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LUNG SCANNING 99m TECHNETIUM MACRO-AGGREGATE AND METHOD OF PREPARATION

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ABSTRACT OF THE DISCLOSURE

A lung scanning agent and method, the agent comprising a 99m technetium **-sulfur** colloid macroaggregate stabilized with a dialdehyde. More specifically, the composition comprises a 99m TcO_4 solution of the desired activity together with gelatin, an acid, and thiosulfates and perrhenates of the metals of Group IA of the Periodic Table of the Elements. The composition is heated to produce the desired macroaggregate particles and a dialdehyde such as glutaraldehyde is added to stabilize the particles. A high percentage of the particles produced upon injection are initially distributed throughout the lungs and upon clearance distribute themselves throughout the reticuloendothelial system.

BACKGROUND OF THE INVENTION

Pulmonary emboli have been found in recent studies to be present in a high percentage of adult patients dying from all causes. Many emboli are never detected because they produce no symptoms and oftentimes resolve without creating ill effects. Yet pulmonary embolism may cause a variety of symptoms which are similar to other disorders or diseases. The condition created by blood clots trapped in the pulmonary arteries and their branches may exist in a grave form without being diagnosed by physical examination. Emboli often originate in the large pelvic veins or veins of the lower extremities and are found in those areas as a result of poor blood circulation. This condition frequently occurs in patients who are confined to bed as a result of surgery, pregnancy or almost any physiological problem which results in poor blood flow. The emboli migrate through the great vessels and lodge in the heart or lungs. Damage to the lung depends upon the size of the embolus, and its location within the pulmonary vasculature and the cardiovasculature. The emboli may be of such size or so located as to be broken down rapidly into smaller embolic proteolytic enzymes. If these mechanisms are defeated the areas distal to the location of the emboli may be damaged due to inadequate blood supply.

There are presently several methods by which pulmonary blood flow may be measured but unfortunately there is no single examination that is accurate, specific, safe and inexpensive enough such that it may be utilized as a screening test for every suspected case of pulmonary embolism. The most common methods employed are chest roentgenogram, pulmonary angiography and scintillation scanning techniques.

The chest roentgenogram, while valuable in diagnosing lung conditions may not demonstrate severe pulmonary emboli and consequently is not entirely satisfactory for the evaluation of pulmonary emboli. Pulmonary angiography is a complicated and possibly hazardous procedure dure involving the rapid injection of a large amount of radio-opaque dye. Following the injection, as many as 20 serial X-rays may be taken to trace the flow of the dye through the lung vasculature. This technique, while it may precisely locate emboli, is not desirable for screening a large population of hospital patients.

Organ scanning with radioactive materials is a method of particular value in the detection of pulmonary embolism. Such a method is currently accomplished utilizing macroaggregated human serum albumin labeled with Iodine–131. This material is a heat-treated albumin which exists as particles typically from 10 to 90 microns in diameter. When injected intravenously, particles of this size will lodge in the capillaries of those portions of the lungs being perfused with blood. Once the particles locate in the lung via the pulmonary artery, a scintillation crystal detector is mechanically passed over the lung fields. The information monitored by the detector is converted into electrical impulses which are used to expose a photographic emulsion, thus producing a picture of the activity distribution.

Lung visualization by this rectilinear scanning technique is accurate, presents little danger to the patient and provides a method for screening large numbers of suspected cases of pulmonary embolism and other diseases causing decreased pulmonary perfusion. For example, such preparations of aggregated albumin have been used in the evaluation of total and regional perfusion of the lungs including the diagnosis of such specific conditions as emboli formation, emphysema, lung tumors, pulmonary tuberculosis, and the like.

The particles of aggregated albumin are mechanically filtered by the lungs because of the particle size, thus permitting definitive lung scanning by typical scintillation detection equipment. The aggregates concentrate in various parts of the lungs in direct proportion to the blood flow supplied by the pulmonary artery and the amount of radioactivity detected is directly proportional to the concentration of aggregates in various parts of the lungs.

