of 27.6% by weight of iron.

Example 24.

Preparation of injection solution from dry iron composition FeU 37—72.

To a round-bottomed 500 ml flask provided with stirrer, cooler and thermometer, 230 ml distilled water were added and heated to 80°C. 48.2 G of the preparation obtained as described in Example 23 were added to the distilled water over 15 minutes under stirring. The mixture obtained was kept at 80°C for 65 minutes calculated from the start of the addition of the dry preparation. The solution was cooled to 25°C and diluted to 250 ml; it was filtered through Seitz filter plate No. 3/1250 and through a 0.65 μ membrane filter "Millipore" fitted with a A.P. prefilter No. 25 12725. The filtered solution was filled into ampoules which was sterilized at 120°C for 20 minutes. The injection solution obtained had a total iron content of 50.6 mg/ml, a ferrous iron content of 1.21 mg/ml, a viscosity of 2.94 cps and a pH 6.78. Absorption of iron in rabbit muscle after 7 days was 83%. After 24 hours, 14% of the administered iron had been excreted in the urine.

Example 25.

Preparation at 4—9°C of dry iron composition FeU 95—71.

80 G (organic dry substance) of a polymer (U:II 19—71) synthesized analogously and from the same ingredient as polymer U:II 38—70 described in Example 5 were dissolved in 600 ml distilled water. A mixture of 236 ml of 1.88 M FeCl₃ and 24 ml of distilled water was added and the solution was cooled to a temperature of 4°C. 2880 ml of 1N NaOH solution at 4°C was added under vigorous stirring over 60 minutes. The reaction-mixture was held at 4—9°C by cooling in an icebath. After the NaOH solution had been added, the solution was kept at 4°C for 60 minutes under stirring. The temperature was raised to 25°C and the solution filtered through a Seitz filter plate. No. 3/1250 and diluted to 3.800 ml. 8860 ml of 95% ethanol were added over 20 minutes under vigorous stirring; the slurry was stirred for 10 minutes. After 75 minutes, the precipitate was filtered and dissolved in a mixture of 1200 ml of distilled water, 20 g of polymer U:II 9—71 (calculated as organic dry substance) and 40 ml of 1N NaOH. The temperature was raised to 80°C over 30 minutes and kept at 80°C for 30 minutes, and the solution then was cooled to 25°C. 1M HCl was slowly added to the solution under stirring until the pH of the solution was 6.8. The solution was filtered through Seitz filter plate EKS. The filtrate was diluted to 2000 ml with distilled water, and 4460 ml of 95% by volume ethanol were added over 20 minutes under vigorous stirring. The slurry was stirred for 2 minutes. After 16 hours, the precipitate was filtered and washed first with 200 ml of 63% by volume ethanol and then with 200 ml of 71% by volume ethanol. The precipitate was then washed 3 times with 300 ml of 95% by volume ethanol; it was dried *in vacuo* at 40°C for 12 hours.

Yield: 1 g of dry substance containing a total iron content of 27.9% by weight.

Example 26.

Preparation of injection solution from dry iron preparation FeU 95—71.

To a round-bottomed 500 ml flask provided with a stirrer, cooler and thermometer, 170 ml distilled water were added at 80°C. 39.3 G of the preparation FeU 95—71 obtained as described in Example No. 25 were added to the distilled water over 15 minutes under stirring. The mixture obtained was kept at 80°C for 65 minutes calculated from the start of the addition of the dry preparation. The solution was cooled to 25°C and diluted to 200 ml; it was filtered through a Seitz filter plate No. 3/1250 and through a 0.65 μ membrane filter "Millipore" fitted with A.P. prefilter No. 25 12725. The filtered solution was filled into ampoules which were sterilized at 120°C for 20 minutes. The injection solution obtained had a total iron content of 49.8 mg/ml, a ferrous iron content of 0.8 mg/ml, a viscosity of 3.03 cps and a pH of 7.84.

Absorption of iron in rabbit muscle after 7 days was 86%. After 24 hours 20% of the administered iron had been excreted in the urine.

Example 27.

Preparation of polymer P 24—1—72 from sorbitol, potassium arabonate and epichlorohydrin.

In a round-bottomed flask, vol. 1 l, provided with a stirrer, dropping funnel, thermometer and cooler, were added at 45°C

60 ml distilled water

11 g NaOH

69 g potassium arabonate

120 g sorbitol

100 ml of epichlorohydrin were added continuously over 26 minutes. The temperature was raised to 75°C over 15 minutes calculated from the start of the addition of epichlorohydrin. 95 Minutes from the start of the addition of epichlorohydrin, the temperature was raised to 85°C and kept there until 205 minutes had passed after the start of the addition of epichlorohydrin. The temperature was lowered to 75°C, which temperature was maintained during the remaining part of the polymerisation, which was carried out under effective stirring.

The following reagents were added in the portions specified in the following Table.

65 g NaOH were dissolved in 88 ml of distilled water. The solution was diluted to 91 ml.

36 ml epichlorohydrin.

Time min.	Epichlorohydrin (ml)	NaOH solution (ml)
45		2.8
55		2.8
65		5.6
75		5.6
85		5.6
95		5.6
105		5.6
115	20	5.6
125		5.6
135		5.6
145		5.6
155		5.6
165		5.6
175		5.6
185	16	
195		5.6
205		5.6
215		7.0

When 260 minutes, calculated from the start of the first addition of epichlorohydrin, had passed, the reaction mixture was cooled to 60°C. During continued cooling to room temperature, the pH was adjusted to 0.6 using 6 M HCl. The

mixture was diluted with distilled water to 450 ml, and then 1125 ml of 99.5% ethanol were added while stirring. The next day the mother liquor was sucked off and the precipitated syrup which contained crystals was filtered. The remainder on the filter paper was washed with ethanol diluted to the same concentration as the mother liquor. The washing liquor was carefully mixed with the filtrate. In all 51 ml of distilled water was added, including the water contained in the washing liquor. 510 ml of 99.5% ethanol (that is 2 volumes based on the undiluted filtrate) were added. After 45 minutes, the mother liquor was sucked off and the precipitated syrup (volume 200 ml) was mixed with 40 ml of distilled water. 400 ml of 99.5% ethanol were added while stirring. The mixture was allowed to stand for 30 minutes; the mother liquor was then sucked off. The precipitated syrup was washed twice each time using 100 ml 99.5% ethanol, and five times using 100 ml of acetone. The washed syrup was dried *in vacuo* over two hours at about 50°C. It was then diluted with distilled water to 181 g. The product is designated SEG 1/72 F 9.

Analysis:

Loss of weight at drying	21.6%				
K ⁺ Content	2.0%	calculated	on	dried	sample
Na ⁺ Content	2.9%	"	"	"	"
Cl ⁻ Content	6.0%	"	"	"	"

Example 28.

Preparation of dry iron composition SEM 1—72 containing polymer 1—72 F 9 prepared from sorbitol, potassium arabonate and epichlorohydrin.

