Microwave Preparation of Technetium-99m Sulfur Colloid

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Technetium-99m sulfur colloid (^{99m}Tc-SC) has been useful in reticuloendothelial imaging, and in particular in liver/spleen and more recently bone marrow scintigraphy. Technetium-99m SC can also be employed to localize acute gastrointestinal bleeding and has been used in lung ventilation studies. The standard radiolabeling method requires a heating period in a boiling water bath. A comparison of a standard boiling technique (5 min) and a microwave technique (20 sec) for the preparation of ^{99m}Tc-SC was performed. Radiochemical purity results and particle sizing data were analyzed, and a qualitative visual assessment of the change from a clear solution to an opaque one was performed. Both methods of preparation routinely yielded products with greater than 97% bound, particle sizing of greater than 82% between 0.1 μm and 1.0 μm, and a consistent opaque appearance of the radiopharmaceutical upon completion. Preliminary evaluation in patients demonstrated rapid blood clearance and excellent images. Microwave heating significantly reduces preparation time and yields a consistently acceptable radiopharmaceutical.

Technetium-99m sulfur colloid (^{99m}Tc-SC) has been routinely used for reticuloendothelial system scintigraphy since the mid-1960s. Although commercially available formulations vary slightly from one manufacturer to another, the chemical reaction common to all ^{99m}Tc-SC kits is acid decomposition of sodium thiosulfate in the presence of various stabilizing agents (*1*). The heating of the reaction vial containing ^{99m}Tc sodium pertechnetate, thiosulfate, and hydrochloric acid is critical to the preparation of ^{99m}Tc-SC. A common protocol for heating is to place the reaction vial in a shielded boiling water bath for 3–10 min. In order to expedite the preparation of ^{99m}Tc-SC, we examined and ultimately adopted a microwave oven heating technique. Use of a microwave oven for the preparation of ^{99m}Tc-SC was first described by Hall et al. (*2*) in a review of parameters affecting the in vitro properties of ^{99m}Tc-SC. Recently, ^{99m}Tc-sestamibi (Cardiolite) has been prepared by a microwave oven technique (*3*). The purpose of this study was to compare a standard boiling water bath technique with a microwave oven technique for the preparation of ^{99m}Tc-SC, by evaluating radiolabeling efficiency and the distribution of radioactive particle size, as determined by membrane filtration, and to demonstrate preservation of clinical properties and utility.

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MATERIALS AND METHODS

The ^{99m}Tc-SC kit utilized was obtained from the London Regional Nuclear Pharmacy (University Hospital, University of Western Ontario, London, Ontario, Canada). The kit is comprised of 3 vials. Vial A (10 cc evacuated reaction vial) contains 1.5 ml of a solution containing 3.0 mg sodium thiosulfate, 2.25 mg gelatin, 0.675 mg disodium ethylenediaminetetraacetic acid, 0.78 mg potassium perrhenate, and 6.8 mg dipotassium hydrogen phosphate. Vial B contains 0.5 N hydrochloric acid. Vial C contains a phosphate buffer in which 1 ml contains 66 mg sodium phosphate dibasic and 1 mg sodium phosphate monobasic.

Boiling Water Bath Technique

To a shielded Vial A, 5,000 MBq of ^{99m}Tc-pertechnetate in a volume of 3.0 ml normal saline was added. Then, 0.5 ml of Vial B was added to Vial A. Vial A was then heated in a shielded boiling water bath for 5.0 min. The reaction vial was removed from the boiling water and placed in a lead pot with cold running water for 1.0 min. The reaction vial was removed from the cold water bath, and 1.0 ml of Vial C (phosphate buffer) was added and the vial vented to equalize the pressure. Visual appearance, radiochemical purity, and particle size distribution were examined immediately after preparation and again after 8 hr of storage at room temperature.

