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RADIOPHARMACEUTICAL GENERATOR KIT

Filed Aug. 19, 1971

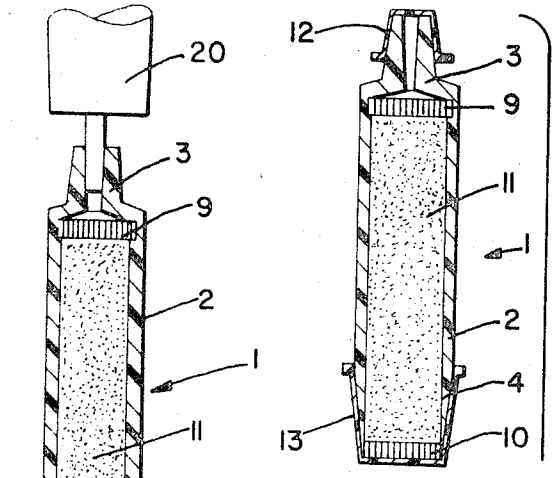


FIG_1

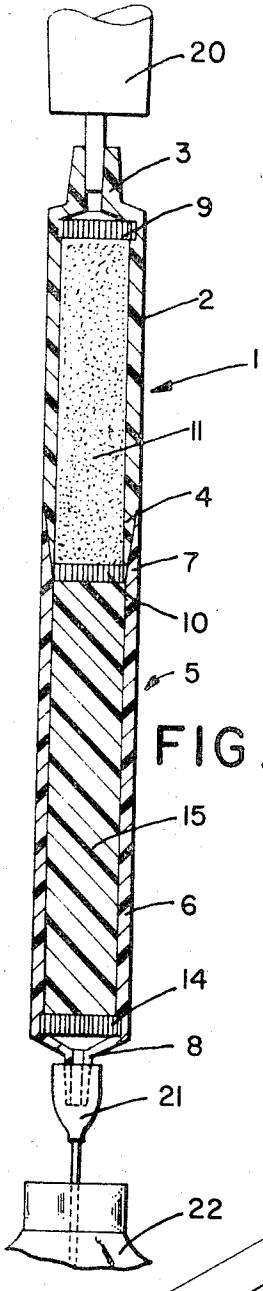
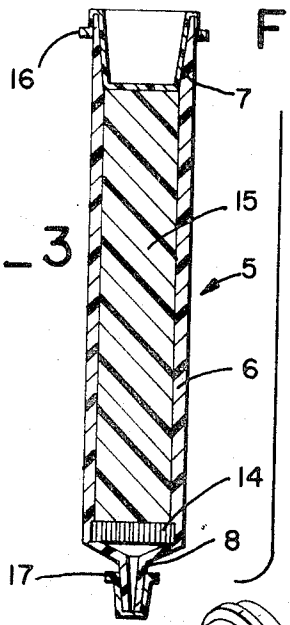


