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^{188}Re radiopharmaceuticals for radiosynovectomy: evaluation and comparison of tin colloid, hydroxyapatite and tin-ferric hydroxide macroaggregates

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Abstract

Background: Radiosynovectomy is a therapy used to relieve pain and inflammation from rheumatoid arthritis and related diseases. In this study three ^{188}Re particulate compounds were characterized according to their physico-chemical properties and their biological behavior in rabbits. The results were compared in order to establish which was the radiopharmaceutical that better fits the requirements of this kind of radiotherapy.

Methods: Three radiopharmaceutical formulations, tin colloid, hydroxyapatite particles (HA) and ferric hydroxide macroaggregates coated with tin colloid (FHMA), were physically characterized (number, volume and surface of the particles). For this purpose laser diffraction methodology was used. To evaluate cavity leakage of activity the following studies in New Zealand rabbits were performed: scintigraphic images for 48 hr after intraarticular injection of each radiopharmaceutical, biodistribution at 48 hr and urine samples collection during the first 24 hr post-radiopharmaceutical administration.

Results: Labeling procedures for ^{188}Re -HA and ^{188}Re -Sn-FHMA were labour intensive while ^{188}Re -Sn was easily prepared. Furthermore, ^{188}Re -Sn colloid offered the greatest surface area in the 2–10 microm range and was obtained with a radiochemical purity over 95%, while percentage of bound activity for ^{188}Re -HA and ^{188}Re -Sn-FHMA were 55% and 92% respectively. Stability was verified for the three radiopharmaceuticals for 24 hr. Scintigraphic studies and biodistribution in rabbits after intraarticular administration of the radiopharmaceuticals showed relevant activity only in the knee, this being over 90% of the residual activity in the whole body at 48 hr in every case. Renal elimination of ^{188}Re -Sn colloid and ^{188}Re -Sn-FHMA was detected by activity measurements in urine samples, during the first 12 hr post-radiopharmaceutical injection.

The percentage of activity retained in the knee was 69.1% for ^{188}Re -Sn colloid, 55.1% for ^{188}Re -Sn-FHMA and 33.6% for ^{188}Re -HA.

Conclusion: The ^{188}Re -Sn colloid was easy to prepare, minimum facilities were required, was stable for 24 hr and showed minimal leakage from the joint after intraarticular injection into the rabbit's knee. Furthermore, ^{188}Re -Sn colloid has greater retention in the knee when it is compared with the other radiopharmaceuticals, so it could provide the best therapeutic effect/absorbed dose ratio for the patient.

Background

Three principal diseases associated with synovia hypertrophy are rheumatoid arthritis, hemophilic joint disease (principally related to bleeding into the joint), and some cases of traumatic joint disorders. The number of hemophilic patients is relatively small. In contrast, rheumatoid arthritis affects 1–2% of the world's population with a preponderance of men over women [1,2]. Cellular recruitment and proliferation, with subsequent formation of synovial granulation tissue (pannus) and an increased secretion of synovial fluid characterize the inflammatory process. Progression of the disease leads to the destruction of the joint or loss of function. Surgery is the last option as a conventional technique for treating intractable joint disease after pharmacological therapies have failed, but removal of all the tissue is not frequently achieved and so there is high recurrence after 3 to 5 years [2]. Radiation synovectomy provides an interesting alternative because cartilage is relatively radioresistant, so a radioactive agent with effective soft tissue penetration can be administered directly into the joint, causing no harm to the adjacent cartilage. As beta radiation can penetrate only a few hundred cell diameters, microparticles labeled with beta emitting radionuclides are effective in treating the disease by radiation in confined spaces without endangering nearby normal tissues [2]. Radiopharmaceutical particle size must be small enough to be phagocytosed by the superficial cells of the synovium, but not so small as to facilitate a fast biological clearance by diffusion from the joint [2,3].

Many beta emitters, and many other particulate chemical compounds have been used as radiosynovectomy agents [4-6]. In this study ^{188}Re is the chosen radionuclide as it is readily available on routine basis from the $^{188}\text{W}/^{188}\text{Re}$ generator. The radionuclide ^{188}Re , has a β -ray emission of sufficient energy (2.11 MeV) to penetrate 5–10 mm of thickened synovial membrane, and its low-level γ -ray emission (155 keV) makes scintigraphic monitoring possible, without harming patients or practitioners. Its half-life (16.9 hr) is adequate in terms of obtaining an appropriate therapeutic effect or for handling of the agent, avoiding hazardous residual effects.