Microwave Technique

In order to determine the length of microwave time necessary to simulate the boiling water bath heating process, a practice preparation of ^{99m}Tc-SC was performed. To a sample Vial A, from a sulfur colloid kit, 3.0 ml normal saline was added followed by 0.5 ml of Vial B. The reaction Vial A was then fitted with a styrofoam cap and microwaved at the highest intensity until the contents of the vial were noted to be boiling. It was assumed that at this point the contents of the vial had reached 100° C. This occurred after 20 sec. The microwave oven technical specifications are shown in Table 1.

TABLE 1. Microwave Oven Technical Specifications

Power Source	120 VAC 6 Hz
Power Consumption	0.95 KW (8.2 A)
Cooking Power	80–500 W
Oscillation Frequency	2450 MHz
Time	99 min 99 sec
Outside Dimensions (W × H × D)	18″ × 9½″ × 12¼″
Oven Dimensions	11″ × 5½″ × 11″
Oven Volume	0.4 ft^3

To a shielded Vial A, 5,000 MBq of ^{99m}Tc-pertechnetate in a volume of 3.0 ml of normal saline was added. Then, 0.5 ml of Vial B was added to Vial A. Vial A was fitted with a styrofoam cap over the aluminum cap of the vial to prevent sparking while the vial was being microwaved. Vial A was placed in the middle of the cooking area of the microwave oven. The microwave was set at the maximum intensity and the time was initially set for 20 sec. After completion of microwaving, the vial was briefly swirled and was then left to stand for 1.0 min. The reaction vial was then cooled in a shielded cold running water bath for 1.0 min. Following cooling, 1.0 ml of Vial C was added to Vial A and the vial vented to equalize the pressure. Visual appearance, radiochemical purity, and particle size distribution were examined immediately and again after 8 hr of storage at room temperature. Various times of microwaving the ^{99m}Tc-SC at the highest intensity were evaluated. A series of 6 products were prepared at both 10 and 20 sec, and 1 product was prepared by microwaving for 30 sec at the highest intensity.

In Vitro Assessment

Visual inspection of the product served as a qualitative assessment; we observed the change from a clear to an opaque solution and the point at which this occurred during preparation.

Radiochemical purity was assessed using instant thin layer chromatography (ITLC). ITLC-SG strips (Gelman Sciences, Ann Arbor, MI) were eluted with 0.9% NaCl solution. Calculation of labeling efficiency was as follows.

$$\frac{\text{net MBq top half (solvent front)} \times 100}{\text{net MBq top half} + \text{net MBq bottom half (origin)}}$$

Radioactive particle size distribution was performed by membrane filtration (Nucleopore Corp., Pleasanton, CA) (*4*). Aliquots of 0.1 ml of the colloid preparation were passed through pre-wetted 13-mm diameter filters of 0.1-μm and 1.0-μm pore size. The ^{99m}Tc-SC aliquot was then followed by 1.0 ml of normal saline. The percentage of activity retained on the filter was determined by counting the filter, and expressing this activity as a percentage of the total activity (i.e., filter + filtrate + washing).

In Vivo Assessment

Patients who were undergoing a ^{99m}Tc-SC liver/spleen scan or bone marrow scan were randomly assigned to receive either boiled or microwaved ^{99m}Tc-SC. Each patient was positioned supinely under a large field-of-view gamma camera. The patient received an intravenous bolus injection of 120 MBq of ^{99m}Tc-SC. Images were acquired on a computer system at a rate of 3 frames per min over the first 15 min. Regions of interest were placed over the heart, liver, and abdomen, and time activity curves were generated. An exponential half-time was generated for the rapid early clearance phase of the heart curve (0–5 min after injection) to determine the rate of blood clearance. In addition, the percentage of peak activity remaining in the heart at 5 min and 15 min after injection was determined. Finally, the ratio of activity in the liver to heart was determined at 5 min after injection.

Five patients with a mixed variety of hepatic and nonhepatic illnesses received boiled ^{99m}Tc-SC and six received microwaved ^{99m}Tc-SC.

RESULTS

The labeling efficiency and the particle size distribution of ^{99m}Tc-SC prepared by the standard boiling water bath technique are shown in Table 2. The product displayed a normal opaque appearance and slightly orange coloration. Average preparation time was 32 min.

