Dec. 26, 1972 D. O. KUBIATOWICZ 3,707,353

RADIOACTIVE LABELING KIT

Filed March 26, 1970

FIG. 1

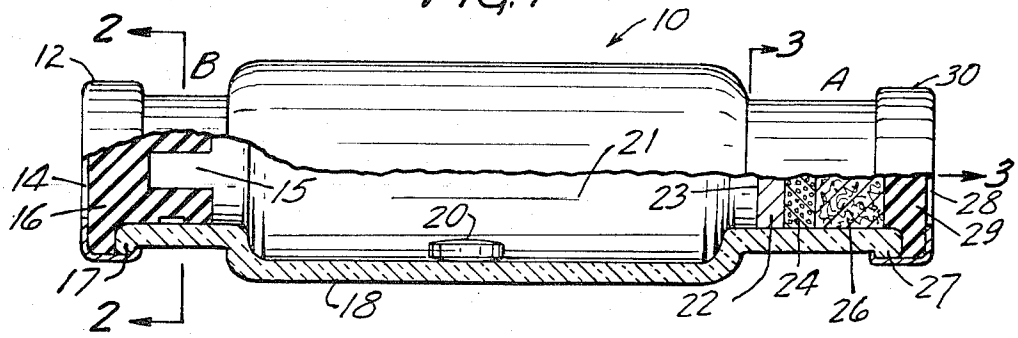


FIG. 2

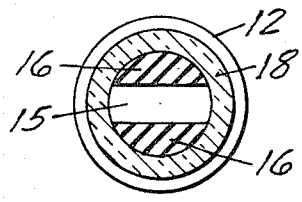
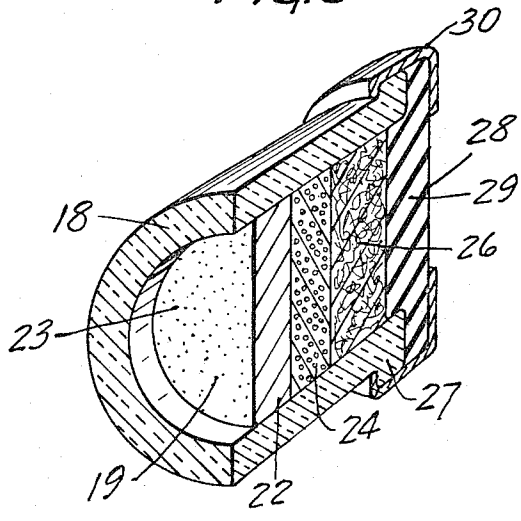


FIG. 3



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RADIOACTIVE LABELING KIT

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ABSTRACT OF THE DISCLOSURE

A single-unit labeling kit for radioactively labeling biodegradable microparticles for medical diagnosis and the like comprises, generally, a container having at least one open end; a porous filter plate mounted within the container separating the container into first and second compartments; a plurality of biodegradable microparticles in the first compartment; a solid source of hydrogen ion in the second compartment; a reagent tablet in the first compartment, the tablet comprising a reducing reagent and a non-reactive, non-toxic wetting agent to aid in forming a suspension of the microparticles when a liquid is introduced into the container; and means to temporarily seal the open end of the container, such means capable of receiving a syringe needle for placing a liquid in the container and for the removal of radioactively labeled microparticles. The microparticles are labeled by introducing a solution containing radioactive technetium into the end of the container carrying the solid source of hydrogen ion, acidifying the solution by passing it through the solid source of hydrogen ion and through the porous filter plate into the first compartment, agitating the acidified solution to suspend the microparticles and dissolve the reagent tablet, heating the container to complete the labeling reaction, cooling the container, and removing the supernatant containing unreacted radioactive elements and spent reagents, leaving the labeled microparticles behind on the porous filter plate which may thereafter be removed for use.

BACKGROUND OF THE INVENTION

The present invention relates to a labeling kit for radioactively labeling biodegradable microparticles for medical diagnosis. More particularly, the invention relates to a simplified system for labeling biodegradable microparticles by using a special reaction container containing therein all the necessary ingredients for such labeling exclusive of the short half-life labeling radionuclide.