Imaging the perfused lung areas by the scintillation scanning technique unfortunately has some disadvantages, the most serious of which are the time required to obtain a picture and the radiation exposure of the patient. Also, the patient must lie motionless for long periods of time. This disadvantage can be overcome with stationary imaging devices now available, such as scintillation cameras, an example of which is the Anger camera. The crystal of the Anger cameras with appropriate collimation is large enough to view the entire lung field at the same time. Consequently the entire detection equipment may be moved easily to accommodate the patient's most comfortable position.

Unfortunately, however, the presently used aggregated radio-iodinated human albumin achieves a crystal efficiency of only about 21%. Consequently, imaging of the lungs with an Anger camera employing conventional doses of macroaggregated albumin labeled with Iodine 131 requires more than 20 minutes per view. In order to obtain sufficient counting rates, an injection of 3 mc. of activity would be required. The expense for a dosage of this size would be prohibitive, would deliver 12 rads to the lungs, and would deposit an undesirably large amount (3½ to 4½ mg.) of albumin in the pulmonary capillaries.

SUMMARY OF THE INVENTION

When imaging the lungs with a scintillation camera there is a need to have a high count rate in order to take full advantage of the capabilities of the instrument. Three properties which should be present in a lung scanning agent for use in man are: (1) the material must be non-antigenic, (2) it must not be harmful to the pulmonary system, and (3) the amount of significant information obtained by injection of the material must be in realistic proportion to the radiation exposure suffered by the patient. The ideal lung scanning agent for a scintillation camera should have a short physical half-life, be a mono-energetic γ-emitter, have a photon energy of 100 to 150

kev., be devoid of β-radiation, harmless, inexpensive and simple to prepare.

It is apparent that iodine-tagged radiopharmaceuticals do not take advantage of the imaging speed of the scintillation camera. Tagged to a suitable pharmaceutical 99m technetium would fulfill the noted criteria. While technetium can be incorporated into macroaggregates of albumin the process is time consuming and difficult and requires technical ability not generally available in a small isotope laboratory. Technetium because of its desirable physical characteristics delivers a very high count rate and greatly shortens the scanning time when performed by a stationary imaging device. Using a scintillation camera and a diverging collimator, anterior, posterior, right and left lateral, and right and left oblique human lung scintiphotos can be obtained in approximately 10 minutes with a 3 mc. dose of macroaggregated 99m technetium. This shortened scanning time enables studies to be performed on seriously ill or very dyspneic patients who cannot tolerate the longer procedure with Iodine–131 tagged radiopharmaceuticals.

It has been found that suitable technetium 99m **-sulfur** colloid macroaggregates can be formed in the presence of gelatin, sodium thiosulfate, sodium perrhenate and an inorganic acid. The particles formed must be large enough to lodge in the lungs and fragile enough so that they will migrate from the lungs after an appropriate period. At the same time they must be stable enough so that they do not break down and are not promptly released into the liver and spleen. Any particles which promptly pass into the liver will cause a shadow and distort the scintiphoto of the lung. Preferably, no more than 2% of the particles should pass into the liver although some experts in the field will accept up to 15%. A lung-liver ratio of particle distribution of 25:1, i.e. with 4% of the particles passing into the liver is generally considered satisfactory. It has further been found that the macroaggregate particles thus formed can be stabilized by the addition of small amounts of dialdehydes. It is believed that the gelatin molecules are gently cross-linked with the dialdehydes, thus hardening them and increasing the melting point without changing other chemical properties of the molecule.

DETAILED DESCRIPTION

All of the components used in the composition and technique to be described were prepared in bulk amounts and sterilized by passage through a .22 micron millipore filter into sterile, pyrogen-free, evacuated vials. All of the components except for the dialdehyde were prepared and filtered. The sodium thiosulfate, gelatin and sodium perrhenate are filtered as a unit and the acid and buffer are filtered separately. Due to the consistency of the gelatin it is necessary to warm this mixture to secure its passage through filters of this porosity. Compositions prepared in this manner may be stored at 3° C. for several months.

