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M. E. DEUTSCH 3,743,714

NOVEL CARRIER PREPARATIONS FOR INJECTABLE RADIOACTIVE COMPOSITIONS

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FIG. 1

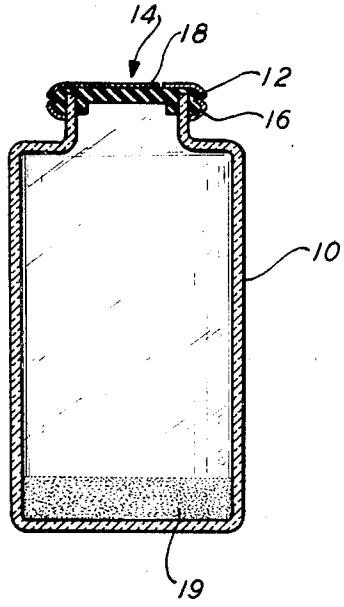


FIG. 2

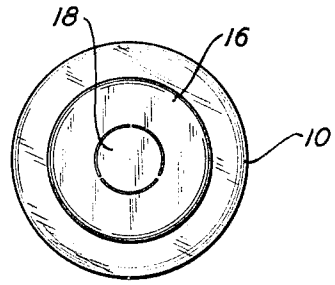


FIG. 3

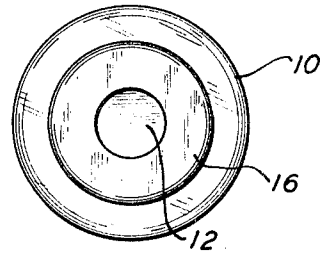


FIG. 4

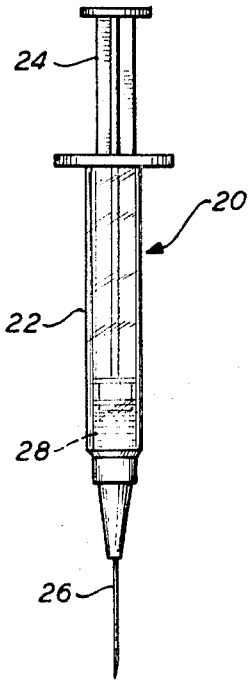
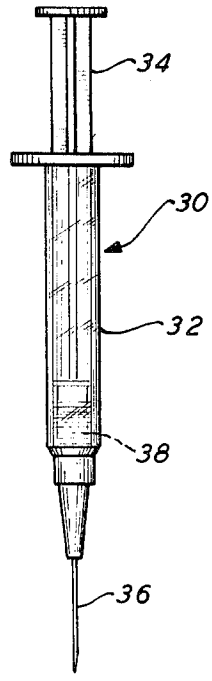


FIG. 5



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NOVEL CARRIER PREPARATIONS FOR INJECTABLE RADIOACTIVE COMPOSITIONS

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U.S. Cl. 424—1 10 Claims

ABSTRACT OF THE DISCLOSURE

There is provided a novel method of producing injectable carrier compositions for radioactive compositions which are characterized by high stability and long shelf life. In particular these compositions are directed to those requiring the absorption of the appropriate radio tracer onto a colloidal substance such as colloidal sulfur and colloidal ferric hydroxide. There are also provided means for maintaining said compositions in stable form.

DESCRIPTION OF THE PRIOR ART

The use of radioactive isotopes in injectable compositions for diagnostic purposes is well known in the medical arts. These radioisotopes must, of necessity, have a rather short half life since it is not desirable for radio active materials to remain in the system of a patient for any substantial length of time. Since the half life of most of these isotopes is of the order of hours it is customary to prepare a suitable carrier composition and mix it with the radio tracer immediately before diagnostic administration to the patient.

Recent advances in the diagnostic arts have made it possible to examine specific organs by utilizing particular carriers for the radio tracer. It has been found that certain carriers are concentrated by the physiological functions of the body in certain organs, thus if these carriers have absorbed thereon radio tracers, diagnostic measurements can be made upon these organs either by quantitative measurement of the amount of radio activity or by radiographic measurements, a technique similar to X-ray radiography but using a source of radiation inside of the body to be examined rather than a source of radiation external to said body.