At present, radioactively labeled microparticles are used in hospitals and clinics as the desired radioactive emissions of these particles are useful for diagnostic, prophylactic, and therapeutic purposes. For example, such tagged or labeled microparticles may be injected into the blood stream to be later filtered out by the lung. A lung scanner may then be used to scan the body to obtain an outline of the lung on an oscilloscope, paper, photograph, and the like. If such tagged particles are not found in the lung, the physician may determine that there is not proper circulation in that lung. Similarly, if a tumor is present in the body, such tumor, if vascular, would need a high concentration of blood. Thus, the labeled microparticles in the blood would tend to concentrate at the tumor.

A radioactive nuclide commonly used to label particles is radio-technetium (^{99m}Tc) obtainable from a commercial generator which is generally available in most hospital and clinics. Presently, the components used to label the particles are maintained separately outside the container in which the labeling is to be done. Dry microparticles are suspended in a detergent and water, technetium is

added, sodium thiosulfate, a reducing reagent necessary for labeling with ^{99m}Tc, is added to the mixture, after which an acid is added to aid in the labeling, all of these ingredients being separately maintained outside the mixing vial. After the labeling reaction, not all of the radiotechnetium is attached to the particles, leaving some in the solution. It is not desirable to inject unbound technetium into the body because it will go to other places in the body resulting in a poor lung scan and may also expose other areas of the body to an undesirable radiation dose. Thus, the unbound technetium must be separated from the labeled microparticles. This is done by allowing the beads or particles to settle down and thereafter decanting or drawing off the waste reaction products and technetium. This is difficult because some of the labeled particles are also drawn off. Attempts have been made to label microparticles in a filter vessel which obviates the need to decant or draw off waste reaction products and technetium. However, all of the components used to label the particles are maintained separately outside the filter vessel. Applicant is not aware at this time, of any convenient, single-unit radioactive labeling kit for labeling microparticles.

SUMMARY OF THE INVENTION

According to the present invention, a labeling kit system for conveniently labeling or "tagging" biodegradable microparticles with a radioactive nuclide employs a special reaction container which contains all the necessary labeling ingredients therein exclusive of the nuclide. The labeling kit comprises, generally, a container having at least one open end; a porous filter plate mounted with the container and separating the container into first and second compartments; a plurality of pharmaceutically acceptable microparticles in the first compartment; at least one labeling reagent in said container; and means to temporarily seal the open end and capable of receiving a syringe needle for placing a liquid in the container and for the removal of radioactively labeled microparticles. The components of the kit may vary depending upon the radio nuclides used to label the microparticles.

A non-reactive, non-toxic wetting agent may additionally be placed in the first compartment to aid in the suspension of the microparticles. Further, where radio-technetium is employed, there is a reducing agent in the first compartment serving as the labeling reagent, and a solid source of hydrogen ion is in the second compartment.

The term "labeling reagent" is used herein to describe a material which causes either the microparticles or the radio nuclide used to label the microparticles, to assume a suitable state for attaching the radioactive nuclide to the microparticles. For example, one labeling reagent is sodium thiosulfate which serves as a reducing agent, the purpose of which is to reduce the original pertechnetate to a usable lower oxidation form of technetium, the reduction being in the presence of acid. In this case, both the reducing agent and a source of hydrogen ion are necessary ingredients in the labeling kit. Similarly, sodium paratoluene chloro-sulfonamide, an oxidizing agent, is used as a labeling reagent with radio-iodine to oxidize the iodide to a usable labeling form which is done in the presence of suitable buffers, both the oxidizing agent and the buffers being components of the kit. On the other hand, no labeling reagents are necessary when using radio-iron or radio-indium, although, even here, a labeling reagent is preferred to insure the best results. Such a labeling reagent would be ferric chloride in the presence of suitable buffers. The actual mechanistic pathways involving the labeling reactions are uncertain at present. It is known, however, that certain labeling reagents are necessary when using certain radio nuclides, which are hereinafter described.

The invention will be better understood with reference to the drawing wherein:

FIG. 1 is a partially cut-away view of the labeling kit of the present invention,

FIG. 2 is an end view of the labeling kit along lines 2—2 of FIG. 1, and

FIG. 3 is a sectional view, in perspective, taken along 3—3 of FIG. 1.

The following description is directed to one preferred embodiment which is a single-unit labeling kit for labeling microparticles with radioactive technetium. Various modifications of the kit when using other radionuclides would be obvious to one skilled in the art.