Macroaggregates of 99m technetium were prepared in three steps as hereinafter described. The procedure was carried out in 10 ml. bottles since these are suitable for centrifuging in a table-top centrifuge.

EXAMPLE 1

To 1 ml. of water containing 2.15 mg. of gelatin, 2.15 mg. of sodium thiosulfate and 1.07 mg. of sodium perrhenate, were added 4.5 ml. of 99m TcO_4 solution of the desired activity and 2 ml. of 2 N HCl acid. The solution was heated for 10 minutes at 100° C. and the pH adjusted to 4 to 4.5 with 2 ml. of 2 N sodium hydroxide after which 0.6 ml. of 25% glutaraldehyde was added. The solution was heated while shaking for an additional 3 minutes at 100° C. The resultant suspension was centrifuged and the supernatant withdrawn. The remaining particles were washed with saline solution and again centrifuged. After the supernatant was removed, the particles were suspended in 6 ml. of saline solution.

Approximately 1 minute after the initiation of heating, colloid particles of minute size are formed. On further heating at the same temperature fragile brown macroaggregates of larger diameter appear. In adjusting the pH following the addition of the sodium hydroxide, only a few drops of 2 N NaOH or HCl will bring the pH into the 4 to 4.5 range. The faster the solution is shaken during the heating period the smaller and more uniform the particles become. Following the final heating the preparation is centrifuged for 45 seconds at approximately 2000 r.p.m. and the supernatant removed using a sterile, disposable 20 ml. syringe. The particles are washed with normal saline solution to remove any remaining dialdehyde and reconstituted in the desired amount of saline solution. Virtually all of the original radioactivity is incorporated into the macroaggregates.

The presence of gelatin, sodium thiosulfate, sodium perrhenate and acid is required for the formation of macroaggregates. The number of particles formed is proportional to the amount of each component present. The effective range of acid is inversely proportional to the period of heating. The size and number of the particles can in part be controlled by the period of heating, the amount of gelatin, sodium thiosulfate, sodium perrhenate and acid.

Accordingly, while it is evident that a host of combinations of the various components can be effectively utilized, the following ranges are set forth for convenience. Gelatin, 0.9 to 6.9 mg.; a thiosulfate of one of the metals of Group IA of the Periodic Table of the Elements, 2.15 to 8.6 mg.; a perrhenate of one of the metals of Group IA of the Periodic Table of the Elements, 0.2 to 3 mg., all in 1 ml. of water, to which is added 4.5 ml. of 99m TcO_4 solution of the desired activity and 2.0 cc. of 0.5 N to 5 N HCl. After heating the solution, the pH is adjusted to 4.0–4.5 and then 0.3 to 0.6 ml. of 25% glutaraldehyde is added before further heating and centrifuging.

It was found that there is a relationship between the amount of gelatin and acid to particle production. Also the incubation time in which agglutination occurs is definitely shorter when a greater concentration of acid is present. As acid concentration is increased the percentage of colloidal agglutination rises markedly. For example, with the acid concentration remaining constant at 0.3 ml. of 1 N HCl, the percentage of agglutination rapidly increased with decreasing amounts of gelatin with about 20% agglutination with the addition of 5 mg. of gelatin and about 90% agglutination with 3 mg. of gelatin.

Likewise, a relationship was found between the heating time and quantity of acid. If low concentrations of acid are used, aggregates of a colloid would not form. However, by heating longer or increasing the acid, aggregates would form after 3 minutes of heating. The longer the heating and the higher the acid content, the larger the individual aggregates become. It was determined that a high acid concentration in the presence of no more than 4 mg. of gelatin, 2 mg. of sodium thiosulfate and 1 mg. of sodium perrhenate in a total volume of 3 ml. of saline solution would produce aggregates up to 100 microns in diameter. These particles, however, were extremely fragile and would break down into their individual components upon the slightest shaking only to re-form when allowed to stand. Accordingly, such particles would be unsuitable for lung scanning since they would rapidly pass through the lungs and lodge in the liver and spleen.