The labeling efficiency and size distribution of microwave-produced ^{99m}Tc-SC varied with the length of the heating time (Table 3). The mean labeling efficiency of kits microwaved for 10 sec was only 39.3%. Particle size distribution for the ^{99m}Tc-SC microwaved for 10 sec was not performed due to the unacceptable labeling efficiency results. There appeared to be an excessive build-up of pressure inside the closed system of the reaction vial for the one vial microwaved for 30 sec. Upon completion of the 30 sec microwave cycle, the rubber stopper was buckled from the strain of the internal pressure in the reaction vial. This product also exhibited the usual opaque appearance, but with a darker coloration than the product prepared by the boiling water bath technique. Also, particle sizes tended to be higher (Table 3).

The ^{99m}Tc-SC prepared by microwaving for 20 sec was similar to the boiling water product. Visually it looked identical. There was no appreciable difference between the two preparations with regard to labeling efficiency or particle size

TABLE 2. Quality Control of Technetium-99m Sulfur Colloid Prepared Using a Boiling Water Bath Protocol

	0 hr	8 hr
Mean Labeling Efficiency (%) (n = 6)	97.7%	97.6%
Mean Particle Size Distribution (μm) (n = 6)	0.1 < 82.8% < 1.0 range 76.5–87	0.1 < 82.5% < 1.0 range 75.8–86.9

TABLE 3. Quality Control of Technetium-99m Sulfur Colloid Prepared by Using a Microwave Oven Protocol

	0 hr	0 hr	0 hr	8 hr
Heating Time	10 sec (n = 6)	20 sec (n = 6)	30 sec (n = 1)	20 sec (n = 6)
Mean Labeling Efficiency	39.3%	98.7%	99.2%	98.6%
Mean Size Range (μm)		0.1 < 82.9% < 1 81.5–84.6	0.1 < 63% < 1	0.1 < 83.4% < 1 81.6–85.9

(Tables 2 and 3). Average total preparation time was 7 min. Swipe test results from the interior of the microwave each day, for ten consecutive days of microwave preparation, revealed no traces of radioactive contamination.

In patients, there was rapid clearance of microwaved ^{99m}Tc-SC from the blood stream (Fig. 1) and excellent images of the liver and spleen were obtained (Fig. 2). There was no significant difference (unpaired Student's t-test) between the two ^{99m}Tc-SC products for any of the quantitative parameters examined (Table 4).

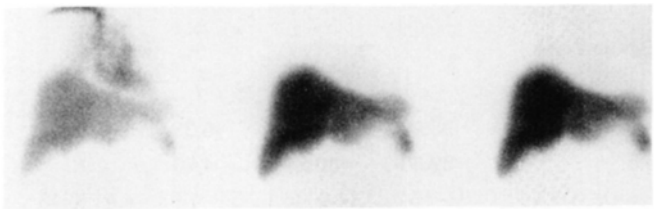

FIG. 1. Sequential 1-min anterior images obtained over liver of patient without known hepatic disease. Patient had received an injection of 120 MBq of ^{99m}Tc-SC prepared by the microwave technique using a 20-sec heating time.

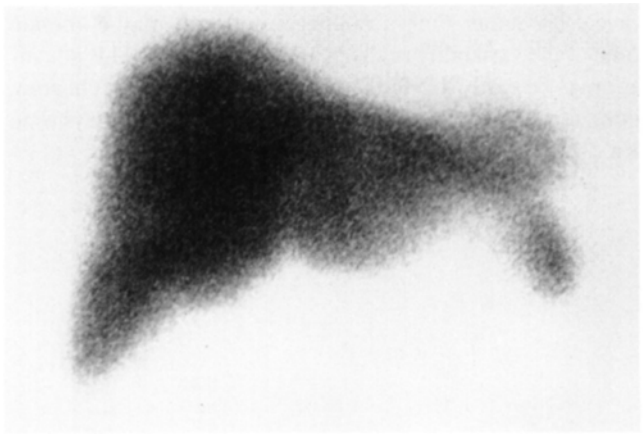

FIG. 2. Anterior images of liver of same patient 15 min after injection of microwaved ^{99m}Tc-SC.

