

# Free (Unreacted) Pertechnetate in Technetium-Sulfur Colloid Preparations

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Combined clinical and radiopharmaceutical studies (1) have shown that an optimal technetium-sulfur colloid preparation for liver or bone marrow (reticuloendothelial system) imaging should contain less than 5% free technetium and uniform small particles that are from 0.5 to 1.0 micron in diam. The presence of an unusually large portion of unreacted technetium or of solubilized technetium-colloid in a technetium-sulfur colloid preparation leads to a high blood background and decrease in target-to-nontarget ratio. In the case of free technetium it will result also in labeling of organ systems such as the thyroid, salivary glands, upper gastrointestinal tract, and kidney. For particle size, the limiting quality control factor is greater than 10 microns; particles of that size localize in the lung. Besides causing poor image quality, these factors result in unnecessary radiation to the patient.

Although for liver imaging a less stringent adherence to these criteria may be marginally acceptable, for a good bone marrow scan an optimal technetium-sulfur colloid product is required. A number of factors may interfere with this optimal preparation: (A) those inherent in the formulation of the commercial kit itself (e.g., pH of final product and the type and quantity of stabilizer); (B) those due to faulty preparation in the laboratory (e.g., incorrect order of mixing or false time or temperature in heating step); and (C) those due to an inadequate effluent from the technetium generator (e.g., presence of oxidants or aluminum).

The radiopharmaceutical product generally functions according to the manufacturer's specification, but occasionally the final image suggests that either an unusual amount of free pertechnetate is present or the particle size is abnormally large.

We have evaluated a method of rapid testing for completeness of tagging. This method is faster than the conventional chromatographic method and gives identical results. We have also

evaluated factors that may lead to an undesirable amount of free (unreacted)  $^{99m}\text{Tc}$  in sulfur colloid preparations.

## Material and Methods

Consecutive preparations of  $^{99m}\text{Tc}$ -sulfur colloid were examined for free unreacted technetium with paper chromatography in 90% methanol and with Millipore filtration. Three commercial kit preparations (A, B, and C) \* were used. The kit from Supplier A was used except when specified; the other two kits were used for comparison later in the study. The molybdenum generator used throughout the study as the source of  $^{99m}\text{Tc}$  was also obtained from Supplier A.

**Chromatography.** The percentage yields of the colloid and residual free pertechnetate were determined by paper chromatography using Whatman 3MM filter paper strips and 90% methanol as a solvent. The colloid remains on the point of application while the free pertechnetate migrates with the solvent front. Chromatograms were then exposed to no-screen x-ray films for autoradiography. The colloid yield was defined as the percentage of total radioactivity on the chromatogram that was found around the point of origin ( $R_f < 1$ ). Free pertechnetate was defined as that area of activity near the solvent front ( $R_f < 0.8$ ). The tailing seen between the two major points was considered to be partially reduced pertechnetate (Fig. 1).

**Microscopy.** Because we were not able to adapt our Coulter counter for accurate particle size measurements, a light microscope was used to scan a standard hemacytometer chamber for large particles. This examination was performed irregularly throughout the study in the form of

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\* Supplier A, Squibb; Supplier B, Mallinckrodt; Supplier C, New England Nuclear.

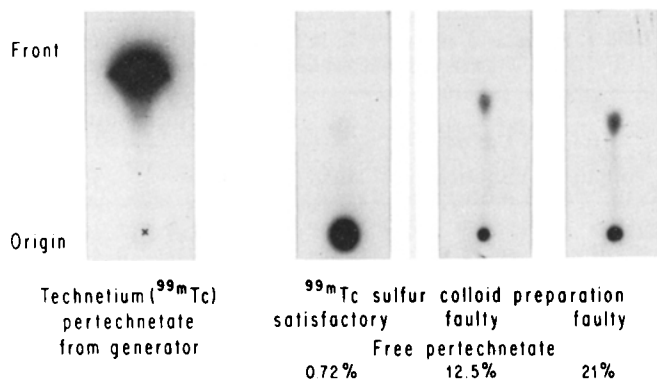


FIG. 1. Paper chromatographic appearance of free  $^{99m}\text{Tc}$  and  $^{99m}\text{Tc}$ -sulfur colloid. Note that  $^{99m}\text{Tc}$ -sulfur colloid remains at origin ( $R_f < 1.0$ ) and free  $^{99m}\text{Tc}$  travels with solvent front ( $R_f > 0.8$ ). Trailings between origin and front probably represent partially reduced pertechnetate.

spot checks. This method allows detection of particles exceeding 10 microns in diam; particles between 1 and 10 microns in diam cannot be detected easily with standard radiopharmaceutical procedures (1).