Referring to the drawings, particularly FIG. 1, the preferred labeling kit **10** of the present invention comprises generally an elongated vial **18** designed to have necks **17** and **27** on each end, each neck being open and capable of receiving stoppers **16** and **29** to seal the container. In the neck at one end of the container (designated as A) is mounted a porous filter plate (e.g. sintered) **22**. Preferably, the plate **22** is a glass frit and has deposited on the face **23** thereof, a plurality of biodegradable microparticles **19** which are to be labeled with a radionuclide and injected into the body for clinical diagnosis and the like.

In one useful embodiment the diameter of the vial, as illustrated, is about 25 mm. outer diameter in the center and about 17 mm. outer diameter in the neck. Thus, the porous filter plate **22** has a diameter of about 13 mm. The dimensions of the vial may vary depending on the use desired. The porous filter plate **22**, however, must be of a diameter to completely fuse to the vial around the periphery of the plate. The thickness of the plate is preferably about 2½ mm. as such thickness is suitable for holding the microspheres and yet allowing saline solution introduced into the container during labeling to pass freely therethrough. The pores of the porous filter plate are from about 5.5 to 6.5 microns. The finely porous filter plate **22** may be made from suitable materials other than sintered glass, for example, porcelain, metal, plastic and the like. The material used should be non-reactive with the ingredients in the vial and the pores should be such that they will prevent the microparticles from passing through.

Immediately adjacent said plate **22** is deposited a plurality of small acid resin particles **24**. The acid resin **24** is present to provide hydrogen ions which create an acid solution necessary to complete the labeling reaction. The resin particles are held in place by means of a packing material **26** which in turn is held in place by a pharmaceutical rubber stopper **29**. On the other end of the container (designated as B), the neck of the vial **14** is also stopped by means of the pharmaceutical rubber stopper **16**, having an indentation **15** therein. The purpose of the indentation **15** is to provide a space for the creation of reduced pressure in the vial during manufacture of the labeling kit. Other suitable means for creating such reduced pressure could be employed, thus eliminating the need of a stopper having a certain configuration. The stoppers are sealed in the vial by means of aluminum caps **12** and **30** which are crimped onto the vial. Located in the central compartment **21** of the vial is a reagent tablet **20** containing, where necessary and desirable, a reducing reagent for the labeling reaction and a wetting agent to aid in suspending the microparticles.

In the preparation of one embodiment of the labeling kit, sterile microparticles are suspended in an inert volatile solvent such as a mixture of diethylether and 1,1,2-trichloro-1,2,2-trifluoroethane the latter ingredient available as "Freon 113," the mixture preferably being ⅓ ether, ⅔ Freon. The suspension is aseptically dispensed into an empty sterile labeling vial with the end designated as B in an upward position. The ether-Freon mixture is withdrawn by suction through end A at **28**, allowing the microparticles, usually having a diameter of from about 15 to 30 microns, to be retained by the porous glass frit or plate **22**, the pores of which are smaller than the diameter of the

microparticles. The sterile reagent tablet **20** is then added to the compartment through B and end B is temporarily closed with a rubber stopper **16**. The vial is then turned over with end A up and sterile acid resin particles **24** are added to the compartment through end A and are held in place with packing material **26**. End A is then stoppered and capped. Finally, the vial is subjected to reduced pressure through end B to create a slight vacuum of about ⅓ atmosphere after which end B is also capped. The microparticles, however, do not have to be deposited on the plate **22** although this is preferred as the particles may conveniently be dispensed in a known volume of solvent rather than having to be weighed. For example, the microparticles could be merely placed loosely in the container or could be included in the reagent tablet.

Although the configuration of the glass vial **18** as illustrated in FIG. 1 is preferred, the vial can be made longer, shorter, broader, or thinner varying the dimensions in a number of ways, it being important only that the vial have at least one open end for receiving the appropriate liquids and for removing liquids and the labeled microparticles. The vial may be made from materials other than glass which are sterilizable, non-reactive, non-toxic and capable of withstanding relatively high temperatures, for example, polytetrafluoroethylene (Teflon). Glass is preferred because the labeling reaction may be visually observed, it is chemically inert, and because of its pharmaceutical acceptability.

The microparticles which may be used for purposes of the present invention are particular compositions comprising a physiologically acceptable, solid, substantially water-insoluble (at body temperature) material which can be metabolized or degraded in a manner which does not form toxic residues when solubilized (apparently by enzymes or other metabolic mechanisms) in the parental body fluids, such as blood, serum, plasma, lymph, and the like. When so metabolized or degraded, these substances are solubilized. Suitable materials for the particular composition are physiologically acceptable proteinaceous substances, such as albumin, gelatin, hemoglobin, and the like, or polysaccharides such as amylose, inulin, glycogen, and starch or the same material containing a physiologically acceptable carrier such as ferric hydroxide, silver iodide, or the like. When the particles have been labeled, they are resistant to leaching of the radionuclide when immersed in water at about 37° C. for at least about 15 minutes.