It was found that the size of the macroaggregates could be controlled by time of heating. The longer the heating, the larger the individual aggregates become. For example, proper particles sizes, 5 to 30 microns in diameter, are formed at 17 minutes of heating. When heating is extended to 20 minutes, aggregates up to 100 microns are produced. These particles, however, are extremely fragile and break down into small particles (1 micron or less) upon shaking, washing and centrifugation. As noted, such particles would be unsuitable for lung scanning so

that need for stabilization of the particles was apparent. The particle size must be large enough so that the particles are mechanically filtered by the lungs thus permitting definitive lung scanning by typical scintillation detection equipment and yet fragile enough so that they are gradually broken up and released.

It was further found that the macroaggregates formed by the gelatin, sodium thiosulfate, sodium perrhenate and acid could be stabilized with a dialdehyde. It is believed that stabilization occurs because of a cross-linking between the gelatin molecules and the dialdehyde. Accordingly, when varying amounts of a dialdehyde such as pentanedial (glutaraldehyde) are added to the preformed particles and heated the particles become firm and of an appropriate size, 5 to 30 microns in diameter, for lung scanning. It is believed that once the macroaggregates are formed the dialdehyde reacts with the amine groups of the gelatin-coated colloidal particles binding them together. By varying the amounts of glutaraldehyde, it was found that 0.3 ml. of a 25% solution in a total volume of about 9 ml. of suspension was the least amount that could be used effectively as a stabilizing agent. Below this amount, many of the colloidal particles remained unclumped. Any unreacted dialdehyde is removed by washing the particles in saline solution as previously described. Suitable dialdehydes are ethanedial of 2 carbon atoms up to octanedial of 8 carbon atoms.

Particle formation occurred freely in 99m technetium eluants which contained only saline solution. With small amounts of the compositions previously described no particles would form with a 99m technetium saline solution containing sodium hypochlorite. Some commercial 99m technetium generators require the presence of sodium hypochlorite to maintain the +7 valence of technetium atoms in order to assure an adequate yield of 99m technetium upon elution of the generator. Since the perrhenate ion in solution would not be expected to react with the sodium hypochlorite, it is believed that the sodium hypochlorite reacts with the sodium thiosulfate, thus prohibiting the formation of the sulfur colloid. In reactions with 4.5 ml. of 99m technetium in a saline solution containing 0.9% sodium hypochlorite, no colloid was formed below a sodium thiosulfate concentration of 4.75 mg. As the concentration increased above 5.35 mg., colloid was present but few aggregates were formed until the concentration reached 8.15 mg.

While studies have indicated that large numbers of particles can safely be injected, it is desirable that the number of particles per ml. be maintained in the range of 100,000 to 2,000,000. A suitable composition for preparing a scanning agent containing approximately 1,000,000 particles per ml. is as follows: to 2.15 mg. of gelatin, 8.6 mg. of sodium thiosulfate, and 1.6 mg. of sodium perrhenate in 1 ml. of water is added 2 ml. of 0.5 N hydrochloric acid and 3.5 ml. of 99m TcO_4 solution. After heating for 17 minutes at 100° C. the pH is adjusted to 4 with .4 M Na_2HPO_4. Six-tenths of a ml. of 25% glutaraldehyde is added and the mixture is heated at 100° C. for an additional 3 minutes. After centrifuging, the supernatant is removed and the particles are washed with 5 ml. of saline solution. The suspension is centrifuged a second time, the supernatant is removed and the particles are then resuspended in 6.5 ml. of saline solution. A suitable dose for lung scanning is 2 ml. containing 2 to 3 mc. of activity.