It has been found that colloidal sulfur has a tendency to accumulate in the liver and spleen and, to a lesser extent to the lungs, and colloidal ferric hydroxide has a tendency to accumulate in the lungs. It has further been found that technetium-99 has a remarkable ability to be absorbed upon colloidal sulfur having a particular size up to 2.0 microns, although the best results are achieved by using a particular size less than 1.2 microns. Similarly indium-113 has a tendency to be absorbed on ferric hydroxide in colloidal form.

The standard technique of preparing the colloidal sulfur comprises the provision of an aqueous solution containing gelatin and sodium thiosulfate to which is added an aqueous solution of radio tracer such as sodium pertechnetate, acid is then added and the solution heated briefly, suitably in boiling water to convert the sodium thiosulfate into colloidal sulfur. The solution is then cooled and substantially neutralized with a physiologically acceptable base. The kits for this purpose which have been provided heretofore comprise an aqueous solution of gelatin and sodium thiosulfate, a source of acid and a source of base, suitably compounded with a buffer.

This mode of packaging suffers from two serious disadvantages. The gelatin and the sodium thiosulfate are already in aqueous solution, the addition of the other components which are also in aqueous solution makes for the use of rather substantial quantities of aqueous

injectable medium which so dilutes the radioisotopes that large volumes must be injected into the patient which in turn often give rise to a poorer scan in addition to subjecting the patient to discomfort and possible hazard.

A further disadvantage of the provision of an aqueous solution of gelatin and sodium thiosulfate is that such a combination has poor stability and short shelf life. Upon standing at ambient temperatures for substantial periods of time, aqueous solutions of sodium thiosulfate have a tendency to decompose into compounds which will not form a sulfur colloid.

It is therefore desirable to provide a combination of gelatin and sodium thiosulfate which is readily soluble in small amounts of water (which ordinary gelatin is not) and which has a substantially indefinite shelf life.

SUMMARY OF THE INVENTION

The present invention comprises the provision of a mixture of gelatin and sodium thiosulfate in readily soluble form together with means for adding acid and means for adding base thereto.

In the principal embodiment of the present invention, a solution of gelatin is prepared by suspending it in pyrogen-free, substantially particle-free distilled water, steam sterilizing the suspension and cooling the resultant solution. There is also prepared a solution of sodium thiosulfate, suitably sodium thiosulfate pentahydrate in cool, pyrogen-free distilled water which is then filtered through a Millipore filter into a clean sterile vessel.

Calculated quantities of each of these solutions are then transferred into sterile containers, frozen, and freeze-dried using aseptic technique. The containers are then sealed, suitably using a puncturable sealable closure such as a rubber cap or rubber stopper. These are also prepared sterile, pyrogen-free solutions of acid and also of base, suitably the base being in the presence of a buffer, which are each packaged into sterile means for introduction thereof into the sterile containers charged with the freeze-dried mixtures of gelatin and sodium thiosulfate. It has been found suitable to utilize disposable plastic syringes for the purpose.

It has been found that the freeze-dried mixture of gelatin and sodium thiosulfate is extremely readily resoluble in small quantities of water, said combination also has substantially indefinite shelf life.

In order to prepare the injectable composition an aqueous solution of the radio tracer, for example sodium pertechnetate is injected into the container charged with the freeze-dried gelatin and sodium thiosulfate, suitably using a syringe, mixing the components together, adding the requisite quantity of acid, remixing and heating at an elevated temperature for a short time. The colloidal sulfur having the radio tracer absorbed thereon is thus produced. The mixture is cooled and the base, suitably containing the buffer, is then injected to adjust the pH to the appropriate value. The composition is then injected into the subject patient.

The principle is also applicable to other injectable colloidal carriers for example to colloidal ferric hydroxide. In this modification in place of sodium thiosulfate there is utilized ferric ethylate which may be readily hydrolyzed, suitably, but not necessary, in an alkaline environment to produce salt free colloidal ferric hydroxide, upon which a radio tracer, such as induim-113 is absorbed.

