A RAPID AND ACCURATE METHOD FOR SIZING RADIOCOLLOIDS

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Thin polycarbonate film filters (Nuclepore) were used to determine the size distribution of technetium–sulfur colloid preparations and the results compared with those obtained using cellulose membrane filters (Millipore) used in previous studies. Data obtained from experiments employing 0.005 and 0.05-μm ^{198}Au colloids revealed that the cellulose filters exhibited a trapping mechanism unrelated to pore size. The effect of this finding was shown in a comparison of three commercial sulfur colloid preparations using the two types of filters.

Testing of four commercial preparations using the polycarbonate filters indicates essentially similar distributions in each case with 15% of particles being less than 0.1 μm, 70% less than 0.4 μm, 80% in the range 0.1–1.0 μm, and 5% being greater than 1 μm. A fifth preparation showed 96% of all particles to be less than 0.4 μm in diameter.

Technetium-99m-labeled sulfur colloid is extensively employed as a scanning agent for the reticuloendothelial system. Several methods of preparation are cited in the literature (*1–10*), and the biologic distribution of the various products has been studied in both animals and man (*4,5,11,12*).

The rate of removal of the sulfur colloid particles from the blood stream is dependent upon both the blood flow to the reticuloendothelial system and the efficiency with which the particles are phagocytized. The literature indicates that the efficiency of phagocytosis is influenced in part by the physical and chemical properties of the agent: particle size, number of particles, presence of carrier, presence or absence of stabilizer, and the nature of the stabilizer (*1–12*).

Although the relative importance of these parameters and the mechanisms of their influence are not well understood, the concern over the size and number of particles has resulted in the development of several methods for estimating particle-size distribution. Included in these techniques are cellulose membrane filtration (*5,10,11,13,14*), ultracentrifugation (*4*), optical microscopy (*9,10,13,14*), and electron microscopy (*6,12,14,15*). Unfortunately, the utility of each of these methods is limited by the technical difficulties of attempting to measure a colloid in a relatively complex mixture of chemicals such as that in a ^{99m}Tc-sulfur colloid sample.

This paper considers a technique not previously applied to the determination of the particle-size distribution, or, more accurately, the activity-size distribution of ^{99m}Tc-sulfur colloid. The method, which employs filtration with polycarbonate film filters (Nuclepore, from General Electric Co., Vallecitos, Calif.) is both accurate and simple to perform, involves no special sample preparation, and avoids some of the drawbacks of cellulose membrane filters.

In this paper, the distribution of three commercially available sulfur colloid kits are compared using Nuclepore and Millipore (Millipore Corp.,

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TABLE 1. PERCENT RETENTION OF ^{198}Au-COLLOIDS FILTERED THROUGH MILLIPORE (M) AND NUCLEPORE (N) FILTERS

	Pore size (μm)							
Colloid size (μm)	0.1 N	0.1 M	0.4 N	0.45 M	1.0 N	1.2 M	3.0 N	5.0 M
0.05	1.2	92.0	1.3	46.9	0.7	46.5	0.4	59.3
0.005	0.2	8.2	0.2	12.2	0.3	26.7	0.2	17.9

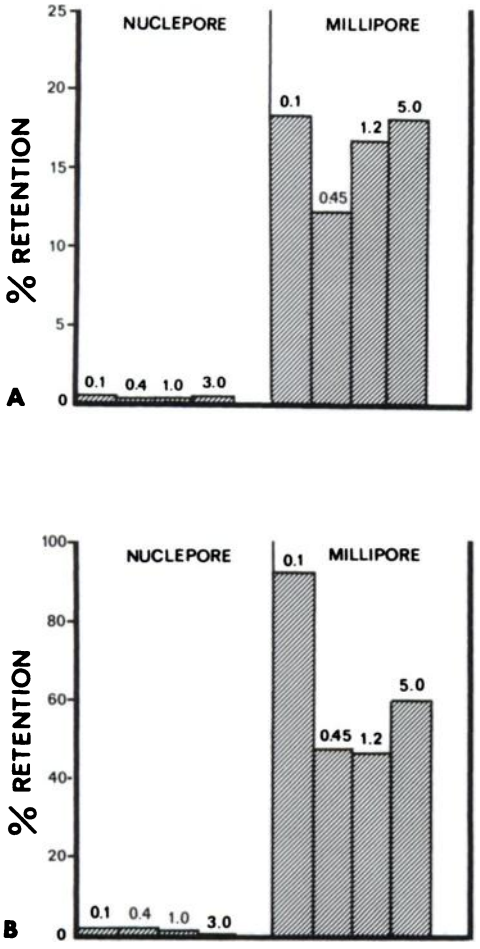

FIG. 1. Percentage of total activity retained by Nuclepore and Millipore filters using (A) 0.005 and (B) 0.05-μm ^{198}Au colloids. Numbers above columns refer to nominal pore size (μm).

