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Dworkin et al.

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[45] **Jan. 8, 1974**

[54] **PROCESS AND APPARATUS FOR MAKING RADIOACTIVE LABELED PROTEIN MATERIAL**

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[52] **U.S. Cl.** ..... **204/131,** 204/1 R, 204/137 R, 204/271, 204/286, 204/297 R, 128/1.1

[51] **Int. Cl.** **B01k 1/00**

[58] **Field of Search** ..... 136/90; 204/195 R, 204/271, 286, 297 R, 297 M, 131, 137; 128/1.1, 1.2

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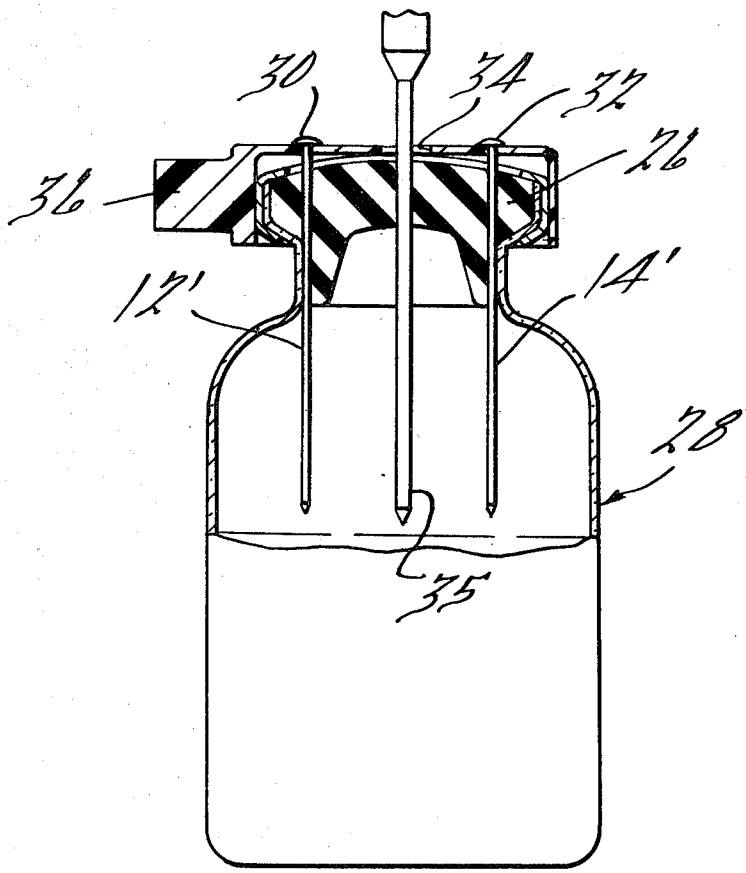
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[57] **ABSTRACT**

A closed sterile electrolytic system for tagging human serum albumin and other compounds and/or substances including proteins with a radioactive isotope, such as the 99m isotope of technetium, producing a radioactive tracer material which is suitable for biological studies and medical uses.

14 Claims, 5 Drawing Figures



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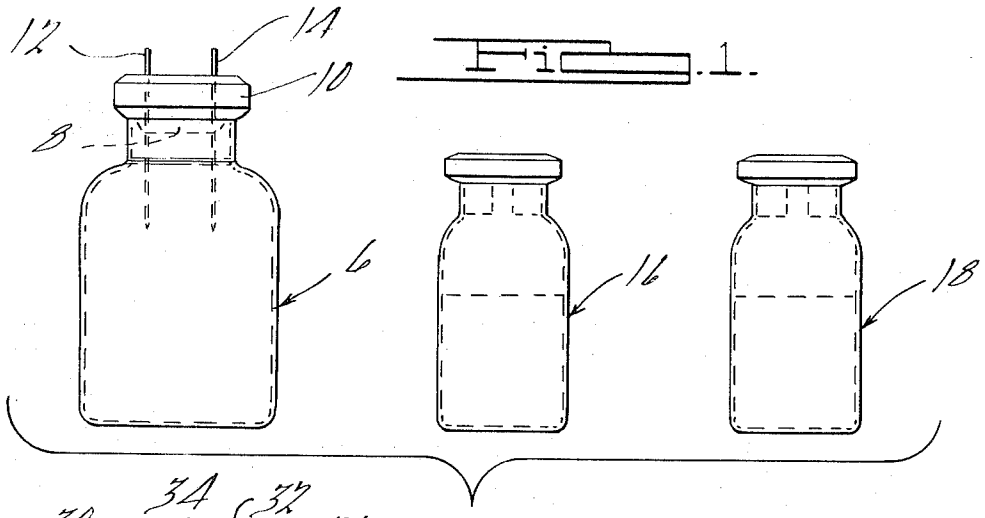


Fig. 1.