In this study, particulate chemical compounds such as tin colloid, hydroxyapatite particles and ferric hydroxide macroaggregates were compared from the physico-chemical and biological point of view.

The most important criteria of therapeutically useful radiolabeled microparticles are their physico-chemical characteristics such as size range, surface area and volume, insolubility in aqueous media and irreversible attachment of radionuclide to the particles [1,2,7]. The best method of particle size determination is electron microscopy and more recently laser scattering, both of which provide

information on particle number, size and size distribution. The last of these is used in this study.

Radiopharmaceutical leakage from the knee was evaluated by the acquisition of scintigraphic images over 48 hr after intraarticular administration of the radiolabeled preparations to New Zealand rabbits. Biodistribution studies were also performed.

The results were compared in order to establish which was the radiopharmaceutical that best fits the requirements of this kind of therapy.

Methods

Radiopharmaceutical composition

Four radiopharmaceutical kits were prepared according to the following formulations:

^{188}Re -Tin colloid [8]

- 15 mg $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$
- 0.5 mL HCl 0.1 N
- N_2 atmosphere

^{188}Re -Hydroxyapatite particles (Indirect method) [1]

First step: preparation of ^{188}Re -HEDP kit

- 10 mg HEDP (free acid)
- 3 mg gentisic acid
- 0.3 mg KReO_4
- 3.8 mg $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$

Second step: preparation of ^{188}Re -Hydroxyapatite (HA) particles kit:

- 40 mg Hydroxyapatite (Ceramed, Type II, 20 μm , CAT N° 157-2000)
- 650 μL 0.9% saline solution
- 50 μL of 20% Tween 80 (in water)
- 100 μL of $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ solution (4 mg/mL)
- N_2 atmosphere

^{188}Re -Hydroxyapatite particles (Direct method) [9]

- 40 mg Hydroxyapatite (Ceramed, Type II, 20 μm , CAT N° 157-2000)
- 20 mg $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$
- 13.7 mg $\text{K}_2\text{C}_2\text{O}_4 \cdot \text{H}_2\text{O}$

pH was adjusted to 1.5 with HCl 0.75 N

¹⁸⁸Re-Ferric Hydroxide Macroaggregates, modified from Castro M, Portilla A. [10]

First step: preparation of ¹⁸⁸Re-Tin colloid:

- 15 mg $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$
- 0.5 mL HCl 0.1 N
- N₂ atmosphere

Second step: preparation of ¹⁸⁸Re-Ferric Hydroxide Macroaggregates (FHMA):

- 1.8 mL $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ (7.36 mg/mL)
- 0.7 mL NaOH 0.1 N
- 1.1 mL 0.9% saline solution
- 0.6 mL PVP K30 (16 mg/mL)
- 3 mL PVP K30 (16 mg/mL) pH 8.5

All reagents used were analytical grade.

Equipment

- Dose calibrator system: Capintec Radioisotope Calibrator CRC 5
- Solid scintillation counter NaI(Tl) 3 × 3": EG&G ORTEC Multichannel Analyzer
- Particle size analyzer: Particle Size Analyzer Coulter®
- Gammacamera: Sophy Camera DSX

Labeling procedure and quality control

The ¹⁸⁸Re used in all formulations were eluted from a ¹⁸⁸W/¹⁸⁸Re generator (Oak Ridge Laboratories, United States).

¹⁸⁸Re-Tin colloid

The ¹⁸⁸Re-Sn colloid was labeled by the addition of 500 μCi (18.5 MBq) of ¹⁸⁸ReO₄⁻ to the kit formulation

described above, then it was autoclaved for 1 hour. pH was adjusted to 6.0 with the addition of NaOH 1.0 N.

Radiochemical purity was determined by paper chromatography (Whatmann 1) using 0.9% saline solution as the mobile phase. Radioactivity was measured with a NaI(Tl) solid scintillation counter.

