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PREPARATION OF ^{90}Y-LABELED TIN FLUORIDE COLLOID FOR RADIOSYNOVECTOMY

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Abstract

In this study, tin fluoride colloid (SnF-c) was prepared, labeled with ^{90}Y and characterized with respect to its physicochemical properties.

Particle size of SnF-c, at constant concentration of SnF_2, was dependent on pH, concentration of NaF, temperature and time. The particle size of SnF-c decreased with an increase in NaF concentration and a decrease in reaction mixture pH. Radiolabeling yield of ^{90}Y-SnF-c at higher temperature increased and it was greater than 98% for the preparation at 95 ^{o}C. Due to high labeling yield and stability, ^{90}Y-SnF-c might be a promising agent for radiosynovectomy.

Introduction

Radiosynovectomy (RS) was introduced as a modality for the treatment of rheumathoid arthritis as early as 1950's and the number of studies has been growing each year [1, 2]. Due to its convenience, long-term effects, repeatability and surgery avoidance, RS has been used for the treatment of resistant synovitis of individual joints after failure of long-term systemic pharmacotherapy and intra-articular steroid injections. The method is based on local intra-articular injection of β-emitting radionuclides in colloidal form to counteract and control synovial inflammation. Particle size, shape, charge and stability of a radiocolloid suspension are significant parameters that determine its organ distribution in vivo. The selection of proper radiopharmaceutical for the treatment of large, medium or small joints depends on the penetration range of β-emitting radionuclide and colloid particle size [3]. Yttrium-90 (^{90}Y) is a clinically acceptable β-emitting radionuclide and due to a half-life of 64.4 hours, $E_{max\beta-}$ of 2.27 MeV and a mean/maximum penetration depth of 3.6/11 mm it is ideal for therapy purpose. Our experiments included investigation of the factors influencing preparation of SnF-c and ^{90}Y-labeling, as well as the stability of the prepared radiocolloid.

Experimental

$^{90}YCl_3$ was purchased from Polatom, Poland, in a no-carrier-added form. All other reagents and solvents purchased from commercial sources were used without further purification.

To prepare ^{90}Y-SnF-c, 1 ml aliquots of nitrogen purged water for injection, containing 0.125 mg SnF_2 and different amounts of NaF with pH maintained at 5.1 and 5.9, were filtered (0.22 μm, Millipore Co.), dispensed into vials under nitrogen atmosphere and lyophilized for 24 h. The level of NaF was varied: 0.2, 0.5, 1, 2.5 and 5 mg/mL designated as SnF-c1, SnF-c2, SnF-c3, SnF-c4 and SnF-c5

formulation, respectively. The final pH of suspensions was kept at 5.1 and 5.9. Freeze-dried formulations (in triplicate) kept in shielded vials were reconstituted with 5 ml of water for injection. Then 5-15 µl of $^{90}YCl_3$ stock solution (about 185 MBq) was added to each vial. The reaction vials were shaken at room temperature (RT) or at 50 and 95 ^{o}C for 15, 30 or 60 min and cooled to room temperature. Then, the suspensions were additionally shaken at low speed up to 3 h.

The radiolabeling yield (RY) of radiolabeled colloid was determined by instant thin layer chromatography (ITLC). Particle size distribution, polydispersity index and zeta potential (ZP) were measured by Dynamic Light Scattering (DLS) technique using a Zetasizer Nano ZS (Malvern, UK) with 633 nm He-Ne laser and 173^{o} detection optics (backscatter detection). The radioactive particle size distribution (RPSD**)** of ^{90}Y-SnF-c was performed by successive membrane filtration steps of a single sample through 1.0, 0.4 and 0.2 µm pore size membrane filters. The stability of ^{90}Y-SnF-c was evaluated for a period up to 7 days by determining its radiochemical purity (RCP) with ITLC at different times after preparation.

Results and Discussion

The main goal of this study, the preparation of ^{90}Y-SnF-c, which can be successfully used for RS was achieved. The SnF-c used in this study as colloid template appears to be very suitable for labeling with beta emitting radionuclides. The SnF-c was prepared in lyophilized form and the particle size of the colloid was adjustable by varying the ratio of SnF_2 to NaF (w/w ratio SnF_2: NaF up to 1:200).