An amount of a polymer (1—72 F 9) prepared from sorbitol, potassium arabonate and epichlorohydrin and corresponding to 50 g of organic dry substance was dissolved in 300 ml of distilled water at room temperature. A solution containing 60 g FeCl₃·6 H₂O dissolved in 100 ml distilled water was mixed with the polymer solution at room temperature. To the mixture thus obtained were added while vigorously stirring 1440 ml of 1M NaOH, the temperature being not allowed to exceed 30°C. After 45 minutes at room temperature, the temperature of the mixture was raised to 80°C. The temperature of the mixture was kept at 80°C over 20 minutes whereupon it was cooled to room temperature and filtered through a Seitz filter plate No. Ko2. The filtrate was diluted to 2000 ml with distilled water; 6000 ml of 99.5% ethanol was then added while vigorously stirring. After 20 minutes, the precipitate obtained was filtered off and dissolved in a mixture of 600 ml of distilled water, 12.5 g of polymer, calculated as organic dry substance, and 20 ml of 1 M NaOH. The temperature was then raised to 80°C and kept there over 25 minutes; the solution was cooled to room temperature. To the cooled solution, 1M HCl was added while vigorously stirring until the solution had pH of 7. The solution was then diluted to 1000 ml with distilled water; 2000 ml of 9.5% ethanol was then added while vigorously stirring. After 60 minutes, the precipitate obtained was filtered off and washed with 100 ml ethanol diluted to the same concentration as the mother liquor; it was then washed three times with 150 ml of 99.5% ethanol. The washed precipitate was dried *in vacuo* at 50°C over 3 hours.

Yield: 42.6 g of product containing 26.6% of Fe calculated on the original sample.

Example 29.

Preparation of injection solution SEM 1/72 A.

To a round-bottomed flask, volume 500 ml, provided with a stirrer, thermometer and cooler, 130 ml of distilled water were heated to 80°C. 28.2 G of the dry iron preparation SEM 1—72 obtained in Example 28 were added to the water over 10 minutes while stirring. The temperature of the mixture was kept at 80°C over 65 minutes, calculated from the start of the addition of the dry iron preparation. The solution obtained was cooled to room temperature, the pH was adjusted to 7.3 using 1M HCl, and the volume was adjusted to 150 ml with distilled water. The solution was then filtered through a Seitz filter plate 3/1250 and through Pyrex glass filter. The filtrate obtained was filled into ampoules and autoclaved at 120°C during 20 minutes.

Analysis:

Total iron content	50.7 mg/ml
Ferrous Iron content	0.46 mg/ml
Viscosity	5.8 cPs
pH	8.0
Absorption of Fe from muscle rabbit after 7 days	89%
Excretion of Fe in urine of rabbit during the first 24 hours after the injection	1%.

5

5

Example 30.

10 Preparation of dry iron composition SEM 16—72 prepared from iron (III) ammonium sulphate. 10

15 An amount of a polymer (U:II 12—71) prepared from sorbitol, gluconic acid and epichlorohydrin in the same way as described for polymer U:II 38—70 in Example 5, corresponding to 70 g organic dry substance was dissolved in 200 ml of distilled water. A solution consisting of 106.7 g of $\text{Fe}_2(\text{SO}_4)_3 \cdot (\text{NH}_4)_2\text{SO}_4 \cdot 24 \text{H}_2\text{O}$ in 200 ml of distilled water was mixed with the polymer solution at room temperature. To the mixture thus obtained 750 ml of dilute ammonium hydroxide, containing 75 ml of a concentrated (28—30% NH_3) ammonium hydroxide solution, were added under vigorous stirring. 500 ml of dilute ammonium hydroxide solution, containing 250 ml of the above mentioned concentrated solution, were added. Finally 100 ml of the concentrated ammonium hydroxide solution were added. After 65 minutes at room temperature, the mixture was heated to 60°C. The mixture was kept at this temperature for 20 minutes whereupon it was cooled to room temperature and filtered through a Seitz filter plate No. 3/1250. The filtrate was diluted to 2000 ml with distilled water and then 4000 ml of ethanol (99.5%) were added under vigorous stirring. After 20 minutes, the precipitate obtained was separated by filtration and washed with 3×150 ml ethanol, diluted to the same concentration as the mother liquor and with 200 ml ethanol diluted to 75% and finally with 200 ml of ethanol (99.5%). The washed precipitate was dissolved in a mixture of 600 ml of distilled water, 17.5 g of the polymer (organic dry substance) and 20 ml of 1M NaOH. The temperature was raised to 60°C and was kept at this temperature for 25 minutes, and then the solution was cooled to room temperature. To the cooled solution, 2M HCl was added under vigorous stirring until the pH was 6.6. The solution was filtered through a Seitz filter Ko2, 3/1250 and EKS. The filtrate was diluted to 1000 ml with distilled water, and then 2000 ml of ethanol (99.5%) were added under vigorous stirring. The obtained precipitate was filtered and washed with 100 ml of ethanol diluted to the same concentration as the mother liquor, and with 100 ml of ethanol diluted to 75% and finally with 3×150 ml of ethanol (99.5%). The washed precipitate was dried *in vacuo* at 50°C. 15 20 25 30 35

40 Yield: 47.2 g

Iron content: 21.9% calculated on the original sample. 40

Example 31.

Preparation of dry iron composition SEM 17—72, prepared from iron (III) sulphate.

45 An amount of a polymer (U:II 12—71) prepared from sorbitol, gluconic acid and epichlorohydrin in the same way as described for polymer U:II 38—70 in Example 5, corresponding to 70 g of organic dry substance was dissolved in 200 ml of distilled water. A solution consisting of 50 g $\text{Fe}_2(\text{SO}_4)_3 \cdot x \text{H}_2\text{O}$ (corresponding to 12.4 g iron) and 200 ml of distilled water was mixed with the polymer solution at room temperature. 750 ml of dilute ammonium hydroxide solution, containing 75 ml of a concentrated ammonium hydroxide solution (28—30% NH_3), was added under vigorous stirring to the so obtained solution. An additional amount of 500 ml of dilute ammonium hydroxide solution, containing 250 ml of the above mentioned concentrated solution, was added. Finally 100 ml of concentrated ammonium hydroxide solution were added. After 70 minutes at room temperature, the temperature of the mixture was raised to 60°C. The mixture was kept at this temperature for 25 minutes, whereupon it was cooled to room temperature and filtered through a Zeiss filter plate No. Ko2. The filtrate was diluted to 2000 ml with distilled water, and then 4000 ml ethanol (99.5%) were added under vigorous stirring. After 30 minutes, the so obtained precipitate was separated by filtration and washed with 3×150 ml ethanol diluted to the same concentration as the mother liquor, and with 200 ml ethanol diluted to 75%, and finally with 200 ml ethanol (99.5%). The washed precipitate was dissolved in a mixture of 600 ml of distilled water, 17.5 g of polymer (organic dry substance) and 20 25 30 35 40 45 50 55 60

- 20 ml of 1M NaOH. The temperature was raised to 60°C and the mixture was kept at this temperature for 25 minutes, and then the solution was cooled to room temperature. To the cooled solution, 2M HCl was added under vigorous stirring until the pH was 6.3. The solution was filtered through a Zeiss filter plate EKS. The filtrate was diluted to 1000 ml with distilled water, and then 2000 ml of ethanol (99.5%) were added under vigorous stirring. The so obtained precipitate was filtered, washed with 100 ml of ethanol, diluted to the same concentration as the mother liquor, and with 100 ml ethanol diluted to 75%, and finally with 3 × 150 ml ethanol (99.5%). The washed precipitate was dried *in vacuo* at 50°C.
- Yield: 41.5 g
- Iron content: 22.7% calculated on the original sample.

Example 32.

Preparation of SEG-polymer 33/71 from hydroxypropylsorbitol, gluconic acid lactone and epichlorohydrin.

