A Multi-institutional In Vitro Evaluation of Commercial ^{99m}Tc Macroaggregated Albumin Kits

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Quality control testing of ^{99m}Tc macroaggregated albumin injection, U.S.P. (Tc-MAA) should include determination of radiochemical purity and particle size. We evaluated the variability in these parameters in vitro among products from five manufacturers of ^{99m}Tc-MAA kits. Radiochemical purity, as determined by supernatant activity determinations, varied from 0.5% to 16.0%. Although mean particle size was similar for all products tested, actual particle size distribution varied considerably among products tested.

The radiopharmaceutical most commonly used for pulmonary perfusion imaging is ^{99m}Tc-macroaggregated albumin (MAA) prepared from commercially produced kits. Quality control testing of this product commonly includes radiochemical purity and particle size determination. These tests not only monitor the safety and efficacy of MAA but may also serve as in vitro parameters in the comparison of different brands of this product. This multi-institutional study was performed to assess the degree of variability in radiochemical purity and particle size among commercially available brands of ^{99m}Tc-MAA.

MATERIALS AND METHODS

Five commercially produced MAA kit preparations were evaluated in this investigation. Table 1 lists each preparation tested and the number of vials per lot for each parameter evaluated. Table 1 also represents the combined data from four separate institutions, each using the same testing methodologies.

Particle Size Determination

For particle size determination, the kits were reconstituted with the manufacturer's minimum recommended volume of 0.9% sodium chloride for injection, U.S.P. For one preparation,* the 0.6 ml particle suspension provided by the manufacturer was evaluated without further dilution.

After adequate shaking to ensure particle dispersion, an aliquot of the MAA suspensions was removed from each vial, placed on a hemacytometer grid, and examined under a light microscope at 450× magnification. Multiple separate fields were photographed and examined so as to include a valid number of particles (i.e., > 100) for statistical evaluation. Using the known dimensions of the hemacytometer grid, a factor for converting photographic measurements to actual micron dimensions was determined. Subsequently, the longest axis of each particle on the photograph was measured and converted to micron dimension. Individual particle sizes were combined into 6-μ intervals. For graphic display of particle size distribution, the number of particles in each interval was expressed as a percentage of the total number of particles evaluated. Mean particle size was calculated according to the following formula:

$$\text{Mean particle size} = \frac{\Sigma N_i R_i}{\Sigma N_i}$$

where N_i is the number of particles of micron dimension R_i.

Radiochemical Purity

For the evaluation of radiochemical purity, each kit was reconstituted using the maximum volume and ^{99m}Tc activity recommended by the manufacturers as indicated in Table 1. Dilution of the kit to achieve maximum volume was performed, if necessary, using 0.9% sodium chloride injection, U.S.P. All kits were allowed to incubate for the minimum recommended time (Table 1) before initial determination of radiochemical purity.

Immediately after the minimum incubation period and at 6 hr after kit preparation, the radiochemical purity of each MAA preparation was evaluated using centrifugation techniques and radiochromatographic separation using either ITLC-silica gel with saline as the solvent or Whatman No. 1 paper with 85% methanol as a solvent.

In order to determine the total quantity of nonparticulate radiochemical impurities within each MAA preparation, centrifugation assays were performed according to U.S.P. XX (*1*). A 1-ml aliquot of the dispersed MAA was removed, transferred to a plastic centrifuge tube, and centrifuged at 2,000 rpm (800 × g) for 10 min. After centrifugation, two 0.1-ml volumes of the supernatant were accurately pipetted into separate test tubes. Likewise, two 0.1-ml volumes of the original dispersed MAA suspension were accurately pipetted into separate test

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TABLE 1. Summary of Manufacturers' Recommendations and Number of Vials Tested

MAA Kit and Lot Number	Number of Vials Tested: Particle Size Determination	Number of Vials Tested: Supernatant Activity	Minimum Recommended Volume (ml)	Maximum Recommended Volume (ml)	Maximum Recommended Activity (mCi)	Minimum Incubation Time (min)
Pulmolite†						
7086	1	2	—	—	—	—
7087	3	10	—	—	—	—
7090	3	10	2	8	50	1
7092	1	4	—	—	—	—
All Lots	8	26	—	—	—	—
Technescan-MAA‡						
0935012	2	6	—	—	—	—
0935013	2	6	—	—	—	—
0934053	1	2	5	10	60	15
0935059	1	2	—	—	—	—
All Lots	6	16	—	—	—	—
Tc-99m-MAA*						
J06E85M	1	2	—	—	—	—
K06F85M	1	2	—	3	90	10
All Lots	2	4	—	—	—	—
Macrotec§						
4J901	3	8	—	—	—	—
5A611	2	6	1	3	50	6
4F903	1	2	—	—	—	—
All Lots	6	16	—	—	—	—
AN-MAA¶						
1291	2	6	—	—	—	—
1289	2	6	—	—	—	—
1283	1	2	3	5	100	6
1284	1	2	—	—	—	—
All Lots	6	16	—	—	—	—