For use in diagnostic procedures or treatment requiring radionuclides to be directed to a particular locale in the body, the material is prepared in a finely divided state, the sizes of the particles being closely controlled by sorting techniques so as to be in a narrow size range adapted to the specific use. Particles thus segregated in the narrow ranges can be from about ½ to 1000 microns in average diameter, and preferably the size ranges chosen do not vary more than about plus or minus 20% from the mean.

Preferably, spheroidal or essentially spherular particles are employed as they are more uniform and more easily controlled with respect to radionuclide content and time of elimination from the body. Spherules from ½ to 60 microns in diameter are most useful for diagnostic purposes. Larger spherules, even up to 1 mm. in diameter, can be used for certain therapeutic purposes. Being uniform in their dimensions, spheroidal or spherular particles are more easily controlled with respect to radionuclide content and time of elimination from the body. Particularly, they are preferred because, by matching the diameter of the spheroid to the size of the body passages, e.g. arteries, capillaries, etc., one can predict their route through a healthy body and determine where they should lodge with high accuracy. The total weight of the microspheres preferably used in the labeling vial of the present invention can vary from about 0.1 to 50 mg. while the size of individual microspheres can vary from about ½ to 100 microns.

The solid source of hydrogen ion is used to acidify the radioactive nuclide solution that passes through the porous filter plate into the container carrying the tablet when radio-technetium is used. The acidification is required to aid in the labeling reaction although the exact mechanism is not known. An example of a useful solid acid material is a strongly acidic cation exchange resin composed of nuclear sulfonic acid exchange groups attached to a styrene divinylbenzene polymer lattice, available commercially under the trade name "Dowex 50X8." Similar types of resins which may be used are "Duolite C–20," "Amberlite IR–120," "Zeocarb 225," "Nalcite HCR," and "S–115." Other types of strong acid resins may also be used. For example, a resin containing methylene sulfonic groups on a phenolic lattice is represented by the following trade names: "Bio-Rex-40," "Duolite C–3ab," and "Zeocarb-215." Crystalline acids such as trichloroacetic acid, citric acid, potassium bisulfate and others can be used in place of the acid resin.

The solid source of hydrogen ion makes available a mobile hydrogen ion which may be exchanged with a sodium ion from the saline solution containing the radionuclide which is introduced into the container. Sodium ions react with the resin to release a chemically equivalent amount of hydrogen ions. Thus, the amount of hydrogen ions released, acidifying the radionuclide-carrying saline solution, is controlled by the amount of the resin that is used. Generally, from about 100 mg. to 500 mg. of resin per vial is satisfactory for most applications. The configuration of the acid resin is preferably spherular to present a relatively uniform surface area for ion exchange to achieve uniform flow rate, for ease of dispensing, and its use results in freedom from small particles. The diameter of the spherules is from about 50–1000 microns, and preferably 500–700 microns.

After the resin is introduced into the vial at A, the resin is held in place by a small amount of packing material **26**. The packing material can be glass wool, cotton, plastic, sponge or other porous materials, or the packing may be eliminated altogether. The packing is helpful to insure that none of the resin will escape the vial during manufacture and also to disperse the resin over a fairly uniform surface area. It is further helpful in insuring that there is a space between the stopper **29** and the resin **24** for the insertion of the solution containing the radionuclide.

The reagent tablet **20** basically comprises sodium thiosulfate, where radio-technetium is used, and a wetting agent such as detergent. The sodium thiosulfate aids in the labeling reaction as a reducing reagent while the wetting agent aids in the suspension of the microspheres to insure uniform labeling The reducing agent aids in the reduction of $^{99m}TcO_4^-$, the state in which technetium is generally obtained, when in the presence of acid. The remaining ingredients in the tablet are generally inert and may be any of several pharmaceutical adjuvants which are generally used in the manufacture of tablets, such as a filler (lactose), binder (polyvinylpyrrolidone) and a lubricant (benzoic acid). The dimensions and composition of the reagent tablet can be varied or the tablet can be eliminated and replaced with sodium thiosulfate crystals or a mixture of sodium thiosulfate and an inert filler such as lactose.

