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A Convenient Route to [^{68}Ga]Ga-MAA for Use as a Particulate PET Perfusion Tracer

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Abstract

A convenient method is described for compounding [^{68}Ga]Ga-MAA (MAA = macroaggregated human serum albumin) with the eluate of a commercially available TiO_2-based ^{68}Ge/^{68}Ga generator. The final [^{68}Ga]Ga-MAA product was obtained with an 81.6 ± 5.3% decay-corrected radiochemical yield and a radiochemical purity of 99.8 ± 0.1% (n = 5). Microscopic examination showed the [^{68}Ga]Ga-MAA product to remain within the original particle size range. The entire procedure, from generator elution to delivery of the final [^{68}Ga]Ga-MAA suspension, could be completed in 25 minutes. Only 4.4 ± 0.9% of the total ^{68}Ge breakthrough remaining associated with the final [^{68}Ga]Ga-MAA product. The procedure allows reasonably convenient preparation of [^{68}Ga]Ga-MAA in a fashion that can be readily adapted to sterile product compounding for human use.

Keywords

Gallium-68; Macroaggregated Human Serum Albumin (MAA); PET; Perfusion

Introduction

Generator-produced ^{68}Ga offers an alternative to the cyclotron-based positron-emitting nuclides (^{15}O, ^{13}N, ^{11}C, and ^{18}F) that are the primary radionuclides employed in research and clinical studies using positron emission tomography (PET). The ^{68}Ge parent has a half-life of 271-days, while the half-life of the positron-emitting ^{68}Ga daughter is 68-minutes (Browne and Firestone, 1986).

Human serum albumin microspheres (Rhodes and Bolles, 1975; Davis, 1975) labeled with ^{68}Ga have found use in PET studies of pulmonary perfusion (Chester, et al., 1975; Mintun, et al., 1986; Schuster and Green, 1987), as well as in studies to validate freely diffusible PET markers of tissue perfusion (Schelbert, et al., 1980; Bergmann, et al., 1984; Steinling, et al., 1985; Mintun, et al., 1986; Schuster and Green, 1987). Albumin microsphere labeling with ^{68}Ga can be effectively achieved either by hydrolysis and precipitation of the $^{68}Ga^{3+}$ ion in the presence of the albumin particles (Chester, et al., 1975; Hnatowich, 1976; Yvert, et al., 1979; Hayes, et al., 1981; Maziere, et al., 1986; Mintun, et al., 1986; Schuster and Green, 1987), or by covalent conjugation of the microspheres with a high-affinity gallium chelating

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ligand (Wagner and Welch, 1979). When the FDA-approved ^{99m}Tc-human serum albumin microsphere product was withdrawn from the U.S. market, the ^{68}Ga-labeling method for albumin microspheres was adapted for use with the commercial kits available for the preparation of [^{99m}Tc]Tc-MAA (macroaggregared human serum albumin) (Even and Green, 1989). Of the commercially available kits for compounding [^{99m}Tc]Tc-MAA, the Pulmolite® product gave the best performance in ^{68}Ga-labeling, but only if the MAA was pre-washed to remove the albumin excipient (Even and Green, 1989).

The previous [^{68}Ga]Ga-MAA labeling procedure employed a SnO_2-based ^{68}Ge/^{68}Ga generator eluted with 1N HCl (Loc'h, et al., 1980), and required a somewhat cumbersome evaporation of that HCl eluate before reconstitution of the ^{68}Ga in acetate buffer and mixing with MAA (Even and Green, 1989). The present study was undertaken to explore preparation of [^{68}Ga]Ga-MAA using the eluate of a newer commercial TiO_2-based ^{68}Ge/^{68}Ga generator, seeking to exploit its less acidic (0.1 N HCl) generator eluate in a labeling procedure that avoids the HCl evaporation step used previously (Even and Green, 1989).