- To a round-bottomed flask provided with stirrer, dropping funnel, thermometer, and reflux cooler were added at 45°C
- 60 ml distilled water
- 24 g NaOH
- 60 g gluconic acid lactone
- 120 g hydroxypropylsorbitol (Atlas No. G—2401) containing about 84% by weight dry substance (Atlas is a Registered Trade Mark).
- 80 ml of epichlorohydrin were added continuously during 45 minutes. The temperature was raised to 75°C over 20 minutes calculated from the start of the addition of epichlorohydrin. From 165 min. the temperature was raised to 85°C and kept thereat for 165 to 300 minutes from the start of the addition of the epichlorohydrin, after which the temperature was lowered to 75°C. The temperature of 75°C was then maintained during the remainder of the polymerisation, which was carried out under effective stirring.
- Reagents were added in portions according to the following Table:
- 34 g NaOH in solid form
- 20.2 g NaOH dissolved in distilled water to a volume of 28 ml
- 36 ml epichlorohydrin

Time (min.)	Epichlorohydrin (ml.)	NaOH (g)	NaOH (ml solution)
60		2	
75		2	
90		2	
120		4	
150		4	
165		4	
180	20	4	
195		4	
210		4	
225		4	
240			5.6
255			5.6
270	16		
185			5.6
300			5.6
315			5.6

415 Minutes after the start of the addition of epichlorohydrin, the reaction mixture was cooled to 60°C. During continued cooling to room temperature, 20 ml of 4M HCl were added and then 6M HCl was added until the pH was 0.9. The reaction mixture which contained crystals was filtered. The solid remainder on the filter was washed with 20 ml of ethanol diluted with one part of water. The washings and 10 ml of distilled water were mixed with the filtrate, and then 1050 ml of 9.5% ethanol were added while stirring. Next day the precipitated crystals were filtered off and washed with 50 ml of ethanol diluted to the same concentration as the mother liquor. The washing liquid was mixed with the filtrate and then 0.5 volumes of chloroform were added under stirring. After 30 minutes, two phases had formed. The heavier phase was separated and mixed with 0.5 volumes of 99.5% ethanol and 1/6 volume chloroform. Two phases were formed which were separated after 2 hours. The heavy phase was mixed with 1/10 volume of water, 1/2 volume of 99.5% ethanol, and 1/6 volume of chloroform. The heavier of the two phases which had formed was separated after 2 hours. Its volume was 190 ml. The separated phase was washed five times with 95 ml acetone and dried *in vacuo* in order to remove the rest of the acetone. The dried product was diluted with 10 ml of distilled water in order to achieve a suitable viscosity.

Yield: 118 g

The product was designated SEG 33/71 F 11

Analysis:

Loss of weight at drying 20.6%

Na⁺ Content 5.9% calculated on dry sample

Cl⁻ Content 8.8% calculated on dry sample.

The polymer obtained was used for preparation of iron complex SEM 12/72 A.

Example 33.

Preparation of dry iron preparation SEM 12/72 using SEG-polymer 33—71 F 11, prepared from hydroxypropylsorbitol, gluconic acid lactone and epichlorohydrin.

SEG-polymer 33—71 F 11 corresponding to 40 g organic dry substance was dissolved in 300 ml distilled water at room temperature. A solution containing 60 g of FeCl₃ · 6 H₂O dissolved in 100 ml of distilled water was mixed with the polymer solution at room temperature. To the mixture so obtained were added under vigorous stirring 1440 ml of 1M NaOH. After 60 min. at room temperature, the temperature of the mixture was raised to 80°C. The mixture was kept at this temperature for 20 minutes whereupon it was cooled to room temperature and filtered through a Seitz filter plate Ko₂. The filtrate was diluted to 2000 ml with distilled water and then 4000 ml of 99.5% ethanol were added while vigorously stirring. The precipitate obtained was filtered off and dissolved in a mixture of 400 ml of distilled water, 10 g of the polymer (calculated as organic dry substance) and 20 ml of 1M NaOH. The temperature was raised to 80°C and kept there for 25 minutes, and then the solution was cooled to room temperature. To the cooled solution 1M HCl was added during vigorous stirring until pH 6.4 was obtained. The solution was filtered through a Seitz filter plate EKS. The filtrate was diluted with distilled water to 600 ml whereupon 1200 ml of 99.5% ethanol was added during vigorous stirring. The precipitate obtained was filtered off and washed with 100 ml of ethanol, diluted to the same concentration as the mother liquor, and with 100 ml of ethanol diluted to 75%, and finally three times with 150 ml of 9.5% ethanol. The washed precipitate was dried *in vacuo* at 50°C.

Yield: 28.6 g

Total iron content: 35.6% calculated on the original sample.

Example 34.

Preparation of injection solution SEM 12—72 A.

To a round-bottomed flask provided with stirrer, thermometer and cooler were added 130 ml of distilled water heated to 80°C. 21.1 G of dry iron preparation SEM 12—72 was added to the water over 5 minutes under stirring. The temperature of the mixture was kept at 80°C over 60 minutes calculated from the start of the addition of the dry iron preparation. The solution obtained was cooled to room temperature; it was diluted with distilled water to 150 ml. The solution was then filtered through a Seitz filter plate 3/1250 and through membrane filter Millipore 0.65 μ. The filtrate was filled into ampoules and autoclaved at 120°C over 20 minutes.

Analysis:

Total iron content	51.1 mg/ml
Ferrous iron content	1.38 mg/ml
Viscosity	1.8 cPs
pH	7.4
Absorption of iron from rabbit muscle after 7 days	56%
Excretion of iron in urine of rabbit during the first 24 hours after the injection	12%.

10	Example 35. Preparation of polymer P 7—4—72 from pentaerythritol, epichlorohydrin, and gluconic acid lactone. To a 3 l round-bottomed flask provided with a stirrer, dropping funnel, thermometer and cooler were added at 40°C	10
15	75 ml distilled water 30 g NaOH 75 g gluconic acid lactone 150 g pentaerythritol	15
20	The temperature of the mixture was raised to 75°C. 120 Minutes after the start, the temperature was raised to 85°C and again lowered to 75°C at 175 minutes after the start.	20
25	100 Ml of epichlorohydrin were added for 55 minutes. In addition, 25 ml were added at 135 minutes after the start and 20 ml at 165 minutes after the start. 75 G of NaOH was dissolved in distilled water to a final volume of 300 ml. The so obtained NaOH solution was added in portions of 10 ml at 90, 95 and 100 minutes and in portions of 20 ml at 105, 115, 120, 125, 130, 145, 150, 155, 160, 180, 185, 190 and 195 minutes and finally a portion of 10 ml at 200 minutes after start (i.e. the start of the addition of the first portion of epichlorohydrin).	25
30	After 210 minutes, the reaction mixture was cooled to room temperature and then 6M HCl was added until the pH was 0.7. The solution was diluted to 1050 ml using distilled water and then 2625 ml of ethanol (99.5%) were added under vigorous stirring. The mixture was allowed to separate overnight. The precipitated white and crystalline solid phase was separated from the clear mother liquor by filtration. The mother liquor was evaporated <i>in vacuo</i> to 600 ml and then 1M NaOH was added until the pH was 1.0. The evaporation was continued until the volume was substantially	30
35	280 ml. The salt crystals being precipitated during the evaporation were filtered and washed with ethanol of the same concentration as the mother liquor. The washings were mixed with filtrate, and then 30 ml of distilled water were added. To the mixture thus obtained, 825 ml ethanol (99.5%) and 412 ml chloroform were added. Two phases were formed. The heavier of these was separated and was allowed to stand overnight and the precipitated salt crystals were removed by filtration. The crystals were washed with diluted ethanol (5 parts of 99.5% ethanol and 1 part of distilled water). The washings were mixed with the filtrate giving a total volume of 245 ml.	35
40	5 Ml of ethanol (99.5%) and 70 ml chloroform were added and two phases were formed. The heavier of these (volume 140 ml) was separated and mixed with 5 ml of distilled water, 70 ml of ethanol (99.5%) and 85 ml of chloroform. Two phases were formed. The heavier of these was separated and washed three times with one volume of acetone and dried <i>in vacuo</i> to remove traces of acetone. The dried product was diluted with 25 ml of distilled water to obtain a syrup which was easier to handle. Yield: 80 g.	40
45		45
50	<i>Analysis:</i> Weight loss on drying 29.5% Na⁺ Content 4.1% w/w Cl⁻ Content 6.5% w/w	50