The detergent which is preferably used for purposes of the present invention is poloxalene which is a non-ionic surfactant of poly(oxethylene), poly(oxpropylene), and poly(oxethylene) polymer commercially available as "Pluronic F–68" from Wyandotte Chemical Co. Another example of a detergent which may be used is a mixture of polyoxethylene ethers of mixed partial oleic esters of sorbitol anhydrides which is commercially available as "Polysorbate 80." Various other detergents may be used providing they are non-toxic and do not interfere with the labeling reaction.

The sodium thiosulfate content of the reagent tablet

may vary from 0.5 mg. to 10 mg. Other known reagents may be used in place of the sodium thiosulfate such as thioacetamide, tin, zinc, stannous chloride, although the sodium thiosulfate is preferred because of its performance in the labeling reaction. Where radionuclides other than radio-technetium are used, other suitable reagents are used where necessary. For example, an oxidizing agent, sodium para-toluene chloro-sulfonamide, available as "Chloramine T," is used with radio-iodine, and, buffer salts such as sodium dihydrogen phosphate and disodium hydrogen phosphate, in combination with ferric chloride, are used with radio-iron and radio-indium. In some cases, for example, when using radio-iron and radio-indium, the use of a reagent is optional although generally preferred for most applications. When a reagent is not used, as with the above radionuclides, labeling may be accomplished by agitating the microparticles in a solution containing the radioactive nuclide, thus not using a wetting agent, solid acid materials, or reducing agents as components of the kit.

Depending upon the radionuclide used, the reagent or reagents may be in either the first or second compartment or both. In the preferred embodiment, the labeling reagent, sodium thiosulfate is in the first compartment designated at **21** whilte the solid source of hydrogen ion or acid resin **24** is in the second compartment so that the solution is acidified when it comes in contact with the reagent. Where sodium paratoluene chloro-sulfonamide is used as the labeling reagent, it may be in either compartment, preferably the first, while the buffer may also be in either compartment, but preferably the second. What is unique is that all of the reagents, whatever they are, are all contained within a single unit.

The radionuclide which is to be used to label the microspheres, is obtained from a commercial generator generally referred to in the art as a "cow." Exemplary of radioactive materials which may be used for labeling microparticles, as previously noted, are radio-iodine, radio-iron, radio-technetium, radio-indium, and other suitable radionuclides, used in conjunction with suitable reagents. Radio-technetium (^{99m}Tc) is preferably used because of its gamma emission energy and general availability. Technetium is eluted from the generator, or "cow," by passing saline solution therethrough which carries the ^{99m}Tc out of the generator and into a collecting vial. The saline solution containing the radio-technetium is then withdrawn from the vial by means of a syringe.

When the particles are to be labeled, the needle of the syringe containing the radio-technetium in the saline solution is pushed through the rubber stopper **29** into end A of the vial at **28**. The reduced pressure inside the vial, which was created during the manufacture thereof, draws the radio-technetium solution over the resin, through the glass frit and into compartment **21** at a controlled rate. The ion exchange between the resin and the isotope-containing saline solution is as follows:

$$Na^{99}TcO_4 + NaCl + H^+ \text{ resin} \rightarrow Na^{99m}TcO_4 + HCl + Na \text{ resin}$$

resulting in an acid solution. Thus, by controlling the size of the needle and the vacuum, one can control the flow over the resin. Preferably, about 10 ml. of the solution is passed over the resin in about 45 seconds at ⅕ atmosphere. The flow rate is important because as the radio-technetium passes over the resin, the sodium ions in the saline solution exchange with the hydrogen ions in the resin. If the solution passes too rapidly over the resin, there will not be a proper exchange of sodium and hydrogen ions. Thus, this rate must be controlled.

The vial, containing the radio-technetium in solution in the compartment containing the tablet may be immersed in an ultrasonic bath to aid in suspending the microspheres deposited on the glass frit and to help dissolve the tablet. As the tablet is dissolved, sodium thiosulfate and the detergent are released. The vial is then immersed in warm,

preferably boiling, water and may be agitated to complete the labeling reaction. The vial may then be cooled after which the supernatant containing the unreacted radio-technetium and spent reagents is withdrawn through the vial at end A, leaving the labeled microspheres behind on the porous filter plate **22** on the face **23** thereof. Saline solution (or other solutions used as a vehicle for injections) containing detergent can be added to compartment **21** through end B for suspension and injection of the labeled microspheres, or the microspheres may be washed once or several times prior to injection with saline which is removed after washing as heretofore described.