FIG_3



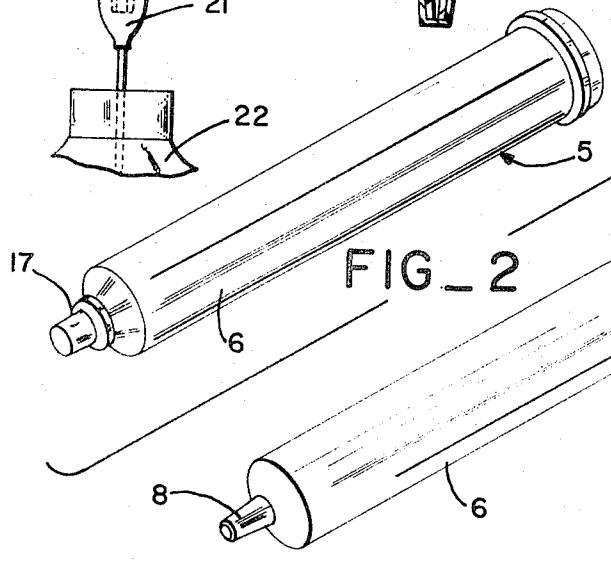


FIG_2

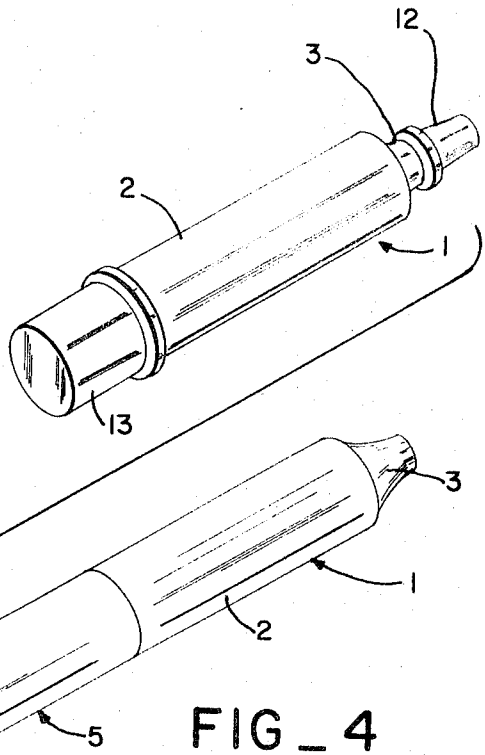


FIG_4

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RADIOPHARMACEUTICAL GENERATOR KIT

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ABSTRACT OF THE DISCLOSURE

A kit readily assembled into essentially a packed chromatographic column for generating technetium-99m labeled pharmaceuticals in a simple two-step process. Technetium-99m pertechnetate in a first step is isolated and its valence state reduced by adsorption upon a reducing agent. Then the reduced technetium-99m in a second step is eluted from the reducing agent by combination with an immediately labeled biological compound, the eluant pH is adjusted and buffered to physiological levels and benign cations are substituted for uncombined reducing agent and isotope ions. A new technetium-99m labeled radiopharmaceutical useful in liver imaging is produced by interaction with the column packing in one specific aspect of the procedure.

This invention relates generally to medical radioisotope organ imaging and function studies and more particularly to simple apparatus and method for producing known technetium-99m labeled radiopharmaceuticals and for producing new technetium-99m labeled radiopharmaceuticals useful in nuclear medicine diagnostic procedures.

One object of this invention is to provide a kit for assembly into a simple radiopharmaceutical generator useful in making technetium-99m labeled radiopharmaceuticals quickly and without the need for a skilled chemist or pharmacist.

Another object of this invention is to provide a simple two-step process for making technetium-99m labeled pharmaceuticals quickly and without the need for a skilled chemist or pharmacist.

Still another object of this invention is to provide apparatus and methods which employ a packing of reducing agent for technetium-99m pertechnetate to isolate and concentrate it to any desired level of radioactivity so that radiopharmaceuticals of known specific concentrations of radioactivity can be made.

An object of this invention also is to provide simple methods and apparatus for eliminating chemical and radionuclidic contaminants from the processed radiopharmaceutical.

One other object of this invention is to provide new and useful pharmaceuticals labeled with technetium-99m.

Other objects and advantages will become apparent from a consideration of the following description and the accompanying drawing wherein

FIG. 1 is a cross-sectional view of the components of the kit of this invention prior to assembly;

FIG. 2 is a perspective view of the kit of this invention shown in FIG. 1 before assembly;

FIG. 3 is a vertical sectional view of the kit of this invention assembled for generation of a radiopharmaceutical; and

FIG. 4 illustrates in perspective the assembled kit of FIG. 3.

This invention includes procedures and apparatus for making pharmaceuticals labeled with technetium-99m which are useful in nuclear medicine for organ imaging. As used herein the term "biological compounds" include single elements, chemical compounds, mixtures of either or both or complexes of other sorts which are chelating agents for reduced technetium-99m that may be administered internally or otherwise without adverse effects to living organisms, particularly to human beings.

The technetium-99m isotope is conveniently available in isotonic solution in the form of the chemically stable pertechnetate ion (TcO^{-}_{4}). Sodium pertechnetate solutions usually are eluted by saline solution in generators or "cows" from the long-lived parent molybdenum-99. The inherent chemical properties of technetium-99m and a number of undersirable characteristics of pertechnetate solutions originating from such generators normally require time consuming and complicated chemicals processing performed by skilled chemists or pharmacists with substantial radiation exposure to make useful technetium-99m labeled pharmaceuticals.

The "cow" eluate frequently contains variable amounts of non-radioactive contaminants such as aluminum and molybdenum ions. It often contains as well, variable amounts of long-lived radionuclidic impurities such as ^{99}Mo, the parent isotope, and neutron activation and fission products such as ^{134}cesium, ^{95}Zr-^{95}Nb, ^{124}Sb, ^{60}Co or ^{46}Sc. The specific concentration of ^{99m}Tc obtained from the "cow" also varies considerably.