The polymer prepared according to the above described method was used for the preparation of iron composition SEM 13/72.

Example 36.

Preparation of dry iron preparation SEM 13—72 in diluted reaction mixture and without lactic acid.

An amount of polymer P 7—4—72 obtained in Example 35 corresponding to 40 g organic dry substance was dissolved in 300 ml of distilled water at room temperature. A solution containing 60 g of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ dissolved in 100 ml of distilled water was mixed with the polymer solution at room temperature. To the mixture thus obtained were added during vigorous stirring 1440 ml of 1 M NaOH solution, the temperature of the reaction mixture not being allowed to exceed 30°C. After 55 minutes at room temperature, the temperature of the mixture was raised to 80°C. The mixture was kept at this temperature over 20 minutes; it was then cooled to room temperature and filtered through a Seitz filter plate Ko2. The filtrate was diluted to 2000 ml with distilled water and then 4000 ml of 99.5% ethanol were added under vigorous stirring. After 90 minutes, the precipitate formed was filtered off and dissolved in a mixture of 400 ml of distilled water, 10 g of polymer (calculated as organic dry substance) and 20 ml of 1M NaOH. The temperature was raised to 80°C and kept there over 25 minutes and then the solution was cooled to room temperature. To the cooled solution thus obtained 1M HCl was slowly added under stirring until the pH of the solution was 6.4. The solution was then filtered through a Seitz filter plate EKS. The filtrate was diluted to 600 ml with distilled water, and then 1200 ml of 99.5% ethanol was added while vigorously stirring. After 18 hours, the precipitate obtained was filtered and washed first with 100 ml of ethanol of the same concentration as the mother liquor and then with 100 ml of 75% ethanol. The precipitate was then washed three times with 150 ml of 99.5% ethanol, and then it was dried *in vacuo* at 50°C over 3 hours. Yield: 33.1 g of dried preparation containing a total amount of 35.0% by weight of iron.

Example 37.

Preparation of injection solution containing iron preparation SEM 13—72.

To a 500 ml round-bottomed flask provided with a stirrer, cooler and thermometer, were added 130 ml of distilled water which was heated to 80°C. 21.5 G of dried iron preparation SEM 13—72 obtained in Example 36 were added to the distilled water over 10 minutes under stirring. The mixture obtained was kept at 80°C over 60 minutes, calculated from the start of the addition of the dried iron preparation. The solution was cooled to room temperature; the pH was 7.4. The volume of the solution was adjusted to 150 ml with distilled water; the solution was then filtered through a Seitz filter plate No. 1250 and through a 0.6 μ membrane filter Millipore. The filtered solution was filled into ampoules which were sterilized at 120°C for 20 minutes. The injection solution obtained contained a total amount of iron of 51.3 mg/ml; 0.91 mg/ml of ferrous iron; the viscosity of the solution was 1.7 cPs; and the pH of the solution was 7.45. The absorption of iron in rabbit muscle after 7 days was 71%. After 24 hours, 24% of the administered iron had been excreted in the urine.

Example 38.

Preparation of polymer SEG 30—71 from dulcitol, gluconic acid lactone and epichlorohydrin.

To a round-bottomed flask provided with a stirrer, dropping funnel, thermometer and cooler were added at 50°C

30 ml distilled water
12 g NaOH
30 g gluconic acid lactone
60 g dulcitol

40 ml epichlorohydrin were added continuously over 48 minutes. The temperature was raised to 75°C over 30 minutes and kept there until 165 minutes had passed. After 165 minutes, the temperature was raised to 85°C. After 300 minutes the temperature was lowered to 75°C. The time is calculated from the start of addition of epichlorohydrin. The polymerisation was carried out under effective stirring. Besides the reagents listed above the following amounts of NaOH and epichlorohydrin were added:

17 g NaOH in solid form
 10.1 g NaOH dissolved in distilled water to 14 ml
 18 ml epichlorohydrin

The addition was carried out portionwise according to the following Table:

Time (min)	Epichlorohydrin (ml)	NaOH solid form (g)	NaOH solution (ml)
60		1	
75		1	
90		1	
120		2	
150		2	
165		2	
180	10	2	
195		2	
210		2	
225		2	
240			2.8
255			2.8
270	8		
285			2.8
300			2.8
315			2.8

415 Minutes after the start of the addition of epichlorohydrin, the reaction mixture was cooled to 60°C. 5 Ml of 4M HCl were added slowly during continual cooling and stirring. 6M HCl was then added until the pH was 0.9. The acidified reaction mixture was filtered and the remainder on filter paper was washed with 10 ml of ethanol diluted with one volume of water. The washings were mixed with the filtrate which then was diluted with water to a volume of 200 ml excluding the volume of the ethanol contained in the washing liquid. 500 Ml of 99.5% ethanol were added under stirring; then the mixture was allowed to stand overnight. The mother liquor was decanted and the remainder, which consisted of a syrup containing crystals, was filtered. The remainder on filter paper was washed with 30 ml of ethanol, diluted to the same concentration as the mother liquor. The washing liquid was mixed with the filtrate, the original volume of which was 93 ml. 9 Ml of water and 186 ml of 99.5% ethanol were added. After 90 minutes, the mother liquor was decanted from the syrup (volume 60 ml) which had formed. The syrup was mixed to 12 ml of water and 120 ml of 99.5% ethanol. The mixture was allowed to stand for 30 minutes. The mother liquor was decanted and the syrup (volume 55 ml), was mixed with 11 ml of water and 110 ml of 99.5% ethanol. After 30 minutes, 50 ml of syrup had formed and was separated from the mother liquor. The syrup was washed with 3 × 25 ml of 99.5% ethanol, and it was dried *in vacuo* at 40°C over 45 minutes in order to remove the ethanol. The dried product was diluted with water to give 46 g of polymer SEG 30—71.

Analysis:
 Loss of weight at drying 19.4%
 Na⁺ Content 3.5% calculated on dried sample
 Cl⁻ Contents 5.2% calculated on dried sample

Example 39.

Preparation of dry iron composition SEM 11—72 containing SEG polymer 30—71 F 13 prepared from dulcitol, gluconic acid lactone and epichlorohydrin.