Bedford, Mass.) filters. Two sulfur colloid preparations of a different nature (one freeze-dried and one delivered in a ready-to-use form) were also tested with Nuclepore filters and compared with the previously tested kits.

METHODS

The colloids were prepared according to the instructions provided by the commercial supplier except for one (denoted 4) which was supplied ready-made. The results presented were obtained 7–9 hr after preparation. The sodium pertechnetate used in the preparation of the commercial kits was obtained from a commercially available ^{99}Mo-^{99m}Tc generator (New England Nuclear). The generator eluants were carefully monitored for aluminum contamination and in no instance contained more than 10 μg/ml. The commercial products used are referred to in the following manner: 1, Mallinckrodt/Nuclear; 2, New England Nuclear; 3, E. R. Squibb & Sons; 4, Cambridge Nuclear; and 5, CIS Radiopharmaceuticals.

In order to compare the activity retention of Nuclepore filters with that of Millipore filters of similar nominal pore size, aliquots of between 0.3 and 1 ml of the colloid were passed through 13-mm diam Nuclepore and Millipore filters followed by flushing with 2 ml of saline and a positive pressure of air. Nuclepore filters of various pore sizes from 0.1 to 3 μm and Millipores in the range of 0.22–5 μm were used. The percentage of activity retained on the filters was determined by counting the filter and the filtrate plus washings. Depending upon the level of activity, either a well scintillation counter or an ionization chamber was used. The proportion of free pertechnetate ion present was determined by ascending paper chromatography (Whatman No. 1) using saline as the solvent.

To investigate the possibility that particles trapped by impaction on the Nuclepore surface might contribute to the activity retained by the filter, two studies were conducted. First, two ^{198}Au colloid suspensions with particle diameters of about 0.05 and about 0.005 μm were filtered using both types of filters. The percentage of colloid retained was determined as before. Similarly, a suspension of 1.3-μm polystyrene latex spheres was filtered through 3.0 and 5.0-μm Nuclepores. The percentage penetration was determined by counting the number of latex spheres before and after filtration using an optical microscope and hemocytometer.

Finally, to determine whether simple retention of free pertechnetate present in the sulfur colloid might contribute to activity retained by the filters, 0.5 ml TcO_4^- solution was passed through various sizes

of Millipore and Nuclepore filters. The filters were then washed with 2 ml of saline and flushed with air. Furthermore, additional pertechnetate was added to ^{99m}Tc-sulfur colloid agents having less than 2% free TcO_4^- bringing the level to 10% free TcO_4^- and these solutions were then passed through the appropriate-sized filters.

RESULTS

Comparison of Nuclepore and Millipore filtration. The results from the ^{198}Au colloid study (Table 1 and Fig. 1) indicate that Nuclepore retention of particles much smaller than the nominal pore size is very low. In addition, the polystyrene latex spheres showed less than 10% retention on being passed through Nuclepores. Taking into account the probable variations in sphere size and the lack of flushing in the measurements, these results confirm those obtained in the ^{198}Au colloid study. Even though the nature of the two colloids differed from the sulfur colloids, thereby creating different charge effects, the results nevertheless indicate that the Nuclepore filters retain only a low number of colloidal particles significantly smaller than the nominal pore size. The importance of charge effects may be appreciated when the results of Lopez and French (*10*) are considered. Using Millipore filtration of stabilizer-free colloid, they found that all the colloid remained on the filter.

The free-pertechnetate study indicated that the Millipore filters retained an average of 2.7, 1.0, and 0.7% of the initial activity using 0.10, 0.22, and 0.45-μm filters, respectively. Two additional washings with 2 ml of saline reduced these values to an average of 1.3, 0.8, and 0.5%, respectively. In the case of the Nuclepore filters, an average of (0.1 ± 0.1)% of the activity was retained. As the actual agents initially contained from 2 to 5% free pertechnetate, the retention on Nuclepore filters was considered negligible.

The comparison between the percent activity retention on Nuclepore and Millipore filters for three commercial sulfur colloid preparations is shown in Table 2 and Fig. 2. In every case the amount of activity trapped by each size of Millipore is greater than that retained by the two Nuclepore filters closest in pore size.