^{99m}Tc in the chemical form of pertechnetate (TcO_4) ion is commonly used to image some areas of the body. But due to the imperfect nature of its biological distribution as the pertechnetate ion, drugs such as perchlorate or iodide ion or atropine are often administered to the patient to suppress uptake in areas that might interfere with scan interpretation or to reduce radiation dose to uninvolved organs. For example before ^{99m}Tc-pertechnate is given for brain scanning, relatively large amounts of the aforementioned suppressive drugs are administered to the patient to suppress characteristic uptake in the salivary glands and choroid plexus—events that might interfere with scan interpretation. Thyroid uptake is suppressed as well, thus rescuing this organ from an otherwise gratuitous radiation dose.

It is therefore beneficial to combine ^{99m}Tc with substances which result in a radiopharmaceutical that has a more specific affinity for the organ of interest and a reduced tendency to concentrate elsewhere. For example, $^{99m}TcO_4$ treated with an iron salt plus ascorbic acid, results in a radiopharmaceutical that concentrates in the cortex of the kidney to such a degree that usefully informative scintiphotographs may be taken of that organ. Other preparations of ^{99m}Tc labeled compounds are useful for liver and lung imaging and for placenta localization. Almost all of the chemical processes required to convert pertechnetate ion to useful pharmaceuticals are time consuming and complex. They require services of a skilled radiochemist and substantial radiation exposure.

THE GENERATOR KIT

The generator kit disclosed in FIGS. 1 and 2 assembles into what is essentially a small chromatographic column

illustrated in FIGS. 3 and 4. The kit includes a first tubular section referred to generally as **1**. It has an elongated tubular shell **2**; an integral liquid inlet **3** at one end, such as the illustrated female luer slip fitting; and at the other end a first joinder means **4**, such as the illustrated male taper which assembles to a corresponding taper in the second tubular section referred to generally as **5**.

The second tubular section **5** includes an elongated tubular shell **6**; a second joinder means **7** at one end, such as the female taper **7** for quick and vacuum-tight assembly to male taper **4** of the first tubular section of the kit as is shown in FIG. 3; and at the other end an integral liquid outlet **8** such as the illustrated male luer slip fitting. A first inert porous disc **9** and a second inert porous disc **10** define with shell **2** a first processing zone within the first tubular section **1** which is packed with a particulate or sintered reducing agent **11** for technetium-99m pertechnetate. The porous discs **9, 10** may be inert coarse filters press-fit into shell **2** or one of them, such as porous disc **9** may be integrally molded with the shell from linear polyethylene or polypropylene or other physiologically and chemically inert materials. The pore size permits liquid flow but confines the reducing agent packing within the first processing zone. Porous disc **10** press-fits into shell **2** after reducing agent **11** is packed. The reducing agent for technetium-99m pertechnetate is a particulate metal powder or sinter which is aseptically packed dry and dry heat sterilized. Plastic caps **12** and **13** over each of its ends, seal the first tubular section **1** and preserve sterility until its use.

The second tubular section **5** carries a third porous disc **14** at its lower end adjacent to liquid outlet **8**. This disc has a pore size in the order of 5 microns in diameter. It may be molded integrally with a polyethylene or polypropylene shell **6** or may be press-fit filter material such as nylon, Teflon, sintered stainless steel or a glass frit. Shell **6** between the end of female taper **7** and porous disc **14** defines a second processing zone packed with a cation exchange resin **15**. Such resins normally are autoclave sterilized and stored wet. Plastic caps **16** and **17** close the ends of the second tubular section **5** of the kit and preserve sterility until its use.

For use in processing a radiopharmaceutical, protective plastic caps **12, 13, 16** and **17** are stripped from the kit components and the first and second tubular sections are assembled into a complete column as is illustrated in FIG. 3. The joint between the tapered joinder means **4** is vacuum tight. Liquids to be processed through the column are introduced through inlet **3** by means of hypodermic syringe **20**. They are moved or assisted through the column by needle **21** attached to outlet **8** and affixed to vacuum bottle **22**.