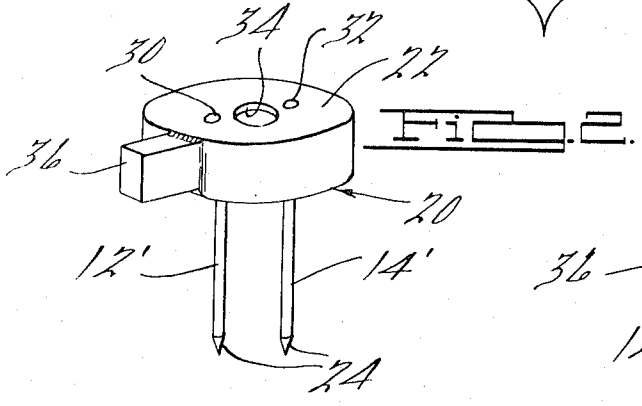


Fig. 2.

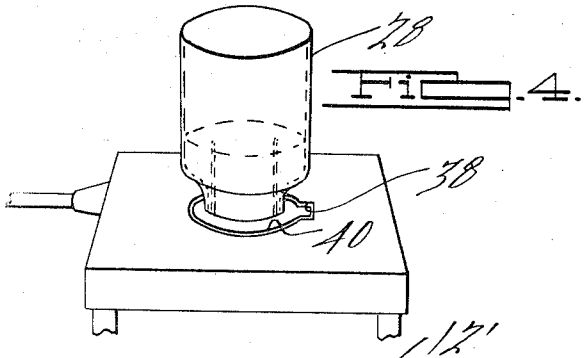


Fig. 4.

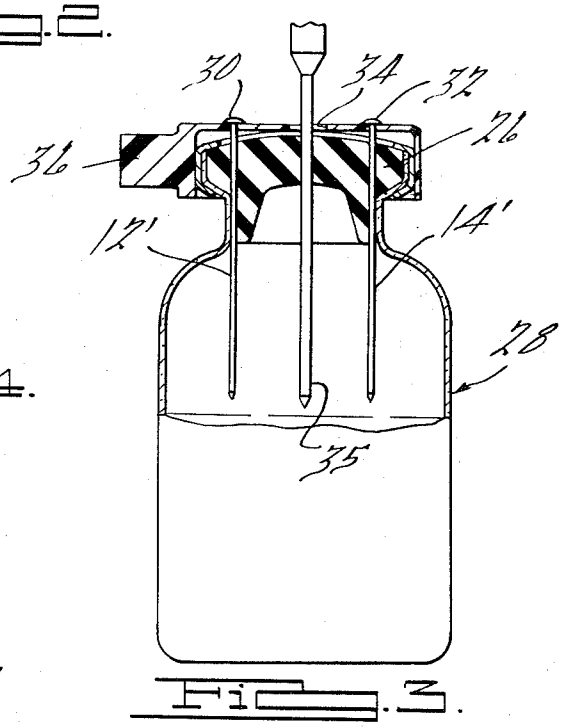


Fig. 3.

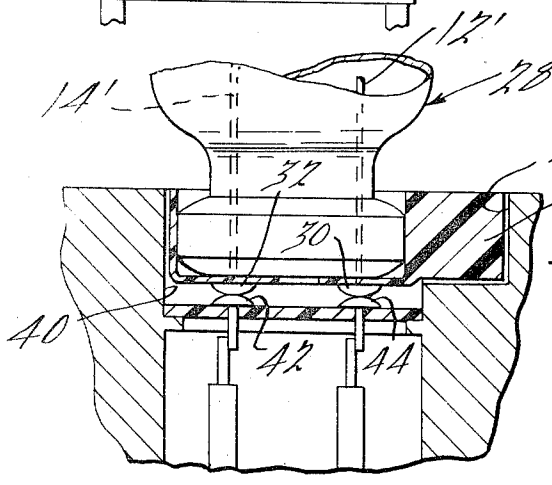


Fig. 5.