Radiolabeling of SnF-c with ^{90}Y is a simple procedure, which provides a very high yield of labeled particles. ITLC-SG/saline method enables quantitative determination of ^{90}Y-labeled colloid remained at the origin and unbound ^{90}Y in the form of $^{90}YCl_3$, which migrates with the solvent front. Although the radiolabeling of SnF-c with ^{99m}Tc occurs nearly instantaneously, the radiolabeling with ^{90}Y required an extended period of boiling. The RY of ^{90}Y-SnF-c increases as a function of temperature and time, reaching the highest value of >98% at 95 ^{o}C, after reaction mixture boiling for 30 min. Obviously, the heating step during SnF-c labeling was essential to get a product with high radiolabeling yield and improved stability. The stability and size-range of all batches of ^{90}Y-SnF-c, prepared by heating and agitation for different times were analyzed. As observed in our set of experiments, temperature, agitation and time affect both the radioactivity tagged to particles and the size of particles. The particles come in contact with each other and the probability of their sticking together depends on repulsive as well as attractive forces, due to increasing temperature and agitation time.

To better understand the formation of ^{90}Y-SnF-c as well as their radiolabeling and to define primary particles (templates), the particle size of lyophilized formulations (for SnF-cT1 to SnF-cT5) reconstituted with water (no YCl_3 added) was measured. Our results of PSD measurement confirmed the existence of primary colloidal particles (templates) with diameter of 123-138 nm in SnF_2-NaF suspensions at room temperature before radiolabeling. These primary particles in all formulations first aggregate, and finally agglomerate as a function of temperature, agitation and aging (schematic presented in Fig. 1).

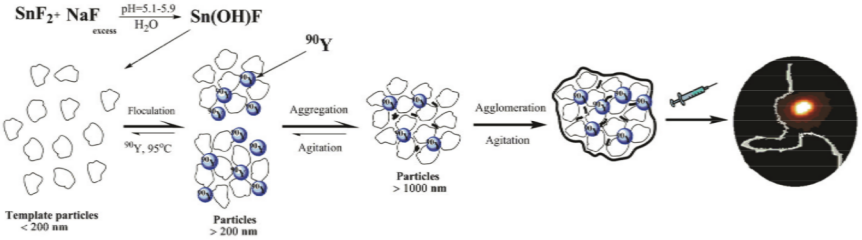

Figure 1. Formation of ^{90}Y-Labeled tin fluoride agglomerates from template particles.

The factors affecting the formation of stable, cemented SnF agglomerates were not well understood. Generally, if an aggregate survives long enough, sufficient cementation will occur to form stable agglomerate that can no longer be ruptured along the lines of contact of the original flocculating particles. To test the formation of stable agglomerate, the sample was withdrawn from the light scattering cell into syringe, re-syringed, put back into the cell and then particle sizes were measured again. The average particle diameter value remained unchanged. According to the results obtained, we conclude that the agglomeration rate increases with increasing temperature during radiolabeling and prolonged time of shaking, and that the large particles are agglomerates of the small ones.

The rate of Sn(II) hydrolysis depends on the concentration of NaF in the reaction mixture. We assumed that SnF_2 in formulations (Y-SnF-c1 - Y-SnF-c3) was partially hydrolyzed because the present NaF concentrations were not sufficient to completely suppress Sn(II) hydrolysis. Higher concentrations of NaF (>1 mg/mL) in the reaction mixture prevented formation of Sn(II) hydroxo complexes in the suspension.

The ^{90}Y-SnF-c demonstrated high *in vitro* stability in either human serum or human synovial fluid at 37 ^{o}C up to 7 days.

Conclusion

The present study has shown that ^{90}Y-SnF-c particles can be prepared with high labeling yield and *in vitro* and *in vivo* stability. The particle size of ^{90}Y-SnF-c was controllable by manipulating the conditions under which the colloids form. The optimum size of colloid particles can be easily designed for different therapeutic applications. Promising results suggest that ^{90}Y-SnF-c depending on particle size, may be of potential use for RS.

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