DISCUSSION

The results show that there is no significant difference between radiolabeling efficiency, particle size distribution, or visual appearance of the ^{99m}Tc-SC produced by the microwave oven technique (20 sec) and that produced by the standard boiling water bath technique. Both products demonstrated a labeling efficiency of >97%. Particle size distribution as performed by membrane filtration (*4*) showed that more than 82% of the particles were between 0.1 μm and 1.0 μm at the time of preparation and 8 hr after preparation, for both products. This is considered acceptable according to the manufacturer's specifications. Pederson (*5*) has emphasized that membrane filtration measures the size distribution of radioactive particles, not the actual size. Technetium-99m SC particles should be between 0.1 μm and 1.0 μm for most clinical uses. Since this project compared the results of two different preparation techniques, we felt that membrane filtration as a sizing technique was adequate.

The total time required for preparing ^{99m}Tc-SC using the boiling water bath technique averaged 32 min. The time needed to heat the water bath to a gentle boil averaged 20 min followed by a 5-min heating period. The heating period with the microwave oven was reduced to a 20-sec cycle followed by a 1.0-min incubation period. The use of a microwave oven brings the preparation of ^{99m}Tc-SC into line with other routine radiopharmaceuticals (i.e., ~5 min from addition of pertechnetate to final assay of the product).

When microwaving any closed system, the build-up of pressure within the system is of concern. Vial A (the reaction vial) is evacuated with the sulfur colloid kit used in this institution. Therefore, the build-up of pressure above normal atmospheric pressure does not cause a problem, when the microwave cycle is maintained within limits. However, when the microwave cycle was set for 30 sec, the rubber stopper was bulging and the aluminum ring around the rubber stopper buckled from the build-up of the pressure within the closed vial. Pressure build-up within the reaction vial, besides being a function of the length of the microwave cycle, also depends on maximum power output of the microwave, internal dimensions of the cooking area, and the individual characteristics of various manufacturers' sulfur colloid kits. We have not examined any of these variables.

A practical solution to the build-up of pressure within a closed system might be to vent the reaction vial during the heating process. This would need to be done with a nonmetallic tool, such as a teflon catheter. The venting device would need to accommodate the use of a styrofoam cap on top of the aluminum ring of the reaction vial. The styrofoam cap prevents electrical sparking in the microwave. We have not tried this method and prefer to maintain a closed system.

Even though the ^{99m}Tc-SC formed by the acid solution of

TABLE 4. In Vivo Measurements Comparing Two Methods of Sulfur Colloid Preparation

	Blood Clearance $T_{1/2}$ (sec)	Blood % at 5 min	Blood % at 15 min	Ratio Liver to Heart at 5 min
Microwave				
Mean	113.67	20.57	10.20	5.93
s.d.	22.66	5.14	3.02	2.37
Range	93–151	15.6–29.8	6.4–14.9	3.3–9.4
Boiling Water Bath				
Mean	98.20	17.68	9.38	5.85
s.d.	39.50	10.24	4.70	1.70
Range	71–164	11.0–35.1	5.9–17.3	4.41–8.48

thiosulfate is a polydispersed colloid, Hall et al. have suggested that using a microwave heating technique contributes to preparing a product with a more homogenous particle size distribution (*2*). Taillefer has suggested that using a microwave oven rather than a boiling water bath may eliminate some of the variability in the heating process (*3*). This advantage may be partly due to the better control over exact heating times, especially when using a microwave which displays time as a digital function.

CONCLUSION

We have shown that ^{99m}Tc-SC prepared in a microwave oven is comparable to ^{99m}Tc-SC prepared using a boiling water bath in terms of radiolabeling efficiency, particle size distribution, visual assessment, and clinical characteristics in vivo. Use of a microwave oven for the heating process has shortened the average preparation time from 32 min to 7 min.

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