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PROCESS AND APPARATUS FOR MAKING RADIOACTIVE LABELED PROTEIN MATERIAL

BACKGROUND OF THE INVENTION

Radioactive isotopes and particularly proteins tagged or labeled with such radioactive isotopes have been found extremely useful in biological studies and medical diagnoses. In particular, human serum albumin tagged with technetium-99m has been found as possessing extreme utility for placental localization, heart blood pool scanning and cisternography. Unfortunately a more widespread use of this and similar radioactive diagnostic materials has been restricted because of the difficulty of preparing such materials and the necessity of using such materials immediately after preparation due to their short effective life and before tests can be completed on the pyrogenicity and sterility thereof. Still further problems and complications are encountered in the preparation of radioactive labeled microaggregated and macroaggregated human serum albumin because of the difficulty in controlling the aggregation procedure so as to attain the desired particle size consistent with the intended diagnostic use of the material. The aggregation procedure, in accordance with prior art techniques, is relatively tedious and time consuming and frequently results in improper particle sizes, requiring the entire batch to be discarded and a repetition of the entire preparation procedure. In an effort to overcome the foregoing problems, highly trained and experienced personnel have been used for preparing such radioactive labeled protein materials utilizing relatively sophisticated laboratory facilities. The costs and difficulties associated with such prior practices has inhibited a more widespread adoption and use of such materials.

The apparatus and process comprising the present invention overcomes the foregoing problems in providing a simple and economical system for preparing radioactive labeled protein materials in a sterile, nonpyrogenic condition, rendering the material ideally suited for a variety of biological studies. The system can be furnished in a convenient kit form, facilitating the preparation of the material by other than highly trained personnel and without resort to sophisticated laboratory facilities.

SUMMARY OF THE INVENTION

The advantages and benefits of the present invention are achieved by providing a closed electrolytic system including a sealed sterilized reaction vial incorporating a pair of electrodes which extend inwardly and are adapted to be immersed in an aqueous solution containing a dissolved radioactive ion and a compound, such as a protein or suspended aggregated protein particles. The passage of electric current through the conductive solution between the electrodes effects a complexing and absorption of the radioactive ions on the protein constituent. In accordance with the practice of the present invention, the several solutions employed to form the electrolytic reaction mixture, namely: the aqueous solution containing the radioactive material; the aqueous solution containing the protein; the aqueous diluent, if required, to dilute the solution to a preselected final volume; and the acidic and basic solutions employed for pH adjustment can all be preliminarily sterilized and subjected to sterility and pyrogenicity testing, assuring that the final product will not produce

any adverse reactions upon injection into the blood stream. Tests conducted on radioactive technetium-tagged human serum albumin prepared in accordance with the closed sterile electrolytic system comprising the present invention have evidenced a superior performance of the tagged albumin in comparison to technetium-tagged albumin prepared by chemical techniques and open electrolytic techniques.

In its apparatus aspects, the present invention provides a novel sealed reaction vial within which the electrolytic tagging of a compound with a radioactive material is effected, utilizing in one of its embodiments, an electrode assembly adapted to be removably mounted on a conventional standard sealed vial converting it into a reaction vial suitable for use in accordance with the practice of the present invention. In a preferred form of the electrode assembly, the cap portion thereof is formed with suitable coacting means thereon for cooperating with corresponding means on an electrical socket for assuring proper electrical connection between the two terminals and the polarity of the electrical power source. It is further contemplated that in addition to the electrolytic sealed and sterilized reaction vial, one or more additional sterilized and sealed vials containing controlled amounts of sterilized solutions required during the course of the preparation of the radioactive tagged protein material can be provided, forming a kit which substantially facilitates the practice of the process aspects of this invention.

Still further advantages and benefits of the present invention will become apparent upon a reading of the description of the preferred embodiments taken in conjunction with the accompanying drawings and specific examples provided.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a side elevation view of a kit comprising an electrolytic sealed reaction vial constructed in accordance with one embodiment of the present invention in addition to supplemental sealed vials containing sterilized quantities of supplemental solutions employed in the electrolytic tagging process;

FIG. 2 is a perspective view of an electrode assembly in accordance with an alternative embodiment of the present invention suitable for mounting on a standard sealed vial for forming a reaction vial suitable for use in the practice of the present invention;

FIG. 3 is a vertical cross sectional view of a standard sealed vial having installed thereon an electrode assembly of the type shown in FIG. 2;