An amount of SEG polymer 30—71 F 13 (from Example 38) corresponding to 20 g organic dry substance was dissolved in 150 ml of distilled water at room temperature. A solution containing 30 g $\text{FeCl}_3 \cdot 6 \text{H}_2\text{O}$ dissolved in 50 ml distilled water was mixed with the polymer solution at room temperature. To the mixture obtained were added during vigorous stirring 720 ml of 1M NaOH. After 65 minutes at room temperature, the temperature of the mixture was raised at 80°C. The mixture was kept at 80°C over 20 minutes and it was cooled to room temperature and filtered through a Seitz filter plate Ko2. The filtrate was diluted to 1000 ml with distilled water and then 2000 ml of 99.5% ethanol were added during vigorous stirring. The precipitate obtained was filtered off and dissolved in a mixture of 300 ml of distilled water, 6.8 g of polymer, calculated as organic dry substance, and 10 ml of 1M NaOH. The temperature was raised to 80°C and kept there over 20 minutes and then the solution was cooled to room temperature. To the cooled solution was added 1M HCl while vigorously stirring until the pH was 6.4. The solution obtained was filtered through a Seitz filter plate EKS. The filtrate was diluted with distilled water to 500 ml and then 1000 ml of 99.5% ethanol were added while vigorously stirring. After 120 minutes, the precipitate obtained was filtered off and washed with 50 ml of ethanol, diluted to the same concentration as the mother liquor and with 50 ml of ethanol, diluted to 75% and finally three times with 75 ml of 99.5% ethanol. The washed precipitate was dried *in vacuo* at 50°C.

Yield: 20.5 g

Total amount of iron: 30.3%.

Example 40.

Preparation of injection solution SEM 11—72 A from dry iron composition SEM 11—72.

To a round-bottomed flask, volume 500 ml, provided with a stirrer, thermometer and cooler were added 95 ml of distilled water heated to 80°C. 18.2 G of dry iron preparation SEM 11—71 was added to the water over 5 minutes while stirring. The temperature of the mixture was kept at 80°C over 60 minutes calculated from the start of the addition of the dry iron preparation. The solution obtained was cooled to room temperature and it was diluted with distilled water to 110 ml. The solution was then filtered through a Seitz filter plate 3/1250 and through a membrane filter Millipore 0.65 μ . The filtrate was filled into ampoules which were autoclaved at 120°C over 20 minutes.

Analysis:

Total iron content
Ferrous iron content
Viscosity
pH

50.2 mg/ml
0.8 mg/ml
3.0 cPs
7.8

Absorption of iron from rabbit muscle after 7 days

89%

Excretion of iron in rabbit urine during the first

24 hours after the injection

13%.

Example 41.

Preparation of polymer SEG 26—71 from mannitol, gluconic acid lactone, and epichlorohydrin.

To a round-bottomed flask provided with a stirrer, dropping funnel, thermometer and cooler were added at 45°C.

150 ml distilled water
60 g NaOH
150 g gluconic acid lactone
300 g mannitol

350 ml of epichlorohydrin were added continuously over 50 minutes. The temperature was raised to 85°C over 60 minutes calculated from the start of the addition of epichlorohydrin. The polymerisation was carried out under effective stirring. Besides the above mentioned reagents the following amounts of NaOH and epichlorohydrin were added:

161 g NaOH in solid form
 50.6 g NaOH dissolved in distilled water to 70 ml
 90 ml epichlorohydrin

The addition was carried out portionwise according to the following Table:

Time (min)	Epichlorohydrin (ml)	NaOH solid form (g)	NaOH solution (ml)
60		5	
75		10	
90		12	
105		18	
120		18	
135		18	
150		20	
165		20	
180	50		
182		10	
195		10	
210		10	
225		10	
240			14
255			14
270	40		
285			14
300			14
315			14

430 Minutes after the start of the first addition of epichlorohydrin the reaction mixture was cooled to 60°C. 25 Ml of 4M HCl were added slowly under continued cooling and stirring. Then 6M HCl was added until the pH was 0.4. The acidified reaction mixture was filtered and the remainder on filter was washed with 100 ml of diluted ethanol (one part ethanol and one part distilled water). The washing liquid was mixed with the filtrate which was diluted with distilled water to a volume of 1025 ml excluding the ethanol contained in the washing liquid. 2560 Ml of 99.5% ethanol were added while stirring and then the mixture was allowed to stand over night. The mother liquor was decanted and the remainder, which consisted of a syrup containing crystals, was filtered off. The remainder on filter was washed with 75 ml of ethanol diluted with water to the same concentration as the mother liquor. The washing liquid was mixed with the filtrate whose original volume was 750 ml. 150 Ml of distilled water and 1500 ml of 99.5% ethanol were added while stirring. After 60 minutes the mother liquor was decanted leaving the syrup which had formed, volume 370 ml. The syrup was mixed with 74 ml of distilled water and 740 ml of 99.5% ethanol. The mixture was allowed to stand for 30 minutes. The mother liquor was decanted and the syrup, volume 320 ml, was mixed with 32 ml of distilled water and 160 ml of 99.5% ethanol. After 60 minutes, the mother liquor was decanted and the syrup was washed with 2 × 160 ml of 99.5% ethanol and with 5 × 160 ml of acetone. The washed syrup was dried *in vacuo* at 45°C over 2 hours in order to remove rest of the acetone. The dried product was then diluted with distilled water

to 271 g in order that a product with a suitable consistency would be obtained. The polymer SEG 26—71 was obtained.

Analysis:

Loss of weight at drying	19.9%
Na ⁺ Content	3.1% calculated on dried sample
Cl ⁻ Content	4.5% calculated on dried sample.

Example 42.

Preparation of dry iron composition SEM 52—71 containing SEG-polymer 26—71 F 11 prepared from mannitol, gluconic acid lactone and epichlorohydrin.

SEG-polymer 26-71 F 11 (from Example 41), corresponding to 40 g organic dry substance, was dissolved in 300 ml of distilled water at room temperature. A solution containing 60 g of FeCl₃ · 6 H₂O dissolved in 100 ml of distilled water was mixed with the polymer solution at room temperature. To the mixture so obtained were added during vigorous stirring 1440 ml of 1M NaOH. After 75 minutes at room temperature the temperature of the mixture was raised to 80°C. The mixture was kept at this temperature over 20 minutes and then it was cooled to room temperature and filtered through a Seitz filter plate 3/1250. The filtrate was diluted to 1930 ml with distilled water and then 3860 ml of 99.5% ethanol were added while vigorously stirring. The precipitate obtained was filtered off and dissolved in a mixture of 600 ml of distilled water, 5.5 g polymer, calculated as organic dry substance, and 20 ml of 1M NaOH. The temperature was raised to 80°C and kept there over 35 minutes and then the solution was cooled to room temperature. To the cooled solution was added 2M HCl during vigorous stirring until pH 6.9. The solution was filtered through a Seitz filter plate EKS. The filtrate was diluted with distilled water to 1000 ml and then 2000 ml of 99.5% ethanol were added while vigorously stirring. The precipitate obtained was filtered off and washed with 100 ml of ethanol, diluted to the same concentration as the mother liquor, with 100 ml of ethanol, diluted to 75%, and finally three times with 150 ml of 99.5% ethanol. The washed precipitate was dried *in vacuo* at 50°C.

Yield: 36.2 g

Total iron content: 29.3% calculated on the original sample.

Example 43.

Preparation of injection solution SEM 52—71 A from dry iron composition SEM 52—71.

