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Iron Dextran Injection

General Notices

Action and use

Treatment of iron-deficiency anaemia.

DEFINITION

Iron Dextran Injection is a sterile colloidal solution containing a complex of iron(III) hydroxide with dextrans of weight average molecular weight between 5000 and 7500.

PRODUCTION

Iron Dextran Injection is produced by a method of manufacture designed to provide an iron-dextran complex with appropriate iron absorption characteristics. This may be confirmed for routine control purposes by the use of an appropriate combination of physico-chemical tests, subject to the agreement of the competent authority.

The method of manufacture is validated to demonstrate that, if tested, the injection would comply with the following test.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

Content of iron, Fe

4.75 to 5.25% w/v.

Content of dextrans

17.0 to 23.0% w/v.

CHARACTERISTICS

A dark brown solution.

IDENTIFICATION

A. Add 5M *ammonia* to 0.2 mL of the injection previously diluted to 5 mL with *water*. No precipitate is produced.
B. Mix 1 mL with 100 mL of *water*. To 10 mL of this solution add 0.2 mL of *hydrochloric acid*, boil for 30 seconds, cool rapidly, add 4 mL of 13.5M *ammonia* and 10 mL of *hydrogen sulfide solution*, boil for at least 4 minutes to remove hydrogen sulfide, cool and filter. Boil 5 mL of the filtrate with 5 mL of *cupri-tartaric solution R1*; the solution remains greenish in colour and no precipitate is produced. Boil a further 5 mL of the filtrate with 0.5 mL of *hydrochloric acid* for 5 minutes, cool, add 2.5 mL of 5M *sodium hydroxide* and 5 mL of *cupri-tartaric solution R1* and boil again; a reddish precipitate is produced.
C. To 1 mL add 20 mL of *water* and 5 mL of *hydrochloric acid* and boil for 5 minutes. Cool, add an excess of 13.5M *ammonia* and filter. Wash the precipitate with *water*, dissolve in the minimum volume of 2M *hydrochloric acid* and add

sufficient *water* to produce 20 mL. The resulting solution yields reaction B characteristic of *iron salts*, Appendix VI.

TESTS

Acidity

pH, 5.2 to 6.5, Appendix V L.

Arsenic

To 5.0 mL in a Kjeldahl flask add 10 mL of *water* and 10 mL of *nitric acid* and heat until the vigorous evolution of brown fumes ceases. Cool, add 10 mL of *sulfuric acid* and heat again until fumes are evolved, adding *nitric acid* dropwise at intervals until oxidation is complete. Cool, add 30 mL of *water*, bring to the boil and continue boiling until the volume of liquid is reduced to about 20 mL. Cool and dilute to 50 mL with *water*. Reserve a portion of the solution for the test for Lead. To 5 mL of the solution add 10 mL of *water*, 15 mL of *stannated hydrochloric acid* and 3 mL of *tin(II) chloride solution AsT*. Connect to a condenser and distil 15 mL into 10 mL of *water*. To the distillate add 0.2 mL of *bromine water* and remove the excess of bromine with *tin(II) chloride solution AsT*. The solution complies with the *limit test for arsenic*, Appendix VII (2 µg per mL).

Copper

To 5.0 mL add 5 mL of *nitric acid* and heat until the vigorous evolution of brown fumes ceases. Cool, add 2 mL of *sulfuric acid* and heat again until fumes are evolved, adding *nitric acid* dropwise at intervals until oxidation is complete. Cool, add 25 mL of *hydrochloric acid*, warm to dissolve, cool and extract with four 25 mL quantities of *isobutyl acetate*, discarding the extracts. Evaporate the acid solution to dryness, adding *nitric acid* dropwise if charring occurs. Dissolve the residue in 10 mL of 1M *hydrochloric acid*, reserving a portion of the solution for the test for Zinc. To 1 mL add 25 mL of *water* and 1 g of *citric acid*, make alkaline to *litmus paper* with 5M *ammonia*, dilute to 50 mL with *water*, add 1 mL of *sodium diethyldithiocarbamate solution* and allow to stand for 5 minutes. Any colour produced is not more intense than that produced by treating in the same manner a mixture of 3 mL of *copper standard solution (10 ppm Cu)* and 1 mL of 1M *hydrochloric acid* beginning at the words 'add 25 mL of *water*…' (60 µg per mL).