DESCRIPTION OF THE DRAWINGS

FIG. 1 is an elevational cross sectional view of a sterile container for the gelatin and thiosulfate.

FIG. 2 is a top plan view of the container of FIG. 1 showing crimp seal in place.

FIG. 3 is a top plan view of the container of FIG. 1 showing rubber seal exposed.

FIGS. 4 and 5 are injection means for acid, and base with buffer.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

In the preferred embodiments of the present invention all of the components utilized should be, where available, clean and sterile. And all water used for solvating components should be pyrogen-free and substantially particle-free. The galatin solution is prepared by suspending gelatin in water and allowing it to imbibe water for a short period of time, thereafter the glutinous suspension is sealed suitably by crimp sealing, and heat sterilized suitably by steam sterilization which, not only sterilizes the suspension but causes the gelatin to dissolve. Although the is referred to as a solution it is of course, strictly speaking, a colloidal sol. Since the gelatin will be freeze-dried in a subsequent step, the amount of water utilized to dissolve the gelatin is in no way critical, however, it has been found convenient to utilize concentrations of the order of 60 to 100 grams of gelatin per litre of water. Gelatin suspensions of this concentration will pick up the optimal amount of water at ambient temperature in about 10 to about 20 minutes, longer immersion is therefore unnecessary.

The sodium thiosulfate, suitably in the form of the pentahydrate, is dissolved in water at ambient temperature or below. The temperature is not critical, however it must be recognized that the solubility at low temperatures is less than that at higher temperatures and that temperatures above ambient are not favored in order to include the premature decomposition of the sodium thiosulfate into colloidal sulfur. While the pentahydrate is preferred as the most readily available form, sodium thiosulfate with other degrees of hydration may of course be employed, similarly potassium thiosulfate may also be employed but the sodium salt is preferred for reasons of cost. The solution is then filtered through a Millipore filter in order to remove particulate matter and bacteria. While, again, the concentration of sodium thiosulfate is not critical at this point, it has been found convenient to utilize the concentrations from about 3 to about 8 grams of thiosulfate per litre of water. It has also been found convenient to utilize a filter having ca. 0.8 micron apertures, this removes all bacteria.

Utilizing aspetic techniques, portions of the gelatin solution and the thiosulfate solution are then transferred into small sterile containers **10**, suitable clean sterile serum vials. It has been found convenient to transfer amounts of solutions corresponding to from about 4 to about 40 mg. of gelatin, preferably about 8 mg. of gelatin and from about 1 to about 4 mg. preferably about 2.5 mg. of sodium thiosulfate pentahydrate into each vial.

The vials are then frozen and freeze-dried using standard aseptic techniques. The vials are then sealed utilizing a puncturable, resealable closure such as a rubber stopper or similar elastomeric closure which is then sealed suitably by crimp sealings.

The vial **10** thus contains a layer **19** of freeze dried gelatin/thiosulfate mixture. The dual sealing device comprises a puncturable rubber stopper **12** which is covered by a metallic crimp seal cap **14** which comprises a retaining portion **16** and a removable center plate **18**. This center plate **18** is removed immediately prior to use permit sterile injection into vial **10**.

The other components of the kit are then prepared. The acid utilized should be one which contains a physiologically acceptable anion. While not limiting the invention thereto, it is generally preferred to utilize an aqueous solution of phosphoric acid or hydrochloric acid suitably about 0.5 to about 0.15 N acid being utilized, acid of about 0.1 N being preferred. The acid is then place in a sterile means for introducing the said acid into the sterile container containing the freeze-dried mixture of gelatin and sodium thiosulfate. For this purpose disposable plastic syringes have been found specially suitable. Where the foregoing quantities of gelatin and sodium thiosulfate have been employed, 5 ml. syringes containing 2 ml. of acid have been found especially useful.