To a round-bottomed flask provided with a stirrer, thermometer and cooler was added 100 ml of distilled water which was heated to 80°C. 17.05 G of dry iron preparation SEM 52—71 was added to the water over 5 minutes while stirring. The temperature of the mixture was kept at 80°C over 55 minutes calculated from the start of the addition of the dry iron preparation. The solution obtained was cooled to room temperature, and then the pH was adjusted to 7.1 with 2M HCl. The solution was then filtered through a Seitz filter plate 3/1250 and through a membrane filter Millipore 0.65 μ. The filtrate was filled into ampoules which were autoclaved at 120°C over 20 minutes.

Analysis:

Total iron content	45.5 mg/ml
Total ferrous iron content	0.4 mg/ml
Viscosity	2.9 cPs
pH	7.4

Absorption of iron rabbit muscle after 7 days 94%

Excretion of iron in rabbit urine during the 24 hours after the injection 2%.

Example 45.

Preparation of polymer P 5—8—69 from glycerol, gluconic acid lactone and epichlorohydrin.

To a 3 l round-bottomed flask provided with a stirrer, dropping funnel, thermometer and cooler were added at substantially 40°C

150 ml distilled water
 60 g NaOH
 150 g gluconic acid lactone (99.5%)
 300 g glycerol (99.5%)

5 The temperature was raised to 75°C and this temperature was maintained 5
 during the whole synthesis. 400 ml of epichlorohydrin were added in portions of
 50 ml at 0, 15, 90, 150, 210, 255, 300 and 330 minutes after the time of the first
 addition of epichlorohydrin. Every addition took 10 minutes. 205 G of NaOH was
 added in the form of pastilles according to the following scheme: 5 g after 15 minutes,
 10 g after 30, 45, 60, 75, 105, 120, 135, 165, 180, 195, 225, 240, 255, 270, 285,
 300, 315, 330, 345 and 360 minutes after the first addition of epichlorohydrin. 390
 Minutes after the first addition of epichlorohydrin the reaction mixture was cooled
 to 60°C. 50 ml of 4M HCl and 212 ml of 6M HCl were added while the cooling
 was continued to room temperature. After these additions of acid, the pH was 1.0
 and the volume was 1180 ml. 20 ml of distilled water and 3000 ml of ethanol
 (99.5%) were added while stirring, and then the mixture was allowed to settle over-
 night. Two phases were formed. The precipitated white and crystalline solid phase
 was separated from the clear mother liquor by filtration and washed with 3 × 50 ml
 of ethanol (99.5%). The washing liquor was mixed with the filtrate, giving a total
 volume of 3900 ml. 780 ml (1/5 vol.) chloroform were added with vigorous stirring.
 After 30 minutes, there was still just one phase and an additional amount of 468 ml
 chloroform was added. (The amount of chloroform required for obtaining two phases
 was determined by titration). After 3 hours the mixture had separated into two phases.
 The heavy phase (vol. 500 ml) was mixed with 250 ml ethanol (99.5%) and with
 83 ml chloroform (1/6 vol. of 500 ml). The mixture was allowed to stand overnight
 whereby two phases were formed. The heavy phase (vol. 420 ml) contained white
 crystals which were removed by filtration. The filtrate was mixed with 210 ml
 (1/2 vol.) of ethanol (99.5%) and 70 ml (1/6 vol.) of chloroform. After 2 hours the
 heavy phase (vol. 330 ml) which formed was mixed with 33 ml of distilled water,
 165 ml of ethanol (99.5%) and 55 ml of chloroform. After 30 minutes, the heavy
 phase (vol. 280 ml) which formed was separated and mixed with 14 ml (1/20 vol.)
 of distilled water and with 140 ml of acetone, and then it was dried *in vacuo* at
 40—50°C.
 Yield: 162.2 g (It is to be noted that this yield can be increased by evaporating
 and further treatment of the light phases).

Analysis:

Weight loss at drying	5.2%
Na ⁺ Contents	2.6% w/w
Cl ⁻ Contents	4.1% w/w

40 **Example 46.** 40
 Preparation of dry iron preparation SEM 57/69 from polymer built up of glycerol,
 gluconic acid, and epichlorohydrin.

51 G of polymer SEG 21—69 F 13 (final product from Example 45) and 20
 ml of lactic acid were dissolved in a 50 ml of distilled water. A separate solution
 containing 80 g of NaOH in 400 ml of distilled water was prepared. 40 ml of said NaOH
 solution were added to the solution of polymer and lactic acid. The mixture obtained
 was heated to 80°C under stirring and then nine portions each of 24 ml NaOH
 solution were added. After each addition of NaOH solution there were added 14 ml
 of ferric chloride solution prepared by dissolving 60 g of FeCl₃ · 6 H₂O in 90 ml of
 distilled water. The eighteen portions of NaOH solution and ferric chloride solution
 were added over 20 minutes. 5 Minutes later, 45 ml of NaOH solution were added
 and then the temperature was kept at 80°C over a further 25 minutes under continued
 stirring. The mixture was cooled to 25°C and diluted to 550 ml with distilled water.
 To the diluted solution were added 1100 ml of 99.5% ethanol. After 30 minutes the
 mother liquor was separated from the precipitate which had formed and the pre-
 cipitate was washed with 200 ml of diluted ethanol (ethanol and water in a proportions
 of 2:1). The washed filtrate was added portionwise over 15 minutes and under
 vigorous stirring to 300 ml of distilled water at 80°C. The temperature was then
 kept at 80°C over a further 30 minutes under stirring. The solution was cooled to
 25°C and the pH of the solution was adjusted to 6.1 with 2N HCl. The neutralized

solution was filtered through a Seitz No. Ko2 filter plate. The solution was diluted to 400 ml with distilled water. 800 ml of 99.5% ethanol were added to the diluted filtrate under vigorous stirring. After 30 minutes, the mother liquor was separated from the precipitate. The precipitate was allowed to stand for 15 hours. The precipitate was then dissolved in 250 ml distilled water and heated to 80°C. for 30 minutes as described above. After cooling and filtering through a Seitz 3/1250 filter plate the solution was diluted to 250 ml with distilled water and 750 ml of 99.5% ethanol were added under stirring. After 20 hours, the mother liquor was separated from the precipitate which had formed and the precipitate was washed twice with 100 ml of ethanol and water (proportions 2:1) and three times with 99.5% ethanol. The precipitate obtained was dried *in vacuo*, to give 20.0 g of dried iron preparation containing 26.9% by weight of iron, calculated on the dry preparation.

Example 47.

Preparation of injection solution SEM 57—69 A from dry iron preparation SEM 57—69.

17.7 G of the dried iron preparation SEM 57—69 obtained in Example 46 were suspended for 5 minutes at 80°C in 90 ml of distilled water. The suspension so obtained was heated in an autoclave at 120°C over 20 minutes. The mixture so obtained was filtered through Seitz filter plate 3/1250. The filtrate was diluted with distilled water to 90 ml and then it was filled into injection bottles which were sterilized at 120°C for 120 minutes. The solution obtained contained 47.3 mg of total iron/ml; had a ferrous iron content of 0.2 mg/ml, a viscosity of 12.5 cPs, a freezing point depression of 0.3°C and a pH of 6.6. The absorption from rabbit muscle after injection of 20 mg of iron per kg bodyweight was 82% 7 days after the injection and the excretion in rabbit urine 24 hours after the injection was 3%.