FIG. 4 is a perspective view of the reaction vial shown in FIG. 3 disposed in inverted installed relationship within a socket of an electrical power source; and

FIG. 5 is a fragmentary vertical sectional view of the electrical disposition of the contacts and electrodes of the socket and reaction vial, respectively, when disposed in the arrangement illustrated in FIG. 4.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

Among the several radioactive isotopes that can be satisfactorily used in accordance with the system comprising the present invention, technetium-99m has been found extremely useful and has received widespread acceptance as a radioisotope for use in various biological studies and medical diagnoses. The tagging of this radioisotope on proteins and specifically human

serum albumin (HSA) in accordance with the present invention has met with particular success, producing radioactive labeled HSA in extremely high yields and purity. While the system comprising the present invention and the preferred embodiments thereof will be described in terms of the use of technetium–99m and HSA as the radioactive isotope and tagged protein carrier medium, respectively, it will be understood that other satisfactory radioactive isotopes, as well as other compounds including other protein materials such as fibrinogen and globulins, can be used which are compatible with and produce satisfactory yields in accordance with the practice of the present invention.

The use of technetium–99m is particularly desirable and preferred over many other radioactive isotopes in view of the relatively short half life of the material, which is about six hours, thereby resulting in reduced exposure of the internal organs to radiation. The relatively short half life of this material also necessitates local preparation of the radioactive isotope since it is ordinarily uneconomical and impractical to effect a preparation and shipment by the manufacturer to a remotely located attending physician. Technetium–99m is obtained as the daughter product of molybdenum Mo^{99} and is separated in the form of the pertechnetate ion (TcO_4^-). The Mo^{99} ion is absorbed on an alumina column and the pertechnetate ion is separated from Mo^{99} by elution with a dilute solution of hydrochloric acid or saline. Such absorption columns containing Mo^{99} can be eluted or milked daily to yield the desired quantities of the radioactive isotope since the maximum growth of radioactivity of technetium–99m occurs in about 23 hours. When employing saline for eluting the column, the eluate comprises a dilute aqueous solution containing aodium pertechnetate technetium–99m which, for the purposes of the present invention, may range in radioactivity from a fraction of a microcurie up to whole curie quantities and generally about 100 millicuries.

A process for preparing a sterile non-pyrogenic radioactive eluate containing technetium–99m is described in detail in U.S. Pat. No. 3,440,423, the subject matter of which is incorporated herein by reference as being typical of one of the various techniques well known in the art for preparing such radioactive aqueous solutions. In accordance with the specific arrangement described in the aforementioned United States patent, a closed and sealed sterile column partly filled with granular alumina having adsorbed thereon radioactive (Mo^{99}) ammonium molybdate is periodically eluted with a sterile, non-pyrogenic isotonic saline to extract the radioactive technetium–99m. The eluate is collected in a sterile collecting container, providing a sterile, non-pyrogenic aqueous solution containing sodium pertechnetate technetium–99m suitable for introduction into the sterile electrolytic reaction vial of the present invention.

The protein constituent to be tagged, such as HSA, is commercially available conventionally in the form of a 25 percent aqueous solution which is sterile and non-pyrogenic. It is also contemplated, in accordance with the practice of the present invention, that HSA in a coagulated or aggregated form can also be electrolytically tagged with the radioactive isotope to provide a particulate radioactive medium for scanning selected organs, such as the lung and liver. In accordance with the system comprising the present invention, particulated HSA, such as macroaggregated HSA, of a particle size generally ranging from about 10 – 50 microns and microaggregated HSA of a particle size generally ranging from about 10 to about 1,000 millimicrons can be prepared in accordance with well known techniques by heat and pH adjustment, followed by classification to proper particle size. The aggregated product is subjected to sterility and pyrogenic testing preliminary to tagging with the radioisotope. In this regard, in techniques formerly employed for tagging such aggregated HSA, it was conventional practice to first tag HSA in solution form, whereafter careful aggregation was performed on the tagged solution HSA, frequently resulting in the formation of tagged particles of improper or undesired size. Such subsequent aggregation was performed in an open system exposing the tagged material to possible contamination, rendering it pyrogenic and non-sterile. In accordance with the practice of the present invention, aggregation of the HSA prior to tagging permits its testing for sterility and pyrogenicity, whereafter only the acceptable aggregated HSA is tagged with the radioisotope material. This provides for a substantial simplification and economy in the preparation of radioactive tagged aggregated HSA.