Typical syringes **20** and **30** are shown in FIGS. 4 and 5 and comprise respectively barrel portions **22** and **32** fitted with plungers **24** and **34** and needle portions **26** and **36**. The acid **28** and base **38** components are located in the portion of barrels **22** and **32** between plungers **24** and **34** and needles **26** and **36**.

Into similar sterile introducing means is placed a base having physiologically acceptable cations and anions and preferably though not criticially, a physiologically acceptable buffer. Among the bases which may be used are potassium or sodium hydroxides or carbonates. As a buffer the commonly used sodium or potassium dihydrogen phosphate may be employed.

There may be employed bases having a concentration from about 0.05 to about 0.15 N preferably about 0.1 N.

The buffer which is, of course, dissolved in the same solution containing the base, may be of a strength of between about 0.1 to about 0.2 M suitably about 0.15 M.

The typical ratio of quantities of components used in the combination of the present invention may be summarized as from about 4 to about 40 milligrams, suitably about 8 milligrams of gelatin, from about 1 to about 4 milligrams suitably about 2.5 milligrams of sodium thiosulfate pentahydrate initially charged, with which are packaged from about 1 to about 5 ml. each of acid solution containing from about 0.1 to about 0.3, suitably about 0.2 milliequivalants of acid and of base solution containing from about 0.15 to about 0.35 suitably about 0.28 milliequivalants of base in the presence of about 0.2 to about 0.4 suitably 3.3 millimoles of buffer. These quantities being calculated so that after mixing all of the components of the injectable composition and processing them appropriately there is achieved a solution having a pH of between 6 and about 6.5 suitably of about 6.3 to about 6.5.

The radio tracer utilized with this injectable composition is usually obtained in the form of an aqueous solution of a salt. Among the radio tracers utilizable with these compositions is sodium pertechnetate. The quantity of radio tracer utilized with the aforementioned quantities of composition is of the order of about 1 to about 10 millicuries. In preparing the injectable composition, the radio tracer solution is injected into the sealed containers containing the freeze-dried gelatin and sodium thiosulfate mixture. The components are thoroughly mixed to provide a solution, and the acid components added thereto. The components are then thoroughly mixed again, suitably by shaking, and heating for a short period of time to produce the colloidal sulfur solution having absorbed thereon the radio tracer. It has been found suitable to heat the mixture on a vigorously boiling water bath, that is to say a bath temperature of from about 90 to about 100° C. for from about 2 to about 10 preferably for about 3 minutes. Prolonged heating is undesirable since this will cause aggregation of the colloidal particles giving rise to particles which are greater than the optimum size which is a size less than 2 microns, preferably less than 1.2 microns. The colloidal solution is then cooled and the requisite amount of basic solution are added thereto. The composition is then ready for injection to the subject patient.

As stated herein above one of the problems pertaining to the prior art compositions was improper absorption of the radio tracer due to excessive dilution. In the tests carried out utilizing the compositions of the present invention the undesirability of excessive dilution has been confirmed. Thus, utilizing sample compositions prepared in accordance with Example 1 hereinbelow with between 0.5 and 3 ml. of a standard sodium pertechnetate solution, particle size of less than 1.2 microns were noted, and, moreover, the amount of free-pertechnetate was too small

to measure. However where 5 milliliters of the same solution were utilized not only did the particle size increase to about 2 microns but approximately 40% of the radioactivity was found to be in the form of free i.e. dissolved rather than absorbed pertechnitate.

It is thus clear that dilution gives rise to larger particle size. These larger particles would become trapped in the lung capillaries, while the smaller, more desirable particles would be picked up, as intended by the reticuloendothelial system.

EXAMPLES

Example 1

Preparation of gelatin-sodium thiosulfate component.—There is prepared a suspension of 1 g. of gelatin in 12.5 ml. of pyrogen-free substantially particle-free distilled water. The mixture is allowed to stand for 10 minutes, transferred to a crimp-sealed serum vial, steam sterilized, and cooled.