**Microfiltration.** The following method was developed in our laboratories: 0.2 ml of prepared sulfur colloid mixture was drawn into a 1-ml syringe. The syringe was put into a dose calibrator to determine total activity of  $^{99m}\text{Tc}$ . The content of the syringe was then passed through a 0.22-micron Millipore filter into a vacuum vial of the same volume as the syringe. The syringe was then reassayed for  $^{99m}\text{Tc}$  activity. The filter was washed with 3 ml of normal saline, and the eluate was assayed. Free  $^{99m}\text{Tc}$  was determined using the following formula:

$$\% \text{ free } ^{99m}\text{Tc} = \frac{\text{Filtered activity}}{\text{Initial syringe counts} - \text{residual syringe counts}} \times 100.$$

## Results

**Microfilter method.** When measurements of free technetium were made with the conventional chromatography method and compared with the filter method, there was good agreement (Fig. 2). This was true for low values, expected in adequate preparations, as well as for high values of free technetium. High values of free technetium in sulfur colloid preparations were obtained by introducing deliberate faults in preparing the radiopharmaceutical. Only a filter with a diameter of between 0.15 and 0.3 micron was found to give results that were comparable to those of chromatography (Fig. 3). As expected, large filter sizes may allow smaller colloid particles to pass and be registered as free technetium. On the contrary, smaller filter sizes apparently lead to occlusion of pores and

do not allow a separation of free technetium from colloid particles. Whether particles exceeding 10 microns in diam would also occlude the pores remains to be evaluated.

**Effect of Generator Eluates on Sulfur Colloid: Preparations.** The  $^{99m}\text{Tc}$ -sulfur colloid was prepared using a commercial colloid kit A and the Mo- $^{99m}\text{Tc}$  generator. The results are summarized in Fig. 4. Consistently with the first eluate and frequently with the second eluate, there was a high percentage of free  $^{99m}\text{Tc}$ . Use of sulfur colloid kits from the two other suppliers gave similar results (Fig. 5). The difference between free  $^{99m}\text{Tc}$  in preparations prepared from the first two and the rest of the eluates of a generator was statistically significant ( $p < 0.001$ ).

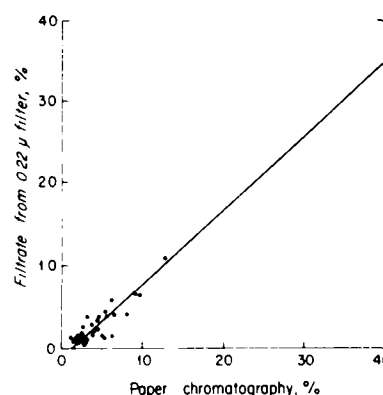


FIG. 2. Comparison of measurements of free technetium by conventional chromatography in 90% methanol and filtration through commercially available Millipore filter (0.22 micron) showed good agreement.

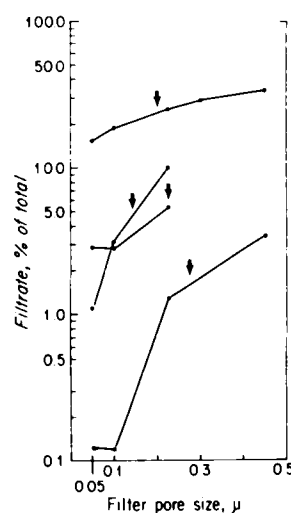


FIG. 3. Results of filtering four different preparations of technetium sulfur colloid through microfilters of different sizes; amount of free technetium (determined by paper chromatography) is indicated by arrows. Use of pore size of 0.15–0.3 micron gave best correlation.

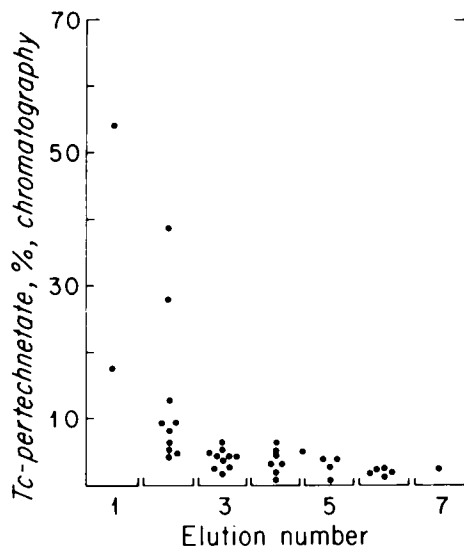


FIG. 4. Free  $^{99m}\text{Tc}$  in sulfur colloid preparations from kit A prepared with different eluates from generator from same supplier. First two eluates yielded unsatisfactory preparations.