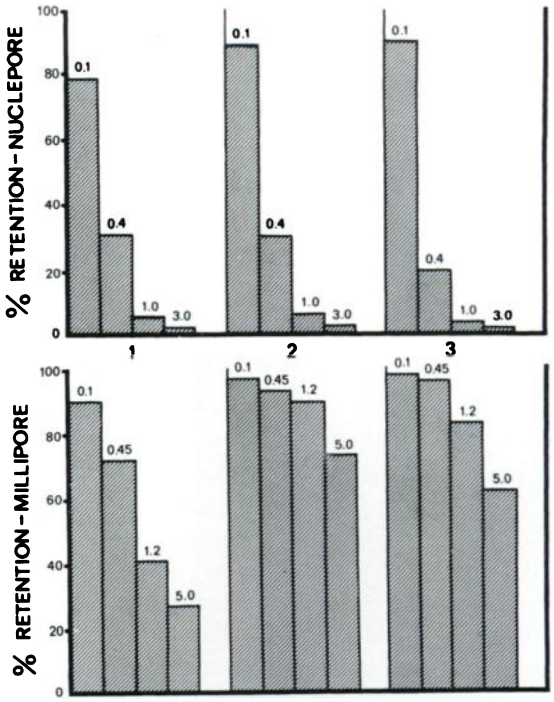

FIG. 2. Retention of commercial sulfur colloids by Nuclepore and Millipore filters of different sizes.

Comparison of different commercial samples. Table 3 shows a comparison of five commercial products using only Nuclepore filters. The same results appear in Fig. 3. In this diagram, the mean percentage of the activity occurring in the various size ranges is depicted. In general, all samples show approximately the same distribution except the final product (CIS).

DISCUSSION

Comparison of Nuclepore and Millipore filtration. The results of the comparison of the Nuclepore and Millipore filters are similar to those reported previously, for example, by Corriere (*13*). The differences in retention are predictable from the charac-

TABLE 2. PERCENT RETENTION OF NUCLEPORE (N) AND MILLIPORE (M) FILTERS USING THREE COMMERCIAL COLLOIDS

	Pore size (μm)							
Colloid	0.1 N	0.1 M	0.4 N	0.45 M	1.0 N	1.2 M	3.0 N	5.0 M
1	79 ± 8	90 ± 5	31 ± 20	72 ± 17	6 ± 2	41 ± 15	2 ± 1	27 ± 13
2	89 ± 4	97 ± 2	31 ± 28	93 ± 4	7 ± 3	90 ± 7	3 ± 2	73 ± 14
3	90 ± 2	98 ± 1	20 ± 11	96 ± 3	4 ± 2	83 ± 9	2 ± 1	62 ± 18

TABLE 3. COMPARISON OF COMMERCIAL PRODUCTS FILTERED THROUGH NUCLEPORE FILTERS

	Retention of filter (%)				
	Pore size (μm)				
Colloid	0.1	0.4	1.0	3.0	Free TcO_4^-
1	79 ± 8	31 ± 20	6 ± 2	2 ± 1	2 ± 2
2	89 ± 4	31 ± 28	7 ± 3	3 ± 2	3 ± 1
3	90 ± 2	20 ± 11	4 ± 2	2 ± 1	1 ± 1
4	82 ± 6	71 ± 9	11 ± 8	3 ± 3	5 ± 2
5	35 ± 13	4 ± 2	1 ± 1	1 ± 1	4 ± 2

teristics of the two types of filters. The Nuclepore filter is a polycarbonate film about 10 μm in thickness with approximately cylindrical pores fairly evenly distributed over the filter. The filters are manufactured by bombarding polycarbonate films with heavy charged particles followed by etching of the tracks for well-defined periods of time to achieve the desired pore diameter. According to the manufacturer, the actual pore size of the lots used in this study is slightly below the nominal value (Table 4), thus discounting the possibility that their smaller activity retention can be attributed to a tendency to allow large particles through because of a wide variation in pore diameter.

In contrast, the Millipore filter is a cellulose fiber membrane somewhat greater than 100 μm in thickness, having tortuous channels through which the particles must pass. The relative thickness and maze-like quality of the filter account for its tendency to trap particles far smaller than the nominal pore size. This is the property that results in erroneous size distribution data. This is demonstrated by the results obtained with the 0.005-μm ^{198}Au colloid where all the Millipore filters showed trapping at a level of about 15% of the activity. The constancy of the observations demonstrates a mechanism obviously unrelated to the nominal pore size. A similar interpretation may be placed on the results obtained with the 0.05-μm ^{198}Au colloid.

The Nuclepore method also has advantages over other techniques of determining particle-size distributions. Accurate estimates are difficult to obtain with optical microscopes because the particles are typically smaller than 1 μm in diameter. In addition, estimates by electron microscopy are unreliable due to the presence in the sample of gel, polysulfides, and nonradioactive colloid, which are all indistinguishable from the radioactive particles. In contrast, the ease and availability of the Nuclepore technique make it extremely useful in the range 0.1–10 μm.