EXAMPLE 2

Biological half-life

A study was conducted to determine if the injected particles would migrate from the lungs. Particles were prepared and labeled with 99m technetium in the manner described in Example 1 with the exception that the suspension contained 8.6 mg. of sodium thiosulfate and 4.3 mg. of sodium perrhenate per ml. The 99m technetium was eluted from a generator with an 0.9% saline eluant and 0.6 ml. of glutaraldehyde was used. After the particles were prepared, each of 24, 150–250 gm. Sprage Dawly rats were injected intravenously with 3 to 4 mc. of the 99m technetium labeled particles. Four animals were sacrificed at each of six time intervals beginning ten minutes post injection and continuing through 48 hours post injection. Activity in the lungs, liver, spleen, intestines, kidneys and carcass was determined with a well ionization chamber. The activity listed in the following table is the average obtained from the organs of each of four animals at the noted time interval and is corrected for decay to time zero.

TABLE 1

Time	Lung	Liver	Spleen	Kidneys	Viscera	Carcass
10 min	96.4	2.5	0.2	0.1	0.2	0.4
2 hr	93.2	5.6	0.5	0.1	0.2	0.5
6 hr	87.0	7.4	0.7	0.3	0.4	1.2
12 hr	83.7	11.9	1.2	0.3	0.5	2.7
24 hr	80.0	12.5	2.2	0.4	0.4	3.7
48 hr	70.0	21.0	3.9	0.8	0.5	3.4

Examination of Table 1 illustrates that as the activity was cleared from the lung, a concomitant rise is seen in the liver and spleen.

EXAMPLE 3

Acute toxicity of the composition would be reflected by pulmonary distress or anaphylaxis. The acute effects from very large doses were studied in one 15 kg. mongrel dog by the following procedure.

The animal was anesthetized by intravenous injection of sodium pentathal at a dose of 15 mg./kg. of body weight. Two hours following sedation a catheter was fluoroscopically placed in the right atrium via a right foreleg vessel and the catheter was attached to a manometer to measure the central venous pressure in centimeters of water. Prior to injection of the particles the following parameters were measured: arterial blood gases, arterial blood pH, and central venous pressure. An intravenous injection of 34 million particles was then achieved via the catheter and thereafter the above-described parameters were measured. Twenty minutes after the first injection an additional 80 million particles were injected via the catheter obtaining the same data as previously noted. Forty-five minutes following the second injection an additional 104 million particles were injected and the same parameters observed. Lung scans of the injected activity were obtained to determine any perfusion defects created by the particle injections.

While injected with a total of 210×10^6 particles within a period of 2.25 hours, no acute pulmonary distress was demonstrated. This was verified by the results of blood gases, pH, central venous pressure and lung scintiphotos. The particles injected into the animal were from 5 to 30 microns in diameter.

EXAMPLE 4

Visualization of pulmonary perfusion defects in dogs

An 18 kg. mongrel dog was injected with 4 million particles labeled with 4.8 mc. of 99m technetium prepared in accordance with Example 1 and a lung scan performed. One week later an embolus measuring 6 mm. in width and 30 mm. in length was inserted via a cutdown of the right jugular vein. One hour later 2 million particles labeled with 99m technetium were injected and a lung scan was performed. Lung scans were repeated at 3, 9 and 16 days post injection of the embolus to observe the effectiveness of the agent to measure perfusion defects in the lung, to observe any toxic effects created by the particles in animals with comprised pulmonary perfusion, and to observe the appearance of any antigenic response to the particles.

Examination of serial scintiphotos of the lung demonstrated that the animal first displayed normal lung perfusion. Following implantation of the clot in the

jugular vein, the embolus apparently fragmented thus decreasing the perfusion to several areas of the lungs. Three days later there was considerable restoration of the perfusion and 9 days later the perfusion defect was clear. The study demonstrated that the injected particles would follow the perfusion patterns of the lung and that by imaging the activity patterns it is possible to locate areas of decreased perfusion. Following each injection, the animal was observed for anaphylaxis due to repeated exposure to the lung scanning agent. At no time did the animal show signs of stress or hypersensitivity.