In addition to a source of a sterile, non-pyrogenic solution containing the radioactive isotope and the solution or suspension of HSA, the system comprising the present invention further requires non-pyrogenic sterile quantities of an aqueous diluent for providing a preselected volume of the reaction solution, an aqueous acid solution for reducing the pH of the reaction solution to within a desired range during the electrolytic tagging and an aqueous alkaline solution for adjustment of the pH to a level approaching that of the blood system prior to injection. The aqueous diluent preferably comprises an isotonic saline solution containing sodium chloride at a concentration of about 0.9 percent. Alternatively, distilled water or other salt-containing aqueous solutions which are compatible with the chemistry of body fluids can be employed. The aqueous diluent is only used to increase the volume of the eluate containing the radioisotope to provide a satisfactory volume of liquid to facilitate subsequent electrolytic tagging in a manner hereinafter to be described. Since the radioactive material is usually eluted from the radioactive column using saline, subsequent dilution of the eluate containing sodium pertechnetate technetium–99m with saline is particularly desirable.

The aqueous acidic solution used for reducing the pH of the reaction solution prior to electrolytic tagging may comprise any suitable acid or mixture of acids which is compatible with the radioactive material and protein substance and also does not produce any adverse effects upon subsequent injection of the radioactive material into the blood stream. While acids such as nitric acid and sulfuric acid forming ions, which are compatible with the system and body fluids, can be satisfactorily employed, hydrochloric acid is preferred in view of the presence of the chloride anion in the other solutions and in the blood stream. For this purpose, sterile non-pyrogenic aqueous solutions containing hydrochloric acid at a concentration sufficient to form about a 1 normal solution are particularly satisfactory for adjusting the pH of the reaction solution. The acidic solution is employed in an amount sufficient to reduce the pH of the reaction solution to within a range of about 0.8 to about 1.5, and preferably within a range

of from about 1.0 to about 1.3, at which particularly high efficiency and yields of tagged HSA are obtained.

The aqueous alkaline solution similarly may contain any suitable alkaline substance which is compatible with the radioactive labeled protein and with the chemistry of the body fluids upon injection of the tagged serum into the blood stream. Of the various alkaline substances that are compatible, such as sodium hydroxide, sodium bicarbonate is particularly satisfactory in that upon neutralization of the acid present in the reaction mixture, carbon dioxide is evolved which passes from the solution, minimizing a further build up in dissolved ions. The alkaline solution is employed in amounts so as to raise the pH of the resultant radioactive tagged HSA solution to about 7.4, corresponding to the pH of the blood stream. While it is possible to inject the radioactive labeled protein solution in an acidic condition without neutralization in view of the small amounts required, the preferred practice is to employ the alkaline constituent for raising the pH to a level corresponding to that present in the blood stream.

Referring now in detail to the drawing, and with particular reference to FIG. **1**, a series of sealed vials are shown which are adapted to be assembled in the form of a kit containing some of the solutions required for preparing the tagged radioactive protein material. The principal component of the kit comprises the sealed reaction vial **6** which defines the closed system within which an electrolytic tagging of the protein constituent is performed. The reaction vial is preferably comprised of glass and is formed with a neck portion defining an aperture or opening adapted to be sealed by a pierceable autoclavable closure, such as a rubber stopper **8**. The rubber stopper **8** is retained in appropriate position in the neck of the reaction vial by means of an aluminum metal collar **10** crimped around the lip portion of the neck and in overlying relationship relative to the stopper. A pair of elongated sharpened electrodes **12, 14** extend downwardly through the rubber stopper in spaced substantially parallel relationship to a position spaced from the bottom wall of the reaction vial. The portions of the electrodes **12, 14** projecting outwardly of the stopper are adapted to be connected to a suitable source of electric current during the electrolytic tagging operation in a manner subsequently to be described.

The particular mechanism for effecting the electrolytic tagging of a compound, such as HSA, with a radioisotope, such as technetium–99m, is not entirely understood at the present time. It is believed, however, that during the passage of current from the electrode **12**, which is comprised of a metal or conductive material coated with a metal selected from the group consisting of zirconium, iron and alloys thereof, to the electrode **14**, which may be comprised of the same material as the electrode **12** or any relatively inert, non-reactive metal, such as platinum, nickel, stainless steel and the like, a solution of a portion of the electrode **12** occurs such that the zirconium and/or iron ions effect a complexing of the radioactive isotope in a manner to enhance absorption thereof by the protein constituent. In the specific embodiment shown in FIG. **1**, the electrodes **12** and **14** extend downwardly into the reaction chamber defined by the interior of the vial **6** a distance of about midway such that the several solutions can be added to the reaction vial without coming into contact or effecting an immersion of the electrodes therein. The vial, accordingly, can simply be inverted at the time the current is to be applied, whereupon substantially complete immersion of the electrodes in the solution occurs. Alternative satisfactory vial constructions also can be employed including those in which the electrodes extend through the walls of the vial, such as by embedment directly in the glass.