250 mg. of sodium thiosulfate pentahydrate is dissolved in 50 ml. of pyrogen-free distilled water at ambient temperature, and filtered through a Millipore filter (0.8 micron aperture) into a clean sterile vial. 0.1-ml. portions of the gelatin solution and 0.5-ml. portions of the thiosulfate solution respectively are combined in a series of clean sterile vials, frozen, freeze-dried, and stoppered with rubber stoppers which are crimp sealed in place.

Example 2

Preparation of the acid and base components.—(a) A 0.111 N solution of hydrochloric acid is prepared in a sterile pyrogen-free water and 2-ml. portions thereof transferred to disposable plastic syringes of 2.5-ml. capacity.

(b) A solution 22.3 g. of sodium dihydrogen phosphate and 5.5 g. of sodium hydroxide is prepared in one litre of pyrogen-free, particle-free water. This solution corresponds to 0.139 N sodium hydroxide and 0.163 M sodium dihydrogen phosphate. 2 ml. portions of this buffered base solution are placed in 2.5-ml. disposable plastic syringes.

Example 3

Preparation of injectable composition.—Into a vial containing freeze-dried gelatin and freeze-dried-sodium thiosulfate as prepared in accordance with Example 1, there is injected 1-ml. of a sterile pyrogen-free, substantially carrier-free solution of sodium pertechnetate. The contents are mixed thoroughly, the contents of the syringe prepared in accordance with Example 2(a) are added, the contents again mixed and placed in a vigorously boiling water bath for three minutes, cooled, and the contents of the syringe of Example 2(b) added.

What is claimed is:

1. A process for the preparation of an injectable carrier for radioisotopes which comprises the steps of:
   (a) dissolving gelatin and sodium thiosulfate in water,
   (b) freeze-drying the solution of step (a),
   (c) adding to the freeze-dried product of step (b) an aqueous solution containing the radioisotopes to be utilized, and mixing thoroughly,
   (d) adding to the solution of step (c) an aqueous solution of a strong acid containing a physiologically acceptable anion and mixing thoroughly,
   (e) heating the mixture of step (d) at a temperature of between 90° and about 100° C. for a short time to produce a colloidal sulfur solution with the colloidal particles being of a size less than 2 microns, preferably less than 1.2 microns, and having absorbed thereon the radioisotope, and
   (f) cooling the colloidal solution of step (e) and neutralizing with a base containing physiologically acceptable anions and cations in the presence of a physiologically acceptable buffer.

2. A process according to claim 1 comprising the steps of
   (a) suspending gelatin in pyrogen-free, substantially particle free water,
   (b) steam sterilizing the resulting solution and cooling said solution,
   (c) dissolving sodium thiosulfate pentahydrate in cool pyrogen-free water and filtering said solution through a Millipore filter,
   (d) combining portions of said gelatin and said thiosulfate solutions in a sterile container and freeze drying said mixed solutions,
   (e) sealing said sterile container with a puncturable resealable cap.

3. A process according to claim 2 comprising the additional steps of
   (a) adding to said sterile container an aqueous pyrogen-free solution of an injectable water soluble composition comprising radioisotopes,
   (b) thereafter adding to said sterile container a sterile aqueous solution of phosphoric or hydrochloric acid,
   (c) keeping said sterile container and contents between 90° and 100° C. (bath) and cooling said contents to ambient temperature,
   (d) adding to said sterile container and contents thereof, a sterile aqueous solution of a base consisting of physiologically acceptable anions and cations, the amount of said being slightly in excess of the relative equivalents of acid previously charged, and a buffer to provide a pH of the resultant mixture in the range of 6 to 6.5.

4. A process according to claim 3 which comprises the additional steps of:
   (a) adding to the sterile container after the freeze-drying step, for each container originally charged with between from about 4 to about 40 mg. of gelatin and from about 1 to about 4 mg. of sodium thiosulfate pentahydrate, as measured prior to freeze-drying, contained therein, from about 0.1 to about 0.3 milliequivalent of acid,
   (b) heating said mixture at between 90° and 100° C. (bath) from about 2 to 10 minutes,
   (c) cooling said mixture,
   (d) adding for each container originally charged with between from about 4 to about 40 mg. of gelatin and from about 1 to about 4 mg. of sodium thiosulfate pentahydrate, as measured prior to freeze-drying, a sterile aqueous solution of from about 1 to about 10 millicuries of radioisotopes,
   (e) adding for each container originally charged with between from about 4 to about 40 mg. of gelatin and from about 1 to about 4 mg. of sodium thiosulfate pentahydrate, as measured prior to freeze-drying, a sterile aqueous solution of from about 3 to about 5 ml. containing from about 0.15 to about 0.35 milliequivalent of base and about 0.2 to about 0.4 millimole of phosphate buffer to achieve a pH of between 6.3 and 6.5.