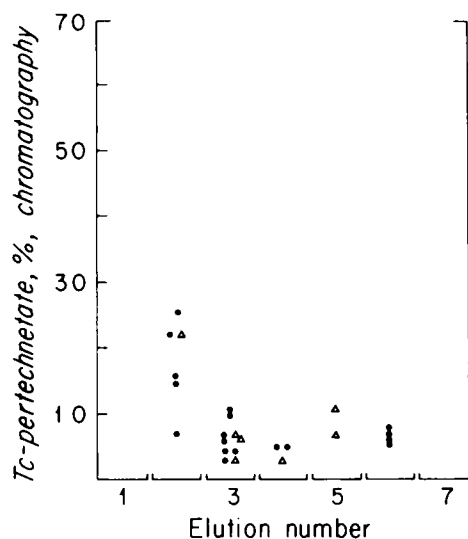


FIG. 5. Free  $^{99m}\text{Tc}$  in colloid preparations made with colloid kits B ( $\Delta$ ) and C ( $\bullet$ ) and with different eluates from generator of supplier A.

**Free  $^{99m}\text{Tc}$  in different colloid kits.** Evaluation of the three different sulfur colloid kits using  $^{99m}\text{Tc}$  from the one Mo- $^{99m}\text{Tc}$  generator was performed. The colloid kit from Supplier A had a significantly smaller percentage of free  $^{99m}\text{Tc}$  than the other two kits (Table 1); there was no difference between the other two kits.

**Particle size.** During the investigation, particle size was studied using a hemometer chamber. No particles were visible, and simultaneous assays for free technetium showed values below 10%. On two occasions, the uptake of colloid particles by the lungs was observed which suggested the presence of particles exceeding 10 microns in size. In each instance, free technetium was in the nor-

Table 1. Percentages of Free  $^{99m}\text{Tc}$  in Sulfur Colloid Preparations Prepared with Different Commercial Kits

Kit supplier	No. of determinations	% free pertechnetate		
		Mean	s.d.	Range
A	28	3.29*	1.48	1.1- 6.2
B	12	6.02	1.86	3.4-10.4
C	6	6.55	2.57	3.4-10.3

\*  $p < 0.001$ .

mal range and microscopic evaluation did not reveal clearly visible particles. This suggests that abnormal particle size does not necessarily result in abnormal values for free technetium and that both parameters should be tested independently. It appears also that the microscopic method is of limited effectiveness in predicting the presence of abnormal particle size.

## Comment

The filter method evidently is as effective as the paper chromatography method in assessing free technetium in sulfur colloid preparations. The filter method takes less time, is easier to perform, and does not require special equipment for chromatography.

We have shown that the technetium used for labeling has a decisive influence on the labeling efficiency in sulfur colloid preparations. The first and second eluates of the generator from Supplier A consistently gave undesirably high values of free technetium. We are not clear as to the reason for this, but the presence of aluminum or an oxidant that is cleared out with subsequent elutions is a possible explanation. We now do not use the first two eluates for sulfur colloid preparations. Whether the same would be true when generators from other suppliers are used remains to be studied. Using the later eluates from the generator of Supplier A, the best colloid preparation with respect to labeling efficiency was obtained when the sulfur colloid kit from Supplier A was used.

Particle size was evaluated only irregularly since the methods available were considered unsatisfactory. However, we found no good correlation between the presence of large particles and the amount of free technetium. Therefore it is not possible to predict abnormalities in particle size from measurements of free technetium.

## Summary

A method of rapid assessment of free technetium in sulfur colloid preparations, based on

Millipore filtration, provides results that are comparable to those obtained with a chromatographic method. Three different commercial sulfur colloid kits and one commercial molybdenum generator were used. The first two eluates of the technetium generator produced undesirably high values of free technetium with the three sulfur colloid kits.

### **Acknowledgment**

This work was presented in part at the meeting of the Society of Nuclear Medicine, Miami Beach, Florida, June 12–15, 1973.

### **Reference**

1. Kelly WN, Ice RD: Pharmaceutical quality of technetium-99m sulfur colloid. *Am J Hosp Pharm* 30:817–820, 1973