EXAMPLE 5

To observe the effects of the lung scanning agent in humans each of the subjects selected had the following procedures initiated: complete blood count (CBC), serum glutamic oxaoacetic transaminase (SGOT), lactic dehydrogenase (LDH), arterial blood gases and pH, respirometry and chest roentgenograms. The subjects were then injected with 1.5 mc. of the 99m technetium aggregates consisting of no more than 8 million particles and lung scintophotos were obtained using a scintillation camera. Immediately following the lung activity visualization, arterial blood gases and respirometry examinations were initiated. One day post injection, venous blood was drawn for the determination of SGOT and LDH. Four days post injection, CBC, SGOT, LDH and chest roentgenograms were obtained.

The study demonstrated that there were no significant changes in any of the parameters measured.

The glutamic oxaloacetic transaminase (SGOT) is an enzyme which catalyzes the reversible transfer of amino groups from glutamic to oxaloacetic acid. High levels of this enzyme are found in the heart, liver and lung. If any of these organs had been damaged due to the injected particles, there would have been an increase in these values over the preinjection levels. Normal values for the SGOT are 10 to 50 Karmen units. Some of these values were elevated in the preinjection specimens but none rose during the test period.

Lactic dehydrogenase (LDH) is an enzyme which catalyzes the reversible oxidation of lactic acid to pyruvic acid. This enzyme is found in high concentrations in the heart, liver and lung. Normal values for the LDH are those less than 270 units. Had either the LDH or SGOT values been elevated, it would have indicated that tissues in the heart, liver or lung were damaged following the injection of the particles. Such was not the case.

The blood count was obtained to measure the effect of the injected particles on the white cell count and the Hematacrit. If these parameters had varied following injection, it may have indicated that the particles had created some hematological problem. No significant change was observed.

TABLE 2

	WBC	HBG	HCT	Platelets	SGOT	LDH	pH	pO_2	pCO_2	Vit. cap.	Chest film
Subject 1	10,200	12.3	39		30	170	7.46	65	42	3.36	Big nodes with increased Hylon markings and calcific areas.
Post injection							7.44	69	42	2.99	
24 hours					22	118					
4 days	9,900	13.4	39	Adequate	27	20					Unchanged.
Subject 2	7,100	13	39	Adequate	14	76	7.44	87	39	6.47	Mass of left lung.
Post injection							7.44	86	39	6.97	
24 hours					16	66					
4 days	9,200	12.8	39		6	40					No change.
Subject 3	12,000	12.7	38	Adequate	68	186	7.47	60	43	2.24	Normal.
Post injection							7.46	63	42	2.29	
24 hours					52	160					
4 days	12,000	14.4	44	Adequate	70	186					Unchanged.
Subject 4	11,400	15.1	46	Adequate	20	99	7.50	84	29	3.22	No evidence of pleural or parenchymal disease.
Post injection							7.52	81	31	3.42	
41-46-31											
24 hours						86					
4 days	10,500	14.9	45	Adequate	16	66					Unchanged.
Subject 5:											
Preinjection	12,600	11.9		Adequate	50	195	7.47	63	35	3.63	Bilateral infiltrates.
Post injection							7.47	63	37		
24 hours					46	145					
4 days	11,200	15.3	47		43	150					No change.
Subject 6:											
Preinjection	10,000	14.3	43	Adequate	80	102	7.42	87	36	3.63	Infiltrate left lung.
Post injection							7.41	84	37	3.65	
24 hours											No change.
4 days	7,900	16.3	50		50	106		Cirrhosis liver			
Subject 7:											
Preinjection	7,900	16	50				7.45	90	35	4.36	Right upper lobe mass.
Post injection							7.45	95	35	4.53	
24 hours											
4 days					50	160					No change.
Subject 8:											
Preinjection	9,500	10.2	31	Adequate	22	140	7.41	45	49	2.23	Infiltrate inferior segment of right lower lobe.
Post injection							7.41	63	48	2.23	
24 hours					14	110					
4 days	10,600	10.6	35		16	123					No change.
Subject 9	5,900	12	36	Adequate	18	50	7.46	62	32	5.0	No evidence of pleural or parenchymal disease.
Post injection							7.49	62	32	4.6	
24 hours					14	66					
4 days	6,400	13	38	Adequate	18	83					No change.
Subject 10	5,300	16.2	44	Adequate	25	86	7.55	98	20	2.9	Negative chest.
Post injection							7.43	76	30	[1] 2.6	
31-42-50					18	66					
4 days	8,400	15.4	44	Adequate	19	40					Negative chest.