Where microspheres smaller than 6 microns are to be labeled, such as those that might be used for liver scanning, the above procedure is followed except that the supernate is not withdrawn through end A. Rather, a suitable buffer, such as sodium dihydrogen phosphate and disodium hydrogen phosphate, in combination, is added to compartment **21** through end B to neutralize the acid of the reaction. The small microspheres are then injected in this buffered solution.

With a slight modification of the labeling kit of FIG. **1**, the kit can be made to contain its own ^{99m}Tc generator such that the user would not need a commercial generator on hand. Such a complete kit would be useful to the investigator whose clinical volume is not large enough to justify the purchase of a separate ^{99m}Tc generator. To so modify the kit, about 100 mg. of granular aluminum oxide is sandwiched between the resin **24** and the packing **26**. About 5 to 100 millicuries, preferably about 20 millicuries of $(NH_4)_2{}^{99}MoO_4$-$^{99m}TcO_4$ (ammonium molybdate), is pipetted onto the top of the aluminum oxide and dried. The amount of ammonium molybdate used must be sufficient to produce an effective labeling amount of radio-technetium. End A is then sealed after which the vial is evacuated through end B and sealed. A needle of a syringe containing about 10 ml. saline solution is pushed through the rubber stopper **29** at A, the inside vacuum of the vial (⅓ atmosphere) draws the saline over the aluminum oxide, over the resin **24**, through the porous filter plate **22** and into the center compartment **21** at a controlled rate. As the saline passes over the aluminum oxide, $Na^{99m}TcO_4$ is stripped from the absorbed $(NH_4)_2{}^{99}MoO_4$ which remains immobile. As the saline containing $Na^{99m}TcO_4$ passes over the acid resin **24**, HCl is obtained such that acidified $Na^{99m}TcO_4$ passes through the porous filter plate **22** into compartment **21**. The kit is then used as heretofore described.

In addition to labeled albumin microparticles being used for clinical diagnosis and the like, labeled colloidal sulfur (also sometimes referred to as "sulfur colloid") has also been used. As the same reagents are used in each case, the labeled colloidal sulfur may be prepared using the labeling kit of the present invention simply by leaving out the microparticles. The same procedure is followed as with labeling micropsheres except that the supernate is not removed but a buffer solution is added to neutralize the acid of reaction and the ^{99m}Tc colloidal sulfur is ready for use. The use of human serum albumin microparticles is preferred, however, because of their constancy of size and physical stability characteristics.

The invention will be further understood by reference to the following illustrative, but non-limiting examples, in which all parts are by weight unless otherwise noted.

Example 1

Four milliliters of a commercially-obtained pharmaceutical grade of human serum albumin (obtained from E. R. Squibb & Sons, New York, N.Y.) were injected, conveniently through a hypodermic needle, in about 1 liter of vegetable oil (cotton seed oil) which was heated to about 30–50° C. The rate of stirring determines the ultimate size of the spherule material obtained. Using a container which was greater in height than in diameter, with a 25 gauge hypodermic needle and stirring at about 500 r.p.m. with a 2½ inch propeller-type stirrer microspherular particles of about 10–20 microns in diameter were obtained. Stirring was continued while heating to 110°–150° C. until all of the water in the microspheres was removed, as was determined by removal from the mixture of a small number of spheres to determine whether or not they were still tacky. After removal of the water, the particles were filtered away from the oil and washed in diethylether. Microspherule particles of albumin were obtained.

Example 2

A radioactive labeling kit according to the present invention was prepared as follows: Sterile human serum albumin microspheres were suspended in 200 ml. of a mixture of diethylether and 1,1,2-trichloro-1,2,2-trifluoroethane (⅓ ether and ⅔ of 1,1,2-trichloro-1,2,2-trifluoroethane). To obtain about 5 mg. of microspheres, 1 ml. of the mixture was withdrawn and aseptically dispensed into an empty sterile labeling vial as illustrated in the drawings with end B in an upward position. The ether and 1,1,2-trichloro - 1,2,2 - trifluoroethane mixture was withdrawn by suction through the opposite end A. The microspheres of 15–30 microns in diameter were retained by the porous glass frit having pores of 5.5–6.5 microns. A sterile reagent tablet was added to the vial through end B which then was temporarily closed with a rubber stopper. The reagent tablet was of the following composition:

	Mg.
Sodium thiosulfate	0.55
Lactose	67.2
Non-ionic surfactant of poly(oxethylene), poly(oxpropylene), and poly(oxethylene) polymer (Pluronic F–68)	0.3
Polyvinylpyrrolidone	1.66
Benzoic acid	6.0

Properties: hardness (Strong Cobb Test) 4.5 kg. Solution time 2–4 min.