For the examples described herein tubular shells **2, 6** were 7–8 millimeters in inside diameter and defined first and second processing zones about 10 centimeters long. While the precise dimensions are not critical, the first processing zone must provide enough reducing agent packing and residence time to adjust the pH of the eluant during the second processing step and to buffer it to physiologically acceptable levels within the range of 5 to 8. On the other hand, the second processing zone must provide enough cation exchange resin and residence time to remove all uncombined reducing agent and radioisotope-carrier ions.

THE PROCESS AND PRODUCT

The described kit is used to generate radioisotope labeled pharmaceuticals by a simple two-step procedure. In a first step hypodermic syringe **20** of an appropriate size introduces the labeling technetium-99m pertechnetate dispersed in a first carrier liquid, such as normal saline solution, to the column through inlet **3** to the first processing zone packed with particulate reducing agent **11**. The particulate reducing agent is a metal more electronegative than hydrogen, such as iron. Needle **21** and vacuum bottle **22** assist the syringe contents to pass through the column.

The reducing agent **11** adsorbs or isolates substantially all of the technetium-99m in the initial portion of the zone—with the dimensions described, within the first one-fourth inch of the packing. Substantially all of the radioactivity collects upon this portion of the packing regardless of the concentration of the technetium-99m pertechnetate in the first carrier liquid or the quantity of the carrier liquid put through the column. Thus, as much radioactivity as is desired may be concentrated on the initial portion of the reducing agent packing. The total amount of trapped radioactivity can be measured directly by its radiation. The first carrier liquid passes through the column and collects in vacuum bottle **22** stripped of substantially all of its radioactive component. With it pass all chemical and radionuclidic impurities in the "cow" eluate that do not adhere to the column packing materials.

In a second step another hypodermic syringe introduces a known volume of special eluant to the column assisted by a second sterile vacuum bottle **22** affixed to needle **21** at the bottom of the column. The eluant is a physiologically benign second carrier liquid carrying a dispersion, either in solution or suspension, of a biological compound that combines irreversibly with the reduced technetium-99m residing on the reducing agent packing in the initial portion of the first processing zone. The biological compound may be one of the group of instantly labeled chelating agents including albumin which are known to concentrate in particular human organs of interest in predictable amounts. It should be effective at physiological ion concentrations (about 150 meq. per liter) and should not precipitate or form large particles during passage through the column. The pH of the special eluant is adjusted, as required, to provide the requisite environment for combination of the biological compound and reduced technetium-99m. The pH of the special eluant initially should be less than 6.

The eluant carries the biological compound, now labeled with technetium-99m, through the remainder of the first processing zone wherein its reaction with the reducing agent packing adjusts the pH to and buffers it at physiologically acceptable levels, in the pH range of 5–8 for example. The second carrier liquid and its dispersion then passes through the second processing zone packed with cation exchange resin. A strongly acidic cation exchange resin composed of nuclear sulphonic acid exchange groups attached to a styrene-divinylbenzene polymer lattice is used. The resin is sodium cycled so that physiologically benign sodium ions are substituted for any uncombined reducing agent or radioisotope or other cations present in the passing eluant.

Pharmaceuticals and desired specific concentration are made by eluting the column in the second step with a volume of eluant that corresponds to the measured amount of radioactivity isolated in the first zone packing. Typical process parameters are shown in the following examples.

Example I.—Technetium-99m-iron-ascorbic acid complex

A technetium-99m iron ascorbic acid complex of the type often used for kidney imaging has been generated by the process and kit described in 5 to 10 minutes by a non-skilled technican. The first zone of the kit was packed with about 6 grams of 325 mesh (U.S. seive size) powdered iron. The second zone was packed with about 8 cc. (wet) of 100–200 mesh sodium cycled cation exchange resin, such as AG50W–X8 manufactured by Bio Rad Company of Richmond, Calif.

About 10 cc. of a normal saline solution carrying pertechnetate ions eluted directly from the ^{99}Mo "cow" at a radioactivity concentration of about 2 millicuries per cc. was introduced by syringe to the assembled kit in a first

step. This material was run through the column at a slow rate on the order of one-tenth cc. per second. Ninety-nine percent of the original radioactivity adhered to the first one to two millimeters of powdered iron in the first zone of the column.

Then a second syringe introduced to the column four millimeters of 0.15 normal aqueous ascorbic acid solution. The net yield of technetium-99m labeled pharmaceutical was 55 percent of the total technetium-99m activity initially present in the "cow" eluate.

The biological distribution of the resulting pharmaceutical in rats three hours after intravenous injection was 8 percent in the kidneys, 53.7 percent in the urine-bladder and 3.5 percent in the liver.