†Dupont-NEN.
‡Mallinckrodt, Inc.
*Medi-Physics, Inc.
§Squibb Diagnostics, Inc.
¶Syncor, Inc.

tubes. Radioactivity content of the pipetted supernatants and original MAA suspensions were subsequently assayed in a radioisotope dose calibrator. Supernatant and original suspension activities were averaged, respectively, and percent supernatant activity calculated according to the following formula:

$$\% \text{ Supernatant activity} = \frac{\text{Supernatant activity}}{\text{Suspension activity}} \times 100$$

RESULTS

All results are expressed as the mean (± standard deviation) of the total data obtained from each study site.

Particle Size Determination

Figure 1 graphically illustrates the particle size distribution of commercially available MAA kit preparations and their mean particle size. Note that the data from all lot numbers of a specific manufacturer were combined for this presentation. No significant differences in mean particle size distribution were observed between respective lot numbers or individual vials of a single manufacturer. However, as shown in figure 1, size distribution did vary among the brands tested. Each of the commercially available MAA kit preparations demonstrated > 90% of the particles having a longest dimension of 10–90 μ. No particles exceeding 150 μ were observed in any vials of MAA.

Radiochemical Purity

Table 2 illustrates the average percent supernatant activity for each lot of the commercially available MAA kit preparations evaluated. Values for both the immediate post-incubation determination and the 6-hr post-preparation determination are included. The average percent of radiochemical impurities associated with the supernatant fraction ranged from < 1% to > 16%. Substantial differences among brands and among individual lots of a single brand were observed. The percentage of supernatant activity demonstrated a general tendency to decrease between the immediate post-incubation and 6-hr post-preparation determinations.

The results of radiochromatographic analysis indicated that each lot of MAA kit preparations demonstrated < 10% of [^{99m}Tc]pertechnetate. The amount of this impurity did not