In addition to the reaction vial **6**, suitable sterile supply vials **16** and **18**, as shown in FIG. **1**, can be provided which are of a construction similar to that of the reaction vial. The supply vials **16, 18** may conveniently contain adequate quantities of sterile, non-pyrogenic aqueous solutions of the supplemental reagents required for the preparation of the radioactive tagged protein constituent such as the aqueous acid solution, the aqueous alkaline solution, the aqueous diluent, the human serum albumin aqueous mixture or suspension, and the like.

Still further flexibility and versatility is provided by the electrode assembly as illustrated in FIGS. **2–4** of the drawing, enabling a conversion of standard medicinal vials into sealed electrolytic reaction vials suitable for practice of the present invention. As shown in FIGS. **2** and **3**, an electrode assembly **20** comprises a cap portion **22** having electrodes **12'** and **14'** affixed thereto and projecting therefrom in substantially parallel spaced relationship. The electrodes **12', 14'** are formed with sharpened ends, indicated at **24**, to facilitate a piercing of a pierceable closure member, such as the rubber stopper **26** shown in FIG. **3**, upon installation of the electrode assembly on a standard vial **28**. The outward projecting ends of the electrodes **12', 14'** terminate in suitable button-shaped contacts **30, 32**, which are adapted to be disposed in electrical contact with a suitable source of electric current.

As will be further noted in FIGS. **2** and **3**, the cap **22** is formed with an aperture **34** centrally between the contacts **30, 32**, thereby providing access to the upper surface of the rubber stopper **26** such as by a hypodermic needle **35**, by which the several solutions are introduced into the interior of the reaction vial and are subsequently extracted therefrom. The cap portion **22** is also preferably formed with a suitable coacting means, such as a protuberance **36**, which is adapted to coact with a corresponding or complementary shaped slot **38** of an electrical socket **40**, as shown in FIG. **4**, providing proper orientation of the contacts **30, 32** relative to a power source contained therein. As best seen in FIG. **5**, the inverted vial incorporating the electrode assembly thereon, when disposed in the electric socket **40**, is positioned by means of the coaction of the protuberance **36** and slot **38** so that the contacts **30, 32** are disposed in electrical connection with contacts **42, 44**, assuring that the proper polarity current is supplied to each electrode.

In accordance with the foregoing arrangement, the electrode assembly **20** can be sterilized, such as by autoclaving or radiation, and installed on a standard medicinal vial **28**, either prior to or after the interior thereof has been filled with a desired amount of the requisite solutions. Thereafter, the vial is inverted in a manner as shown in FIGS. **4** and **5** and placed in the electric socket **40**, such that electric current passes between the electrodes **12', 14'** thereof for a period of time sufficient to effect a tagging of the protein constituent with the radioactive material. The resultant mixture thereafter can be extracted such as by means of

the hypodermic needle shown in FIG. 3 with the assurance that the contents thereof are in a sterile non-pyrogenic condition. In accordance with the foregoing technique, appropriate quantities of radioactive tagged protein materials can be prepared in the sterilized sealed system to supply the normal daily requirements of a hospital or institution. Typically, reaction vials, such as the vial **6** shown in FIG. **1**, having a volume of 20 milliliters are satisfactory for preparing approximately 7 milliliters of a sterile, non-pyrogenic tagged protein suitable for medical diagnoses and biological studies.

In order to further illustrate the sealed system and electrolytic process for preparing a radioactive tagged protein material, the following expample is provided. It will be understood that the example is provided for illustrative purposes and is not intended to be limiting of the scope of the invention as herein described and as set forth in the subjoined claims.