Comparison of chemical ingredients and preparation methods. The commercial sulfur colloid kits 1 and 2 are nearly identical both in their chemical composition and method of preparation and therefore it is not surprising that their activity–size distributions are very similar. Colloid kit 3 is both chemically and preparatively different from the previous two kits in that H_3PO_4 has replaced the HCl and a double heating step is required. The second heating step occurs after the addition of stabilizer and pH adjustment and causes a clearing of the previously milky solution. The fact that the activity-size distribution by Nuclepore filtration and the animal organ distribution data (not presented here) are not significantly different from colloids 1 and 2 is somewhat unexpected and illustrates the complexity of both the chemical and the biological systems in question. Interestingly, the Millipore filtration distribution of colloid 3 showed a marked difference in comparison with the Millipore data of colloids 1 and 2. This difference is thought to be a result of differences in charge rather than in particle size.

Colloid 4 was supplied as an "instant," ready-to-use ^{99m}Tc-sulfur colloid. Although the average particle size was nearly twice that of the other three kits (0.5 μm versus 0.25 μm), because the distributions were similar below 0.1 μm and above 1.0 μm, no significant difference in the in vivo organ distribution was noted.

Colloid 5 is supplied in a freeze-dried form con-

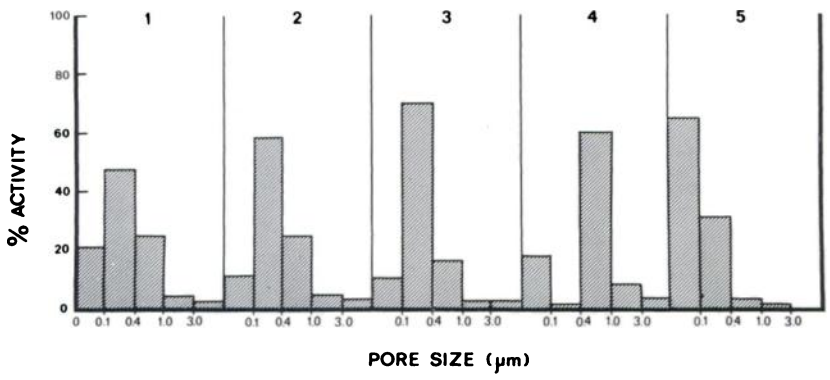

FIG. 3. Activity–size distribution of five commercial sulfur colloids by Nuclepore filtration.

TABLE 4. ACTUAL PORE SIZES AND DENSITIES OF NUCLEPORE FILTERS

Nominal size (μm)	Actual size (μm)	Pore density (cm^{-2})
0.1	0.07	2.9×10^8
0.2	0.19	2.7×10^8
0.4	0.34	1.0×10^8
1.0	0.85	1.9×10^7
3.0	2.7	2.0×10^6
5.0	4.5	4.0×10^5

taining less sodium thiosulfate than the previous kits and requiring only a third to a half as much heating. The manufacturer claims that these factors lead to the production of a colloid with a much smaller mean particle size and the results confirmed this, obtaining an activity–size distribution having greater than 60% of the activity less than 0.1 μm and a further 20% of the activity between 0.1 and 0.2 μm. With greater than 80% of the activity less than 0.2 μm, this colloid is significantly different in size from all others tested and the animal in vivo distribution, as expected, showed a relative decrease in spleen uptake and increase in bone marrow concentration in comparison with the other colloids.

Due to convenience and availability, the colloids were usually sized at 7–9 hr after preparation. Studies on individual colloids 30 min and 8 hr after preparation showed little if any differences in either the particle size or the biologic distribution although the 8-hr suspensions were less milky than at 30 min.

As an extension of this study, it was hoped to determine whether colloid particles lying in a specific size range would have a greater tendency to localize in the reticuloendothelial components of bone marrow. The technique was to subject a sulfur colloid preparation to filtration with Nuclepore filters and inject the colloid passing through the filter into animals. Attempts at resuspending the colloid trapped on the filters by ultrasonic agitation were unsuccessful so that only colloid less than a certain size could be used rather than colloid ranging between two filter sizes. Distribution studies in mice and rats indicated that colloidal particles less than 0.1 μm had a significant increase in bone marrow concentration and a concomitant decrease in splenic activity compared with the unfiltered starting material. Colloid 5 was chosen for clinical evaluation as greater than 60% of this material had previously been shown to pass through the 0.1-μm Nuclepore filter. These particles of less than 0.1 μm showed a two- to threefold increase in bone marrow uptake in animals but the $t_{1/2}$ of the particles in the blood was markedly increased compared with colloids of 0.25 μm. With this fact at hand, clinical studies were performed in six patients with aseptic necrosis of the femoral head. Unfortunately, the qualitative appearance of the scans was no better than that of those obtained with unfiltered colloid 5 or, for that matter, no better than that of those obtained with colloids 2 or 1. We must conclude from this result either that the increased target-to-nontarget ratio (bone marrow: blood) found in the animal model does not occur in patients or that the differences are not great enough to be seen in the qualitative manner undertaken by us.

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