Example II.—Technetium-99m-iron-albumin complex

A new technetium-99m-iron-serum albumin complex has been generated in 5–10 minutes which concentrates in the liver and is useful for liver imaging.

Six grams of 100 mesh (U.S. sieve size) hydrogen reduced iron pack the first zone of the kit and 8 cc. of sodium cycled cation exchange resin as in Example I pack the second zone. Ten cc. of the saline pertechnetate solution as used in Example I was introduced to the kit in a first step as in Example I. The pertechnetate trapping efficiency was about 92 percent. In a second step four milliliters of eluant comprising ten mililgrams per milliliter of bovine serum albumin dissolved in 0.6 normal hydrochloric acid was then introduced to the column.

The net yield of technetium-99m labeled pharmaceutical was 55 percent of the total technetium-99m activity initially present in the "cow" eluate. Combined iron in the effluent pharmaceutical from the column was 0.35 milligram of elemental iron per milliliter or a total of 1.4 milligrams. Biological distribution in rats ½ hour after intravenous injection was 69.5 percent in the liver and 1.0 percent in the spleen. There was no reaction to the foreign protein.

This pharmaceutical is unique in its composition. It is believed to be an albumin-technetium-99m-iron complex which, if particulate, has a particle size of less than 0.22 micron. In this state the complex is useful for liver imaging.

Application of heat, for example heating the pharmaceutical at 100° F. for 5 minutes, agglomerates the complex into particles barely visible to the naked eye. These particles averaging 20–100 microns in size concentrate in the lungs like known technetium-99m labeled macroaggregated human serum albumin.

Example III.—Technetium-99m tin colloid complex

A technetium-99m labeled tin colloid for use in liver imaging was similarly prepared in 5–10 minutes. The packing in the first zone was tin powder of greater than 325 mesh (U.S. sieve size) with the same cation exchange resin and saline solution of pertechnetate ions as in Examples I and II. The trapping efficiency for the pertechnetate ion was 98.8 percent.

In a second step four milliliters of two normal hydrochloric acid was eluted through the column to yield 74.5 percent of technetium-99m labeled pharmaceutical based on the original technetium-99m activity in the "cow" eluate. A high concentration in the liver of experimental rats is observed after intravenous injection.

The radiopharmaceuticals listed below have been prepared using the described procedures and kit with satisfactory yields. They have useful biological distributions and are physiologically benign.

Reducing agent packing	Eluant	Organ of greatest concentration
Iron	Ascorbic acid	Kidney, bladder.
Do	Citric acid	Do.
Do	Diethylene triamine pentacetic acid	Do.
Do	Salicylic acid	Do.
Do	Glycine	Liver.
Do	HCl plus serum albumin	Do.
Do	HCl plus serum albumin plus heat	Lungs.
Tin	HCl	Liver.
mg	Ascorbic acid	Same as TcO_4^-.

The above examples and the described apparatus and procedures are for illustrative purposes only. It will be apparent to those skilled in the art that other technetium-99m labeled pharmaceuticals may be similarly prepared and the process parameters may be modified within the scope of the invention defined in the following claims.

We claim:

1. A kit for assembly into a packed column for making technetium-99m labeled pharmaceuticals comprising
a first tubular section having a first tubular shell;
a liquid inlet at one end of said first tubular shell;
first joinder means at the other end of said first tubular shell;
a first and a second porous disc enclosing a first processing zone within said first tubular shell adjacent said inlet;
a reducing agent for technetium-99m pertechnetate packed within said first processing zone;
a second tubular section having a second tubular shell;
a liquid outlet at one end of said second tubular shell;
second joinder means at the other end of said second tubular shell for airtight assembly to said first joinder means;
a third porous disc adjacent said liquid outlet;
and a cation exchange resin packed within a second processing zone defined in the second tubular shell between said first processing zone and said third porous disc.

2. The kit of claim 1 further comprising removable asceptic sealing means on said liquid inlet, said first and second joinder means, and said liquid outlet.

3. The kit of claim 1 wherein said reducing agent is a metal more electronegative than hydrogen.

4. The kit of claim 1 wherein said reducing agent is one of iron, tin and magnesium.

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JOSEPH SCOVRONEK, Primary Examiner

U.S. Cl. X.R.

250—106 T; 252—301.1 R; 424—1