WHAT WE CLAIM IS:—

1. A physiologically innocuous, water swellable or soluble polymer capable of forming a complex with a polyvalent metal cation, which comprises recurring units derived from

a) at least one hydroxy carboxylic acid component which is arabonic acid, gluconic acid or glucoheptonic acid or a salt or lactone derivable therefrom;

b) at least one polyhydric alcohol component, which is glycerol, a polyglycerol, tetritol, pentitol, hexitol, heptitol, or a partially etherified derivative of one of these alcohols with an alkyl group containing from 1 to 5 carbon atoms, or a partially etherified derivative of one of these alcohols with a hydroxyalkyl group containing from 1 to 5 carbon atoms; and

c) at least one polymerizing agent which is a dihalohydrin as hereinbefore defined, a monoepoxide, as hereinbefore defined or a diepoxide as hereinbefore defined.

2. A polymer according to claim 1 wherein the polymerizing agent is epichlorohydrin.

3. A polymer according to claim 1 or 2 wherein the alcohol is a hexitol, heptitol, or a partially etherified derivative of such an alcohol with an alkyl group of 1 to 5 carbon atoms or a hydroxyalkyl group of 1 to 5 carbon atoms.

4. A polymer according to any one of the preceding claims wherein the hydroxy carboxylic acid component is gluconic or glucoheptonic acid or a salt or lactone thereof.

5. A polymer according to claim 4, which comprises recurring units derived from gluconic acid, sorbitol, and epichlorohydrin.

6. A polymer according to claim 4, which comprises recurring units derived from hydroxypropylsorbitol, gluconic acid, and epichlorohydrin.

7. A polymer according to claim 4, which comprises recurring units derived from dulcitol, epichlorohydrin and gluconic acid.

8. A polymer according to claim 4, which comprises recurring units derived from mannitol, epichlorohydrin and gluconic acid.

9. A polymer according to claim 4, which comprises recurring units derived from sorbitol, glucoheptonic acid and epichlorohydrin.

10. A polymer according to claim 3, which comprises recurring units derived from sorbitol, arabonic acid and epichlorohydrin.

11. A polymer according to claim 2, which comprises recurring units derived from glycerol, gluconic acid, and epichlorohydrin.

12. A polymer according to claim 2, which comprises recurring units derived from pentaerythritol, gluconic acid and epichlorohydrin.

5 solution was filtered through a Seitz No. Ko2 filter plate. The solution was diluted to 400 ml with distilled water. 800 ml of 99.5% ethanol were added to the diluted filtrate under vigorous stirring. After 30 minutes, the mother liquor was separated from the precipitate. The precipitate was allowed to stand for 15 hours. The precipitate was then dissolved in 250 ml distilled water and heated to 80°C. for 30 minutes as described above. After cooling and filtering through a Seitz 3/1250 filter plate the solution was diluted to 250 ml with distilled water and 750 ml of 99.5% ethanol were added under stirring. After 20 hours, the mother liquor was separated from the precipitate which had formed and the precipitate was washed twice with 100 ml of ethanol and water (proportions 2:1) and three times with 99.5% ethanol. The precipitate obtained was dried *in vacuo*, to give 20.0 g of dried iron preparation containing 26.9% by weight of iron, calculated on the dry preparation.

Example 47.

Preparation of injection solution SEM 57—69 A from dry iron preparation SEM 57—69.

15 17.7 G of the dried iron preparation SEM 57—69 obtained in Example 46 were suspended for 5 minutes at 80°C in 90 ml of distilled water. The suspension so obtained was heated in an autoclave at 120°C over 20 minutes. The mixture so obtained was filtered through Seitz filter plate 3/1250. The filtrate was diluted with distilled water to 90 ml and then it was filled into injection bottles which were sterilized at 120°C for 120 minutes. The solution obtained contained 47.3 mg of total iron/ml; had a ferrous iron content of 0.2 mg/ml, a viscosity of 12.5 cPs, a freezing point depression of 0.3°C and a pH of 6.6. The absorption from rabbit muscle after injection of 20 mg of iron per kg bodyweight was 82% 7 days after the injection and the excretion in rabbit urine 24 hours after the injection was 3%.

WHAT WE CLAIM IS:—

1. A physiologically innocuous, water swellable or soluble polymer capable of forming a complex with a polyvalent metal cation, which comprises recurring units derived from
 - 30 a) at least one hydroxy carboxylic acid component which is arabonic acid, gluconic acid or glucoheptonic acid or a salt or lactone derivable therefrom;
 - b) at least one polyhydric alcohol component, which is glycerol, a polyglycerol, tetritol, pentitol, hexitol, heptitol, or a partially etherified derivative of one of these alcohols with an alkyl group containing from 1 to 5 carbon atoms, or a partially etherified derivative of one of these alcohols with a hydroxyalkyl group containing from 1 to 5 carbon atoms; and
 - c) at least one polymerizing agent which is a dihalohydrin as hereinbefore defined, a monoepoxide, as hereinbefore defined or a diepoxide as hereinbefore defined.
- 40 2. A polymer according to claim 1 wherein the polymerizing agent is epichlorohydrin.
3. A polymer according to claim 1 or 2 wherein the alcohol is a hexitol, heptitol, or a partially etherified derivative of such an alcohol with an alkyl group of 1 to 5 carbon atoms or a hydroxyalkyl group of 1 to 5 carbon atoms.
- 45 4. A polymer according to any one of the preceding claims wherein the hydroxy carboxylic acid component is gluconic or glucoheptonic acid or a salt or lactone thereof.
5. A polymer according to claim 4, which comprises recurring units derived from gluconic acid, sorbitol, and epichlorohydrin.
- 50 6. A polymer according to claim 4, which comprises recurring units derived from hydroxypropylsorbitol, gluconic acid, and epichlorohydrin.
7. A polymer according to claim 4, which comprises recurring units derived from dulcitol, epichlorohydrin and gluconic acid.
- 55 8. A polymer according to claim 4, which comprises recurring units derived from mannitol, epichlorohydrin and gluconic acid.
9. A polymer according to claim 4, which comprises recurring units derived from sorbitol, glucoheptonic acid and epichlorohydrin.
10. A polymer according to claim 3, which comprises recurring units derived from sorbitol, arabonic acid and epichlorohydrin.
- 60 11. A polymer according to claim 2, which comprises recurring units derived from glycerol, gluconic acid, and epichlorohydrin.
12. A polymer according to claim 2, which comprises recurring units derived from pentaerythritol, gluconic acid and epichlorohydrin.