EXAMPLE

Typically, a normal day's supply comprising about 7 milliliters of a technetium–99m tagged HSA is prepared employing a reaction vial, such as the reaction vial **6**, having a volume of 20 milliliters. The reaction vial is equipped with a zirconium anode electrode corresponding to the electrode **12** and a stainless steel or zirconium cathode electrode corresponding to the electrode **14** of the reaction vial shown in FIG. **1**. The entire reaction vial, including the electrode assembly, is preliminarily sterilized, such as by autoclaving or radiation, providing a sterile sealed system. The interior of the vial is filled with air or other oxygen-containing gas since it has been observed that the presence of oxygen appears to enhance the efficiency of the electrolytic tagging process.

Approximately 5 milliliters of an isotonic saline eluate containing sodium pertechnetate technetium–99m having a radioactivity of about 100 millicuries is added to the interior of the reaction vial by means of a hypodermic needle and syringe. In the event 5 milliliters of eluate are not available, the deficiency in volume can be made up by a corresponding addition of a sterile, non-pyrogenic isotonic saline solution. The adjustment of the pH of the radioactive eluate in the reaction vial to within a range of about 1 to about 1.3 is conveniently achieved by the addition of about 0.7 milliliters of 1 normal hydrochloric acid solution utilizing a hypodermic syringe, thereby maintaining the sterility and non-pyrogenicity of the reaction solution. The resultant aqueous mixture in the reaction vial is agitated for a period of time to assure a homogeneous solution.

To the resultant solution, 0.1 milliliters of a 25 percent HSA solution is added and the contents of the reaction vial are again agitated to form a homogeneous solution. The zirconium anode electrode and a stainless steel or zirconium cathode electrode, after inversion of the vial, are thereafter connected to a direct current power source at an amperage of 100 milliamps and at a voltage of approximately 3 to 5 volts for a period of time sufficient to apply 4.2 coulombs of electricity therethrough. At the completion of the electrolytic tagging, the current source is disconnected and the solution is gently agitated for an additional period of time at room temperature which has been found desirable to permit a continuance of the tagging reaction. Tests have shown that under the foregoing conditions, about an 80 percent yield of tagged HSA is provided based on the amount of technetium–99m present at the conclusion of the electric current passage, while further tagging occurs during the subsequent agitation period, providing tagging yields of up to 95 percent and above.

At the conclusion of the subsequent agitation dwell period, 1 milliliter of an 8.4 percent sterile non-pyrogenic sodium bicarbonate solution is injected into the reaction vial to effect an adjustment of the pH of the solution to about 7.5. The technetium–99m tagged HSA is now ready for use by injection into the blood streams of humans and animals. The reaction vial serves as a sealed and sterile storage container for the tagged HSA, from which appropriate quantities can be extracted by a hypodermic syringe retained in the sealed integrity of the vial.

In a similar manner, particulate HSA, such as macroaggregated and microaggregated HSA, and albumin spheres can be tagged. It is usually preferred when tagging aggregated protein particles to separate the supernatant aqueous solution at the completion of the reaction, such as by centrifugation, and replace the supernatant reaction liquid removed with isotonic saline for injection producing a product with 90 percent or more of the radioactivity bound.

It is also contemplated in accordance with the practice of the present invention that non-aggregated tagged proteins prior to injection can be passed through a bacterial filter for further assuring the absence of any bacterial contamination in the material.

Sterility and pyrogenicity tests conducted on technetium–99m tagged HSA produced in accordance with the technique as described in the foregoing example hav shown no bacterial or pyrogenic contamination.

Analyses of the resultant product by instant thin layer chromatography and trichloroacetic acid precipitation revealed a tagging efficiency of the HSA with the technetium–99m in accordance with the foregoing example of greater than about 90 percent.

Tests have also been conducted to evaluate the performance of technetium–99m tagged HSA prepared in accordance with the electrolytic technique described in the foregoing example relative to radioactive iodine-tagged HSA and HSA tagged with technetium–99m in accordance with prior art chemical techniques. Radioiodinated HSA, which has been in use for over 20 years as a biological tracer for studying the blood volume and vascular spaces, was employed as the standard for comparing the chemically and electrolytically tagged technetium–99m HSA. The HSA tagged with technetium–99m by chemical techniques was prepared in accordance with well known practice, including a series of chemical steps consisting of acidification and reduction of technetium–99m and, finally, a purification thereof through an ion exchange resin.