With end A up, 200 mg. of sterile "Dowex 50" resin was added to the vial resting on the glass frit and was held in place with cotton packing material. End A was then stoppered with a pharmaceutical rubber stopper and capped. The vial was then evacuated to ⅓ atmosphere and capped.

Example 3

The labeling vial prepared according to Example 2 was used to label human serum albumin microspheres with radio-technetium ($Na^{99m}TcO_4$). The needle of a syringe containing 6 ml. (about 12 millicuries) of $Na^{99m}TcO_4$ in saline solution obtained from a commercial generator was inserted into the resin-containing end of the glass vial. The inside vacuum of the vial (about ⅓ atmosphere) pulled the $Na^{99m}TcO_4$ solution over the Dowex resin, through the glass frit and into the center of the vial where the reagent tablet was located. The vial was then agitated and sonicated in an ultrasonic bath for 2 min. to dissolve the tablet and release sodium thiosulfate and the detergent. The vial was removed from the bath and placed in boiling water and agitated for 6 min. to complete the labeling reaction after which the vial was cooled in tap water for 2 min. The supernate containing unreacted $Na^{99m}TcO_4$ and spent reagents was then withdrawn with a syringe through the end of the vial designated as A in the drawings and containing the resin and packing. The labeled microspheres remained behind deposited on the glass frit. Six ml. of isotonic saline solution containing 0.05% Polysorbate 80 was added to the vial through the other end of the vial designated as B to resuspend the labeled microspheres.

The labeled microspheres were then tested in mice by withdrawing 0.2 ml. of the saline solution with Polysorbate 80 and containing 0.1 mg. of ^{99m}Tc labeled microspheres (about 0.2 millicuries) and injecting the mixture

into the tail veins of white female mice. The mice were sacrificed 30 minutes later and dissected. ^{99m}Tc activity was measured in the animals' carcass, lungs and liver. From this data ^{99m}Tc distribution in the mice was computed. One to three mice were used in the testing of each labeling kit.

In the following table, the percent uptake refers to labeling efficiency while the other numbers refer to distribution of the ^{99m}Tc in white mice ½ hour after injection with the labeled microspheres. Twelve kits were used to obtain this data.

TABLE I

	Average	± Standard deviation (each kit)
Percent uptake	79.0	5.7
Percent in lung	77.0	5.7
Percent in liver	5.8	1.2
Percent in carcass	12.2	4.8
Lung/liver ratio	14.1	4.6

Example 4

Animal testing similar to that of Example 3 was performed using a vial as prepared in Example 2 except that 350 mg. of Dowex resin and 10 ml. of $Na^{99m}TcO_4$ (about 20 millicuries) were used. The reagent tablet had the following composition:

	Mg.
Sodium thiosulfate	1.85
Lactose	65.20
Non-ionic surfactant of poly(oxethylene), poly-(oxpropylene) and poly(oxethylene) polymer (Pluronic F–68)	1.00
Polyvinylpyrrolidone	1.66
Benzoic acid	6.0

Further, the labeled microspheres were washed with 10 ml. of saline solution (containing 0.05% Polysorbate 80, a mixture of polyoxethylene ethers of mixed partial oleic esters of sorbitol anhydrides) which was placed into the vial at B and withdrawn through end A. Another 10 ml. of isotonic saline solution (containing 0.05% Polysorbate 80) was added to the vial through B and the solution containing the labeled microspheres was tested in mice as in Example 3. Fourteen labeling kits were used. The results were as folllows:

TABLE II

	Average	± Standard deviation
Percent uptake	78.6	5.2
Percent in lung	82.9	3.1
Percent in liver	5.4	1.1
Percent in carcass	11.6	2.2
Lung/liver ratio	16.3	5.6

What is claimed is:

1. A single-unit labeling kit for radioactively labeling pharmaceutically acceptable microparticles by means of a labeling reaction, the labeled microparticles being useful for medical diagnosis and the like, comprising:

a container having at least one open end;

a porous filter plate mounted within said container and separating said container into first and second compartments;

a plurality of pharmaceutically acceptable microparticles in said first compartment;

at least one labeling reagent in said container to aid in the labeling reaction; and

means to temporarily seal said open end and capable of receiving a syringe needle for placing a liquid in said container and for the removal of radioactively labeled microparticles.