13. A polymer according to any one of the preceding claims, whose average molecular weight as estimated by gel filtration is from 700 to 5,000.
14. A polymer according to any one of the preceding claims, whose content of carboxyl groups is from 0.2 to 1.5 milliequivalents per g. polymer in dried form excluding the weight of sodium and chloride ion present.
15. A polymer according to claim 1 wherein the alcohol is other than a partially etherified derivative of one of said alcohols with an alkyl group containing 1—5 carbon atoms.
16. A carboxymethylether of a polymer according to any one of the preceding claims.
17. A polymer according to claim 1 substantially as described in any one of Examples 1—12, 14, 27, 32, 35, 38, 41 or 45.
18. A polymer according to claim 1 substantially as hereinbefore described.
19. A process for preparing a polymer as claimed in any one of claims 1—15, 17 and 18 which comprises reacting in solution
- a) the hydroxy carboxylic acid component;
 - b) the polyhydric alcohol component and
 - c) the polymerizing agent
- whereafter if desired the reaction product is purified by precipitation and redissolution.
20. A process according to claim 19 wherein the reaction is carried out in aqueous alkaline solution.
21. A process according to claim 19 or 20 wherein the reaction is carried out at a temperature of 20°C., to the boiling point of the reaction mixture.
22. A process according to claim 21 wherein the reaction is carried out at a temperature of 75°C., to 85°C.
23. A process according to any one of claims 19—22 wherein the hydroxy carboxylic acid component is a lactone.
24. A process according to any one of claims 19—22 wherein the hydroxy carboxylic acid component is an inorganic salt.
25. A process according to claim 24 wherein the hydroxy carboxylic acid component is a sodium salt.
26. A process according to any one of claims 19—25 wherein the hydroxy carboxylic acid component is gluconic acid or a salt or lactone thereof.
27. A process according to any one of claims 19—25 wherein the hydroxy carboxylic acid component is glucoheptonic acid or a salt or lactone thereof.
28. A process according to any one of claims 19—27 wherein the polyhydric alcohol component is a hexitol partially etherified with a hydroxyalkyl group of 1 to 5 carbon atoms.
29. A process according to any one of claims 19—27 wherein the polyhydric alcohol component is a heptitol partially etherified with a hydroxyalkyl group of 1 to 5 carbon atoms.
30. A process according to any one of claims 19—27 wherein the polyhydric alcohol component is sorbitol.
31. A process according to any one of claims 19—30 wherein the polymerizing agent is epichlorohydrin.
32. A process according to claim 31 wherein gluconic acid, sorbitol and epichlorohydrin are reacted in alkaline aqueous solution and the reaction product is purified by repeated precipitation and redissolution.
33. A process according to claim 32 wherein 0.1 to 1.0 moles of gluconic acid and 0.05 to 5 moles of epichlorohydrin per mole of sorbitol are reacted.
34. A process according to claim 33, wherein 0.2 to 1.0 moles of gluconic acid and 0.1 to 4 moles of epichlorohydrin per mole of sorbitol are reacted.
35. A process according to any one of claims 19 to 34 wherein the reaction product is purified by precipitation with an organic solvent.
36. A process according to claim 35 wherein the precipitation is carried out with ethanol as precipitating agent.
37. A process according to any one of claims 20 and 21—36 as appendant to claim 20 wherein the polymerizing agent and alkali separately are added in portions to an alkaline solution of the hydroxy carboxylic acid component and the polyhydric alcohol component.
38. A process according to claim 37 wherein the alkali is sodium hydroxide.
39. A modification of a process according to claim 19, wherein the hydroxy carboxylic acid component and the polymerising agent are reacted together in acidic solution and the reaction product obtained is reacted in alkaline solution with the reaction product of the polyhydric alcohol component and the polymerising agent.



40. A modification of a process according to any one of claims 19 to 39 wherein the reaction product having recurring units derived from (a), (b) and (c) is carboxy-methylated to form a polymer as claimed in claim 16.

41. A process according to claim 19 or 40 substantially as described in any one of Examples 1—14, 27, 32, 35, 38, 41 and 48.

42. A process according to claim 19 or 40 substantially as hereinbefore defined.

43. A polymer according to claim 1 or claim 16 prepared by a process as claimed in any one of claims 19 to 42.

44. A dry complex which can be worked up into a preparation suitable for parenteral administration in human and veterinary medicine, which complex is a complex of ferric iron and a physiologically innocuous water swellable or soluble polymer as claimed in claim 15.

45. A dry complex which can be worked up into a preparation suitable for parenteral administration in human and veterinary medicine, which complex is a complex of ferric iron and a physiologically innocuous, water swellable or soluble polymer as claimed in any one of claims 1—14, 16—18 and 43.

46. A complex according to claim 45 which contains 5 to 40 percent by weight of iron.

47. A complex according to claim 45 which contains 20 to 35 percent by weight of iron.

48. A complex according to claim 45 substantially as hereinbefore described.

49. A process for preparing a dry complex, as claimed in any one of claims 44—48, which process comprises reacting in aqueous solution.

a) at least one water-soluble ferric compound and

b) a polymer as claimed in any one of claims 1—18 and 43 in which the pH of the reaction mixture is adjusted so that at the end of the reaction it is 10 to 14, and then the iron-containing reaction product complex obtained is precipitated and dried, if desired being purified by dissolution and precipitation before drying.

50. A process according to claim 49 wherein the ferric compound is ferric chloride.

51. A process according to claim 49 wherein the ferric compound is ferric sulphate.

52. A process according to claim 49 wherein the ferric compound is ferric ammonium sulphate.

53. A process according to any one of claims 49—52 wherein the reaction between the ferric compound and the polymer is carried out at a temperature of 0°C. to 100°C.

54. A process according to any one of claims 49—53 wherein the reaction between the ferric compound and the polymer is carried out at a pH which is successively increased to a value of 10—14.

55. A process according to any one of claims 49—54 wherein the iron complex formed is precipitated at least once with ethanol and the precipitated iron complex separated from the mixture.

56. A process according to any one of claims 49—55 wherein lactic acid is incorporated in the reaction mixture.

57. A process according to claim 56 wherein the ferric compound in aqueous solution and alkali in aqueous solution are added separately to an aqueous solution of the polymer and lactic acid.

58. A process according to any one of claims 49—55 wherein alkali in aqueous solution is added to an aqueous solution containing the polymer and the ferric compound.

59. A process according to any one of claims 49—58 wherein further polymer in alkaline solution is added at each redissolution of the iron complex.

60. A process according to claim 49 substantially as described in any one of Examples 15, 17—19, 21, 23, 25, 28, 30, 31, 33, 36, 39, 42 and 46.

61. A process according to claim 49 substantially as hereinbefore described.

62. A dry complex prepared by a process claimed in any one of claims 49 to 61.

63. An iron-containing composition suitable for parenteral administration in human and veterinary medicine consisting essentially of an aqueous solution of a complex of iron, as claimed in any one of claims 45—48 and 62.

64. An iron-containing composition suitable for parenteral administration in human and veterinary medicine consisting essentially of an aqueous solution of a complex of iron as claimed in claim 44.

65. A composition according to claim 63 which contains 5 to 100 mg. of iron per ml.
66. A composition according to claim 65 which contains substantially 50 mg. of iron per ml.
- 5 67. A composition according to claim 63 substantially as described in any one of Examples 16—18, 20, 22, 24, 26, 29, 34, 37, 40, 43 and 47. 5
68. A composition according to claim 63 substantially as hereinbefore described.
69. A process for the preparation of an aqueous iron-containing composition as claimed in any one of claims 63—68 which comprises dissolving in water under sterile conditions a dry complex as claimed in any one of claims 44—48 and 62. 10 10
70. A modification of a process as claimed in claim 69 wherein the complex is not dry and has been prepared by a process as described in any one of claims 49—61 omitting the drying step.
71. A process according to claim 69 or 70 substantially as described in any one of Examples 16—18, 20, 22, 24, 26, 29, 34, 37, 40, 43 and 47. 15 15
72. A process according to claim 69 or 70 substantially as hereinbefore described.
73. A composition prepared by a process as claimed in any one of claims 69—72.
- 20 74. A method for the treatment of iron deficiency in a mammal excluding man, which comprises administering to the mammal an iron containing composition as claimed in any one of claims 63—68 and 73. 20

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