The three radioactive tracer materials were injected intravenously into a number of white rats. The performance of the chemical and electrolytically prepared radioactive HSA materials were evaluated by measuring the rate of their disappearance from the blood stream in comparison to that of the radioiodinated HSA. The results of such comparative evaluations, based on a group of 16 rats, are set forth in the following table:

Blood Disappearance of 99mTc Albumin As A Percentage of Radioiodinated Albumin

	Elapsed Time (minutes): 10	20	30	60	90
Electrolytically Prepared 99mTc HSA	96%	95%	90%	85%	84%
Chemically Prepared 99mTc HSA	94%	90%	83%	73%	68%

It is apparent from the data as set forth in the preceding table that the HSA tagged with 99mTc by the electrolytic technique, comprising the present invention, is substantially superior to that of the chemically prepared HSA. The chemically prepared material is more susceptible to extraction from the blood stream via the kidney, suggesting that the electrolytically tagged HSA behaves more like natural human serum albumin and approaches the performance of the radioiodinated HSA.

While it will be apparent that the invention herein disclosed is well calculated to achieve the benefits and advantages as hereinabove set forth, it will be appreciated that the invention is susceptible to modification, variation and change without departing from the spirit thereof.

What is claimed is:

1. In a sealed reaction system for electrolytically tagging compounds with radioisotopes, the combination comprising a container defining a sterile reaction chamber and formed with an aperture having a closure disposed in sealing relationship therein and pierceable by a hypodermic syringe for gaining access to the interior of said chamber, a solution in said reaction chamber consisting essentially of a sterile non-pyrogenic aqueous mixture at a controlled pH containing a radioactive material and a protein compound, a pair of electrodes projecting into said chamber and adapted to become at least partially immersed in said solution contained therein, at least one of said electrodes comprised of a metal selected from the group consisting of iron, zirconium and alloys thereof, and means for electrically connecting said electrodes to an electric power source.

2. The reaction system as defined in claim **1,** in which said electrodes are disposed in the upper portion of said chamber when said container is in its normal upright position and in which position said electrodes are disposed above the level of said solution disposed within and partially filling said chamber.

3. The reaction system as defined in claim **1,** in which said container is comprised of glass and is formed with a neck in the upper portion thereof defining said aperture in which said pierceable closure is disposed in sealing relationship, said pair of electrodes extending downwardly in spaced piercing relationship through said closure to a position spaced upwardly from the bottom wall of said container.

4. The reaction system as defined in claim **1,** further including coacting means on said vial for facilitating connection of said electrodes to the proper polarity of electric current.

5. A process for preparing a sterile, non-pyrogenic aqueous mixture containing a compound tagged with a radioactive isotope which comprises the steps of preparing a closed sterile non-pyrogenic reaction chamber having a pair of electrodes therein of which one is comprised of a metal selected from the group consisting of zirconium, iron and alloys thereof, introducing a sterile non-pyrogenic aqueous mixture into said reaction chamber which contains a radioactive material and a protein compound at a controlled pH, immersing said electrodes in said aqueous mixture and passing an electric current between said electrodes to effect ionization and solution of a portion of said one electrode and an absorption of at least a portion of said radioactive isotope on said compound, continuing the passage of electric current until at least a portion of said compound has become electrolytically tagged with said radioactive material providing therewith an aqueous sterile non-pyrogenic mixture containing an electrolytically tagged compound suitable for use in biological studies.

6. The process as defined in claim **5,** in which the pH of said aqueous mixture is controlled within a range of about 1 to about 1.3 during the passage of electric current.

7. The process as defined in claim **5,** in which said radioactive material comprises the pertechnetate ion technetium–99m.

8. The process as defined in claim **5,** in which said compound comprises a solution of human serum albumin.

9. The process as defined in claim **5,** in which said compound comprises particles of aggregated human serum albumin.

10. Th process as defined in claim **5,** including the further step of introducing a sterile non-pyrogenic aqueous alkaline solution into said reaction vial at the completion of said electrolytic tagging to adjust the pH to a level of about 7.4.

11. The process as defined in claim **5,** including the further step of extracting the resultant sterile non-pyrogenic aqueous mixture containing the electrolytically tagged compound from said reaction chamber with a sterile hypodermic syringe.

12. The process as defined in claim **5,** including the further step of extracting the resultant sterile non-pyrogenic aqueous mixture containing the electrolytically tagged compound from said reaction chamber and passing it through a bacterial filter prior to use.

13. The reaction system as defined in claim **1** wherein said radioactive material comprises the pertechnetate ion technetium–99m.

14. The reaction system as defined in claim **1,** in which said protein compound comprises a solution of human serum albumin.

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