Methods

The required reagent solutions were prepared from 18 MΩ water and ultrapure HCl (30%, Fluka TraceSelectUltra for trace analysis) and ultrapure sodium acetate (Fluka TraceSelect, ≥99.99%, metals basis) to minimize introduction of trace metal impurities. The MAA particles (*ca*. 4.4 million) from a commercial CIS-US (Bedford, MA) Pulmolite® MAA kit [a sterile, non-pyrogenic, lyophilized mixture of: Albumin Aggregated – 1.0mg; Albumin Human – 10mg; Stannous Chloride, Minimum ($SnCl_2$) – 2.4μg; Stannous Chloride, ($SnCl_2$) – 7.0μg; Tin Chloride (stannous and stannic), dihydrate, maximum (as $SnCl_2 \cdot 2H_2O$) – 0.13μg; Sodium Chloride – 10mg] were suspended in 5mL sterile saline, isolated by centrifugation (1.5 minutes at 3000 rcf), the supernate discarded, and the MAA resuspended in 0.5 mL sterile saline. This study employed a 1.85 GBq (50 mCi) TiO_2-based ^{68}Ge/^{68}Ga generator (Cyclotron Co. Ltd., Obninsk, Russia) that is currently distributed in the United States by NUKEM GmbH (MC Pharma GmbH, Bonn, Germany). The generator age was 1.5-years at the time these experiments were performed.

The ^{68}Ga generator was eluted with 5 mL 0.1 N HCl following the manufacturer's protocol. To this 0.1N HCl solution of [^{68}Ga]Ga-chloride was added 0.17 mL 3N NaOAc, bringing the pH to 5–6. The resulting [^{68}Ga]Ga-acetate solution (ca. 225 MBq) was filtered through a 0.2-μm sterile membrane and aseptically added to the washed MAA suspension. After vigorous mixing, the [^{68}Ga]Ga-MAA suspension was incubated in a heat block at 75°C for 15 minutes while swirling at 300 rpm. The resulting ^{68}Ga-labeled MAA was isolated by centrifugation and resuspended in 5 mL sterile saline. Radiolabeling yield was determined by filtration of the final [^{68}Ga]Ga-MAA suspension through a 0.2-μm nylon syringe filter, which will selectively retain the MAA-bound ^{68}Ga.

Results and Discussion

The ^{68}Ge/^{68}Ga generator system employed for the present study is based on a TiO_2 stationary phase and is eluted with 5 mL 0.1N HCl. The generator generally performed in accordance with the manufacturer's specifications: elution yields ≥50% and ^{68}Ge breakthrough <0.01%. Using our generator, elution yields were, in fact, consistently >60%, but did slowly decline over time from an initial high of 80%. While ^{68}Ge breakthrough generally met the manufacturer specifications, occasionally ^{68}Ge breakthrough values as high as 0.02% were observed. Better performance with regard to ^{68}Ge breakthrough has been reported by other investigators using this generator system (Meyer, et al., 2004). As with all radiopharmaceuticals derived from generator-produced radionuclides and intended for human use, careful monitoring of parent

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breakthrough is clearly necessary for accurate estimation (and control) of patient radiation exposure, especially when the product involves a relatively long-lived parent.

Our modified compounding procedure, involving direct addition of acetate-buffered generator eluate to washed MAA particles, followed by brief incubation at 75°C, offers a reasonably convenient route to aseptic compounding of [^{68}Ga]Ga-MAA. The final [^{68}Ga]Ga-MAA had a radiochemical purity of 99.8 ± 0.1% (n = 5) and was obtained with an 81.6 ± 5.3% decay-corrected radiochemical yield. The complete procedure, from generator elution to delivery of the final [^{68}Ga]Ga-MAA suspension, could be completed in 25 minutes. The corresponding end-of-synthesis radiochemical yield was 63 ± 4%. Microscopic examination showed the ^{68}Ga-labeled MAA particles to remain within their original size range (Figure 1).

Our previous studies demonstrated the importance of the pre-washing step prior to addition of ^{68}Ga to the Pulmolite® MAA particles (Even and Green, 1989). With pre-washed Pulmolite® MAA we observed higher labeling yields that seen with other commercial MAA formulations; however, if the pre-wash step was omitted, the Pulmolite® MAA gave the poorest labeling results (Even and Green, 1989). While the pre-wash may be removing some of the Sn(II) associated with the formulation, we believe the improvement of the labeling yield by the pre-wash step derives largely from removal of the free albumin excipient that is present in Pulmolite®, but not the other MAA formulations tested (Even and Green, 1989).

The chemical nature of ^{68}Ga binding to the MAA particles is not known. We hypothesize that the ^{68}Ga adsorbs to the surface of the MAA particles after hydrolysis to insoluble gallium hydroxide; however, specific interactions of the Ga(III) ion with protein lone pairs exposed at the particle surface cannot be excluded as a trapping mechanism by our data.