[1] After dinner.

The chest roentgenogram was considered a valuable method of observing the lung field for changes created by the injected particles. Allroentgenograms on these 10 subjects indicated no change in the heart size, no distention of pulmonary vessels, no apparent increase in fibrous tissue, and no new infitrates indicating infarction or obstruction of pulmonary vasculature.

The blood gases were obtained to measure the ability of the lung to exchange atmospheric gases with the blood. Had either the pCO_2 increased or pO_2 decreased, it would have indicated that the injected particles had influenced this process. Only one individual demonstrated a decrease in pO_2 after injection. This was explained by the fact that a venous arterial mixture of blood was obtained due to a technical problem.

A typical scintiphoto obtained in the study demonstrated the anterior-posterior (AP) view of the lung field. The activity was homogeneously distributed throughout the lung field with the exception of the decreased uptake in a wedge-shaped area of the left lower lobe. This area is normally of lower activity due to the displacement of lung tissue by heart. This scintiphoto was taken with the subject in an upright position and took only 71 seconds to complete, thus reducing the time per view by a factor of 20 when compared to the rectilinear scans utilizing Iodine–131 macroaggregated albumin. A second scintiphoto of the same subject 29.5 hours post inpection indicated a large quantity of the injected dose had migrated to the liver.

What is claimed is:

1. A radiopharmaceutical lung scanning preparation comprising macroaggregates of 99m technetium and sulfur stabilized in a suspension containing perrhenates gelatin and a dialdehyde of from two to eight carbon atoms, said macroaggregates having a particle size of at least 5 microns and less than 100 microns.

2. The preparation of claim **1** in which the macroaggregates are formed with thiosulfates and perrhenates of a metal selected from the group consisting of the metals of Group IA of the Period Table of the Elements, in the presence of an acid.

3. The preparation of claim **2** in which the dialdehyde is selected from the group consisting of ethanedial, pentanedial, hexanedial and octanedial.

4. The preparation of claim **2** in which the dialdehyde is selected from the group consisting of ethanedial and pentanedial.

5. A radiopharmaceutical lung scanning preparation comprising macroaggregates formed from a composition comprising 0.9 to 6.9 milligrams of gelatin, 2.15 to 8.6 milligrams of sodium thiosulfate and 0.2 to 3.0 milligrams of sodium perrhenate, all in one milliliter of water and in the presence of an acid, said macroaggregates being labeled with 99m technetium and having a particle size larger than 5 microns and formed and stabilized in a suspension containing a dialdehyde of from two to eight carbon atoms.

6. The preparation of claim **5** wherein the dialdehyde is pentanedial.

7. The method of preparing a stable radiopharmaceutical lung scanning preparation comprising the steps of:

adding to one milliliter of water, 4.5 ml. of 99m TcO_4 solution of a predetermined activity, 0.9 to 6.9 milligrams of gelatin, 2.15 to 8.6 milligrams of a thiosulfate of a metal selected from a group consisting of the metals of Group IA of the Period Table of the Elements, and 0.2 to 3.0 milligrams of a perrhenate of a metal selected from the group consisting of the metals of Group IA of the Periodic Table of the Elements, in the presence of an acid;

heating the mixture thus formed for a time sufficient to produce macroaggregates of at least 5 microns in diameter;

adjusting the pH of the resulting suspension to about 4;

adding to said suspension, a dialdehyde of from two to eight carbon atoms in an amount sufficient to stabilize the macroaggregates; and

heating the suspension to obtain stabilized macroaggregate particles.

8. The method of claim **7** in which the dialdehyde is selected from the group consisting of ethanedial and pentanedial.

9. The method of claim **7** in which a 25% solution of pentanedial is added to the suspension in an amount of from 0.3 to 0.6 milliliter.

10. The method of claim **9** in which the mixture is heated until stabilization has occurred.

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