2. The labeling kit of claim **1** wherein the labeling reagent is a reducing agent and in said first compartment.

3. The labeling kit of claim **2** additionally having a solid source of hydrogen ion in said second compartment.

4. The labeling kit of claim **3** wherein said solid source of hydrogen ion is a strongly acidic cation exchange resin composed of nuclear sulfonic acid exchange groups attached to a styrene divinylbenzene polymer lattice.

5. The labeling kit of claim **3** additionally having a packing material in said second compartment for preventing movement of said solid source of hydrogen ion.

6. The labeling kit of claim **3** wherein said reducing agent, in combination with pharmaceutically acceptable adjuvants, comprises a labeling reagent in tablet form.

7. A single-unit labeling kit for radioactively labeling pharmaceutically acceptable microparticles by means of a labeling reaction, the labeled microparticles being useful for medical diagnosis and the like, comprising:

a generally elongated container having two open ends opposed to each other;

a glass frit mounted transversely within said container and separating said container into first and second compartments;

a plurality of pharmaceutically acceptable biodegradable microspheres in said first compartment;

a solid source of hydrogen ion in said second compartment;

a reagent tablet in said first compartment, said tablet comprising a reducing agent to aid in the labeling reaction and a non-reactive, non-toxic, wetting agent to aid in the suspension of said microspheres when a liquid in said container is introduced into said container; and

means to temporarily seal said open ends and capable of receiving a syringe needle for placing a liquid in said container and for the removal of radioactively labeled microspheres.

8. The labeling kit of claim **7** additionally having a packing material in said second compartment for preventing movement of said solid source of hydrogen ion.

9. The labeling kit of claim **7** wherein said reducing agent is sodium thiosulfate.

10. The labeling kit of claim **7** wherein said wetting agent is a non-ionic surfactant of poly(oxethylene), poly-(oxpropylene), and poly(oxethylene) polymer.

11. The labeling kit of claim **7** wherein said solid source of hydrogen ion is a strongly acidic cation exchange resin composed of nuclear sulfonic acid exchange groups attached to a styrene divinylbenzene polymer lattice.

12. A single-unit labeling kit for providing a radionuclide and thereafter labeling pharmaceutically acceptable microparticles with said radionuclide by means of a labeling reaction, comprising:

a container having at least one open end;

a porous filter plate mounted transversely within said container and separating said container into first and second compartments;

a plurality of pharmaceutically acceptable microparticles in said first compartment;

a solid source of hydrogen ions in said second compartment;

a layer of granular aluminum oxide deposited on said solid source of hydrogen ion;

an effective amount of ammonium molybdate, for producing an effective labeling amount of radiotechnetium, deposited on said aluminum oxide layer;

a reagent tablet in said compartment, said tablet comprising a reducing reagent to aid in the labeling reaction and a non-reactive, non-toxic wetting agent to aid in the suspension of said microparticles when a liquid is introduced into said container; and

means to temporarily seal said open ends and capable of receiving a syringe needle for placing a liquid in said container.

13. The labeling kit of claim **12** additionally having packing in said second compartment to hold said aluminum oxide layer against said resin and firmly in said container.

14. The labeling kit of claim 12 wherein said microparticles are biodegradable microspheres.

15. The labeling kit of claim 12 wherein said solid source of hydrogen ion is a strongly acidic cation exchange resin composed of nuclear sulfonic acid exchange groups attached to a styrene divinylbenzene polymer lattice and said tablet comprises sodium thiosulfate, a nonionic surfactant of poly(oxethylene), poly(oxpropylene), and poly(oxethylene) polymer, and pharmaceutically acceptable adjuvants.

16. A method of radioactively labeling pharmaceutically acceptable microparticles comprising the steps of:

(a) introducing a solution containing radio-technetium into said second compartment of the labeling kit of claim 7;

(b) passing said solution through said solid source of hydrogen ion providing the acidification thereof;

(c) heating said labeling kit to complete the labeling reaction;

(d) removing the supernatant containing unreacted radio-technetium and spent reagents; and

(e) isolating the labeled microparticles.

17. The method of claim 16 comprising the additional steps of:

agitating the acidified solution to suspend said microparticles and dissolve said reagent tablet after step (b); and

cooling said labeling kit after step (c).

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