Lead

Sample stock solution To 16.0 mL of the solution reserved in the test for Arsenic add 50 mL of *hydrochloric acid* and wash with four 20 mL quantities of *isobutyl acetate*, discarding the oraganic layer. Evaporate the acid solution to dryness and dissolve the residue in 20 mL of *water*.

Use the following solutions:

(1) 12 mL of the sample stock solution.
(2) A mixture of 10 mL of *lead standard solution* (2 ppm Pb) and 2 mL of sample stock solution.
(3) (Blank solution) A mixture of 10 mL of *water* and 2 mL of the sample stock solution.

PROCEDURE

To solutions 1, 2 and 3: add 2 mL of *buffer solution pH 3.5*. Mix and add to 1.2 mL of *thioacetamide reagent*. Examine through Nessler cylinders after 2 minutes.

SYSTEM SUITABILITY

Solution (2) shows a slight brown colour compared to solution (3).

LIMITS

Any brown colour in solution (1) is not more intense than that in solution (2) (25 µg per mL).

Zinc

To 5.0 mL of the solution reserved in the test for Copper add 15 mL of 1M *sodium hydroxide*, boil, filter, wash the residue with *water* and dilute the combined filtrate and washings to 25 mL with *water*. To 5 mL add 5 mL of 1M *hydrochloric acid* and 2 g of *ammonium chloride*, dilute to 50 mL with *water*, add 1 mL of freshly prepared *dilute potassium hexacyanoferrate*(II) *solution* and allow to stand for 20 minutes. Any opalescence produced is not more than that produced when 1 mL of freshly prepared *dilute potassium hexacyanoferrate*(II) *solution* is added to a solution prepared from 3 mL of *zinc standard solution (25 ppm Zn)*, 3 mL of 1M *sodium hydroxide*, 6 mL of 1M *hydrochloric acid* and 2 g of *ammonium chloride* diluted to 50 mL with *water* and allowed to stand for 20 minutes (150 µg per mL).

Chloride

To 5 mL add 75 mL of *water* and 0.05 mL of *nitric acid* and titrate immediately with *0.1M silver nitrate VS* determining the end point potentiometrically. 6.8 to 9.6 mL of *0.1M silver nitrate VS* is required.

Bacterial endotoxins

The endotoxin limit concentration is 0.50 IU per mg of iron, Appendix XIV C.

ASSAY

For iron

To 2 g add 10 mL of *water* and 5 mL of *sulfuric acid* and stir for several minutes. Allow to stand for 5 minutes, cool and dilute to 50 mL with *water*. Prepare a suitable zinc amalgam by covering 300 g of *zinc shot* with a 2% w/v solution of *mercury(II) chloride* and stir for 10 minutes. Decant the solution, wash the residue three times with *water* and transfer it to a column (30 cm × 18 mm) fitted with a sintered-glass disc (ISO 4793, porosity grade 0, is suitable). Activate the zinc amalgam by passing through the column 200 mL of *sulfuric acid (5%)*. Pass the prepared solution slowly through the column and wash successively with 50 mL of *water*, four 25 mL quantities of *sulfuric acid (5%)* and 50 mL of *water*. Titrate the combined eluates with 0.1M *ammonium cerium(IV) sulfate VS* using *ferroin solution* as indicator. Each mL of 0.1M *ammonium cerium(IV) sulfate VS* is equivalent to 5.585 mg of Fe. Determine the *weight per mL* of the injection, Appendix V G, and calculate the percentage w/v of Fe.

For dextrans

Dilute 1 g to 500 mL with *water*, dilute 10 mL of the solution to 100 mL with *water*, transfer 3 mL of the resulting solution to a test tube and cool to 0°. Add, to form a lower layer, 6 mL of a solution prepared and maintained at 0° containing 0.2% w/v of *anthrone* in a mixture of 19 volumes of *sulfuric acid* and 1 volume of *water,* mix and immediately heat on a water bath for 5 minutes. Cool and measure the *absorbance* of the resulting solution at the maximum at 625 nm, Appendix II B. Repeat the operation using 3 mL of *water* in place of the dilution of the injection. From the difference between the absorbances calculate the content of glucose present using a calibration curve prepared by treating suitable amounts of D-*glucose* in the same manner. Each g of D-*glucose* is equivalent to 0.94 g of dextrans. Determine the *weight per mL* of the injection, Appendix V G, and calculate the percentage w/v of dextrans.

LABELLING

The strength is stated as the equivalent amount of iron, Fe, in a suitable dose-volume.