5. A process according to claim 4 wherein there are utilized for each container originally charged with 8 mg. of gelatin and 2.5 mg. of sodium thiosulfate pentahydrate, measured prior to freeze drying,
   (a) 2 ml. of 0.11 N hydrochloric acid,
   (b) between 0.56 and 5 ml. of a sterile aqueous solution of radioisotope tracer having an activity of between 1 and 10 millicuries,
   (c) 2 ml. of an aqueous solution containing 0.139 millimole per litre of sodium hydroxide and 0.163 millimole per litre of sodium dihydrogen phosphate buffer.

6. A process according to claim 5 wherein the radioisotope tracer is a water soluble salt comprising technetium-99.

7. A kit for the preparation of injectable radioisotope solutions comprising
   (a) a sterile container comprising a freeze-dried mixture of gelatin and sodium thiosulfate,
   (b) a sterile means for introducing a strong acid hav-

ing a physiologically acceptable anion into said sterile container, said sterile means containing said acid,

(c) a sterile means for introducing a base having physiologically acceptable anions and cations and a physiologically acceptable buffer into said sterile container, said sterile means containing said base and said buffer wherein the relatives quantities of acid, buffer, and base are such that when mixed with each other and the contents of the sterile container, there will be produced a colloidal solution having a pH of between 6.0 and 6.5 and wherein the ratio of components is from about 4 to about 40 mg. of gelatin relative to between about 1 to about 4 mg. of sodium thiosulfate pentahydrate initially charged prior to freeze drying, coupled with from about 0.1 to about 0.3 milliequivalent of base and to from about 0.2 to about 0.4 millimole of phosphate buffer and from about 3 to about 5 milliliters of water in the acid- and the base-introducing means respectively.

8. A kit according to claim **7** wherein

(a) the acid is aqueous phosphoric acid or hydrochloric acid,

(b) the base is aqueous potassium or sodium hydroxide or carbonate,

(c) said buffer is sodium or potassium dihydrogen phosphate.

9. A kit according to claim **7** wherein

(a) the sterile container contains 8 mg. of gelatin and 2.5 mg. of sodium thiosulfate, both components having been freeze-dried, the weights being measured prior to freeze-drying,

(b) a first sterile introducing means containing 2 ml. of 0.11 N hydrochloric acid in pyrogen-free water,

(c) a second sterile introducing means containing 2 ml. of a pyrogen-free aqueous solution of 0.139 mM. sodium hydroxide and 0.163 mM. of sodium dihydrogen phosphate monohydrate.

10. A process for the preparation of an injectable carrier for radioisotopes comprising the steps of:

(a) dissolving gelatin ferric ethylate in water,

(b) freeze-drying the solution of step (a),

(c) adding to the freeze dried product of step (b) an aqueous solution containing the radioisotopes to be utilized and mixing thoroughly,

(d) adding to the solution of step (c) a base containing a physiologically acceptable anion and cation and mixing thoroughly,

(e) heating the mixture of step (d) at a temperature of between 90° and 100° C. for a short time to produce a colloidal solution with the colloidal particles being of a size less than 2 microns, preferably less than 1.2 microns, and having absorbed thereon the radioisotope, and

(f) cooling the colloidal solution of step (e) and adding thereto an acid containing a physiologically acceptable anion in the presence of a physiologically acceptable buffer to bring the pH into the region from about 7 to 8.

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U.S. Cl. X.R.

424—3, 9; 34—5; 252—363.5, 408, 301.1