The fate of the ^{68}Ge breakthrough from the generator was assessed by gamma counting both the final MAA product, and the combined waste solutions, after allowing >24 hours for decay of the original ^{68}Ga. The ^{68}Ge breakthrough was primarily found in the discarded aqueous supernate from the labeling reaction; only 4.4 ± 0.9% of the total ^{68}Ge breakthrough remained associated with the final [^{68}Ga]Ga-MAA product. Thus, breakthrough measurements for the generator eluate itself will tend to significantly overestimate the ^{68}Ge contribution to total patient radiation exposure from administration of a [^{68}Ga]Ga-MAA product compounded as described.

This labeling procedure can easily be implemented in a fashion suitable for delivery of a sterile, pyrogen-free [^{68}Ga]Ga-MAA product using a sterile laminar flow hood, sterile solutions and disposables, and USP <797>-compliant aseptic techniques for the required open transfers of reagents (U.S. Pharmacopeia, 2007). The product is expected to be suitable for use in PET procedures requiring a short-lived, biodegradable, particulate perfusion tracer akin to [^{99m}Tc]Tc-MAA.

Conclusion

Employing ^{68}Ga from a commercially available TiO_2-based ^{68}Ge/^{68}Ga generator, a procedure was developed that allows reasonably convenient preparation of [^{68}Ga]Ga-MAA in a fashion that can be readily adapted to compounding of sterile product for human use.

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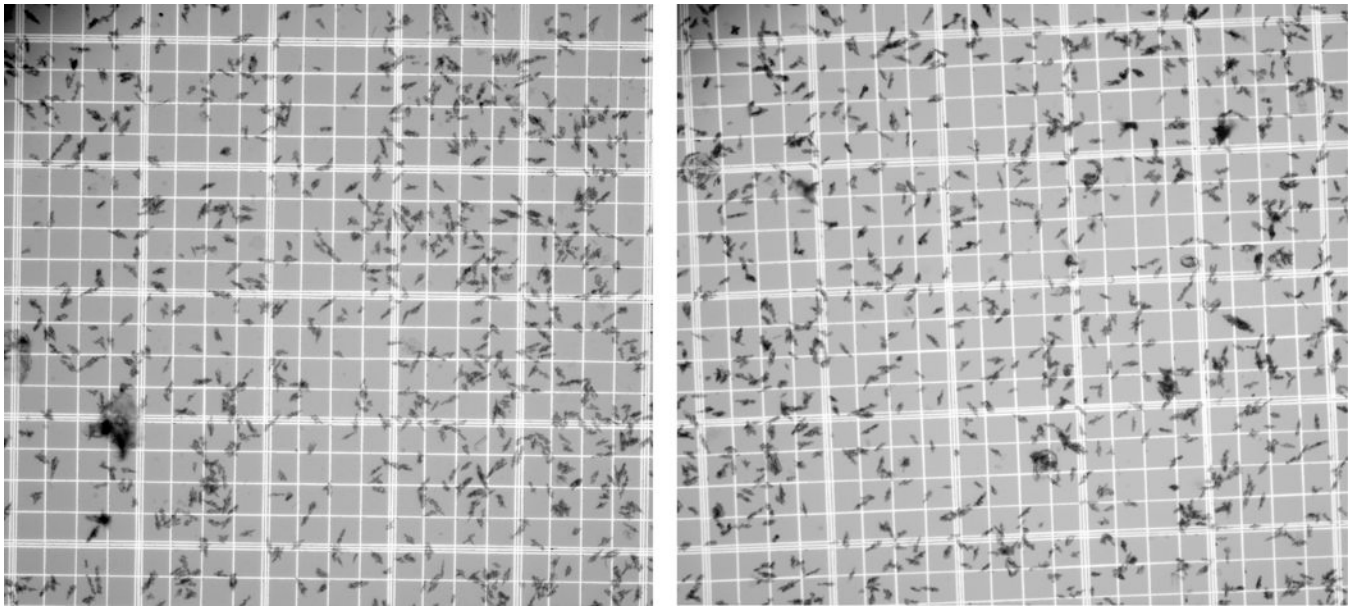

Figure 1.
Representative samples of the MAA particles before (left) and after (right) labeling with ^{68}Ga. The smallest squares of the hemacytometer are □50-micrometers on a side. The ^{68}Ga-labeled MAA particles remain within the specifications for the Pulmolite® kit (i.e., >90% of the particles between 10 and 90 micrometers, with typical average size of 15 to 30 micrometers and none >150 micrometers).