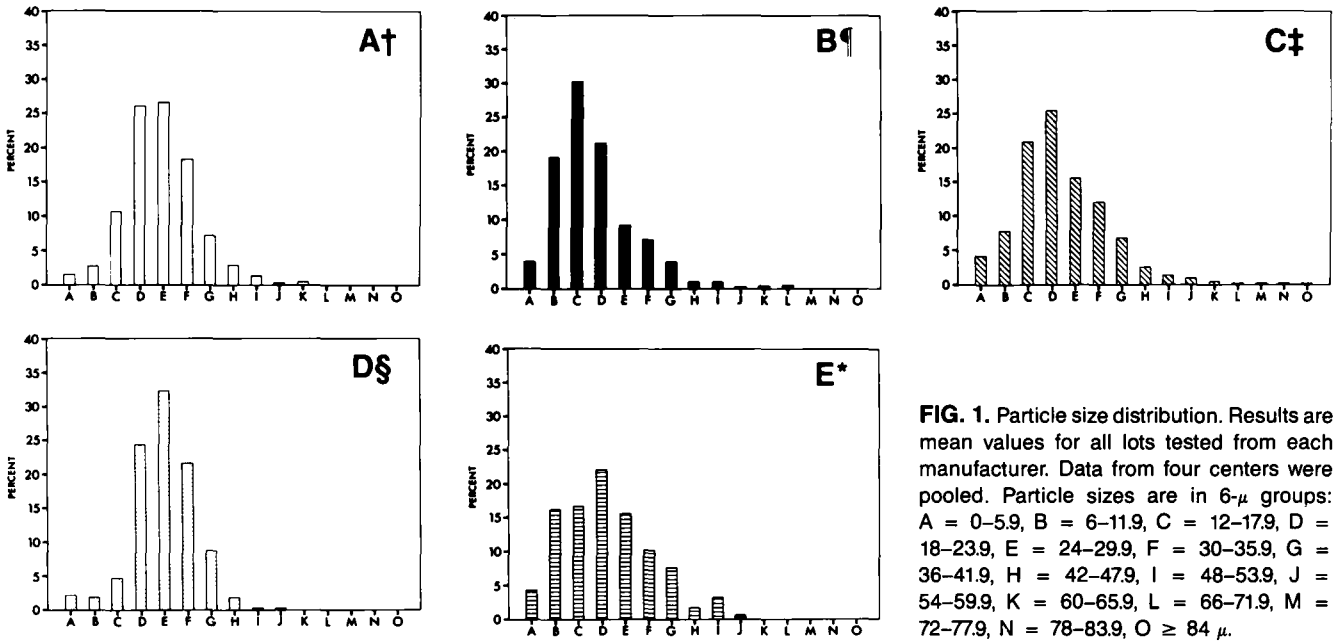

FIG. 1. Particle size distribution. Results are mean values for all lots tested from each manufacturer. Data from four centers were pooled. Particle sizes are in 6-μ groups: A = 0–5.9, B = 6–11.9, C = 12–17.9, D = 18–23.9, E = 24–29.9, F = 30–35.9, G = 36–41.9, H = 42–47.9, I = 48–53.9, J = 54–59.9, K = 60–65.9, L = 66–71.9, M = 72–77.9, N = 78–83.9, O ≥ 84 μ.

vary significantly between the post-incubation and 6-hr determinations.

DISCUSSION

The USP-NF Official Monograph for ^{99m}Tc-albumin aggregated injection specifies that > 90% of the observed aggregated particles have a diameter between 10 μ and 90 μ, and none of the observed particles have a diameter > 150 μ. This compendium also specifies that < 10% of the total radioactivity is found in the supernatant liquid, which in addition to pertechnetate, may also contain other soluble and dispersed (i.e., colloidal) radiochemical impurities (*2,3*).

TABLE 2. Results of Supernatant Activity Determinations

MAA Kit	Lot Number	Supernatant Activity (%) (mean ± S.D.) t = 0 hr	t = 6 hr
Macrotec§	4J901	0.49 ± 0.19	0.43 ± 0.07
	5A611	0.69 ± 0.76	0.44 ± 0.09
	4F903	0.56 ± 0.07	0.47 ± 0.13
Pulmolite†	7086	13.49 ± 4.52	10.44 ± 4.48
	7087	9.58 ± 2.82	8.43 ± 3.47
	7090	16.08 ± 3.79	14.15 ± 3.51
	7092	12.26 ± 5.40	9.72 ± 4.58
Technescan-MAA‡	0935012	6.90 ± 1.21	1.19 ± 0.54
	0935013	8.97 ± 3.23	1.61 ± 0.37
	0934053	12.24 ± 7.77	9.30 ± 8.15
	0934059	3.63 ± 2.52	1.41 ± 0.66
AN-MAA¶	1291	1.40 ± 0.98	0.61 ± 0.33
	1289	2.92 ± 2.80	1.27 ± 0.85
	1283	5.35 ± 4.55	0.64 ± 0.28
	1284	3.10 ± 0.60	9.47 ± 8.90
Tc-99m-MAA*	J06E85M	7.51 ± 1.30	3.39 ± 0.51
	K06E85M	6.85 ± 1.75	3.39 ± 0.51

§Squibb Diagnostics, Inc.
†DuPont-NEN.
‡Mallinckrodt.
¶Syncor, Inc.
*Medi-Physics, Inc.

In this investigation, all of the commercially available MAA kit preparations were shown to have nearly identical mean particle sizes and an appropriate percentage of the particles within the 10–90 μ range specified by the USP-NF XX. However, the actual distribution of particle sizes did vary among the preparations tested. The effect of such variations on MAA biodistribution and diagnostic efficacy are unknown at this time.

Several lots exceeded the USP-NF specification for supernatant activity. Although the clinical and diagnostic implications of exceeding this standard are unknown, it can be assumed that maximum target-to-background ratios in lung perfusion imaging are associated with minimum supernatant activity levels. A detailed evaluation of the exact chemical nature of the radiochemical impurities found in the supernatant of some MAA preparations was not included in this study. However, radiochromatographic analysis indicated that it was not [^{99m}Tc]-pertechnetate. These components may represent ^{99m}Tc-labeled proteins or colloids that will localize in the blood pool or liver, respectively (*2,3*). The USP-NF supernatant activity test is therefore well suited for the determination of radiochemical purity of MAA since all nonparticle bound impurities can be detected.

CONCLUSION

This investigation suggests that variability exists in regard to the particle size distribution and radiochemical purity of commercially available MAA kit preparations. Similar findings have been found by other investigators who have examined

the quality of various MAA preparations (*4–6*). Although in vitro evaluations such as this may provide objective data for the basis of radiopharmaceutical product selection decisions, it must be recognized that other important factors (i.e., manufacturing conditions, particle hardness, and rate of lung clearance) also contribute significantly to the overall safety and diagnostic efficacy of the MAA preparation used for lung perfusion imaging.

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FOOTNOTES

*Medi-Physics Inc., Richmond, CA.
†DuPont Co., N. Billerica, MA.
‡Mallinckrodt Inc., St. Louis, MO.
§Squibb Diagnostics, New Brunswick, NJ.
¶Syncor Inc., Sylmar, CA.

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