¹⁸⁸Re-Hydroxyapatite particles (Direct method)

40 mg of hydroxyapatite particles were mixed in a centrifuge tube with 13.7 mg $\text{K}_2\text{C}_2\text{O}_4 \cdot \text{H}_2\text{O}$ and 20 mg $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ with 0.3 mL of distilled water. 3 mCi (111 MBq) of ¹⁸⁸ReO₄⁻ (contained in 0.4 mL) was added to the tube. The pH of the reaction mixture was made acidic (pH 1.5) by slow addition of HCl 0.75 N. The suspension was vortexed and incubated at room temperature for 1 hour. 1 mL of ascorbic acid (10 mg/mL) was added to the suspension at the end of the hour and was centrifuged at 2000 rpm for 2 minutes. Activity in supernatant and particles was measured in a dose calibrator system. The particles were washed twice with 2 mL of ascorbic acid. The activity of the particles and washings was also measured. The final suspension was made in ascorbic acid (10 mg/mL, pH 5).

The percentage of bound activity was determined by measuring the activity of both particles and supernatant solution in a dose calibrator. From these data the percentage of labeled particles yield was calculated.

¹⁸⁸Re-Hydroxyapatite particles (Indirect method)

First step: preparation of ¹⁸⁸Re-HEDP. ¹⁸⁸Re-HEDP was prepared by adding 1 mL of a ¹⁸⁸ReO₄⁻ solution (11 mCi / 414 MBq) to a vial containing the lyophilized HEDP kit formulation described above (pH \approx 1). The solution was heated in a water bath for 10 minutes at 100°C.

Radiochemical purity of ¹⁸⁸Re-HEDP was determined by the paper chromatography method using a solution of HEDP 0.01 M in saline/Whatmann 3 MM and acetone/Whatmann 1 to determine ¹⁸⁸ReO₄⁻, ¹⁸⁸Re-HEDP and reduced hydrolyzed ¹⁸⁸Re species respectively.

Second step: preparation of ¹⁸⁸Re-HA. ¹⁸⁸Re-Hydroxyapatite particles were prepared by sequential addition of the following materials to a centrifuge tube containing 40 mg of hydroxyapatite particles: 650 μL of N₂-purged saline, 200 μL of ¹⁸⁸Re-HEDP (4 mCi / 148 MBq), 50 μL of 20% Tween 80 in water and 100 μL of a N₂-purged $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ solution (4 mg/mL). The mixture was incubated for 1 hour at room temperature with occasional stirring. 4 mL of saline solution was added to the contents of the tube and then centrifuged at 2000 rpm for 4 minutes. The supernatant and the particles were separated. The ¹⁸⁸Re-Hydroxyapatite particles were resuspended with 3 mL of saline solution.

The percentage of bound activity was determined by measuring the activity of both particles and supernatant solution in a dose calibrator. From these data the percentage of labeled particles yield was calculated.

¹⁸⁸Re-Sn-Ferric Hydroxide Macroaggregates

First step: preparation of ¹⁸⁸Re-Sn colloid: The ¹⁸⁸Re-Sn colloid was labeled by the addition of 500 μ Ci (18.5 MBq) of ¹⁸⁸ReO₄⁻ to the kit formulation described above, then it was autoclaved for 1 hour.

Radiochemical purity was determined by paper chromatography (Whatmann 1) using 0.9% saline solution as the mobile phase. Radioactivity was measured with a NaI(Tl) solid scintillation counter.

pH was adjusted to 7 with NaOH 1.0 N.

Second step: preparation of ¹⁸⁸Re-FHMA: 1 mL of ¹⁸⁸Re-Sn colloid and 1.8 mL of ferrous sulfate solution (7.36 mg/mL) were mixed in a centrifuge tube, 0.7 mL of NaOH 0.1 N and 1.1 mL of saline solution were added. The contents of the tube were vortexed for 10 seconds. 0.6 mL of Polivinylpyrrolidone (PVP) solution (16 mg/mL) were added, vortexed and centrifuged at 1400 rpm for 4 minutes.

The precipitate particles were separated and the labeled FHMA were washed as follows.

¹⁸⁸Re-FHMA were mixed with 3 mL of a PVP solution (16 mg/mL, pH 8.5), vortexed and centrifuged at 1400 rpm for 4 minutes. The supernatant and the macroaggregate were separated and the activity of both was measured in a dose calibrator.

The ¹⁸⁸Re-FHMA was resuspended in 1.5 mL of saline solution and 1.0 mL of phosphate buffer 0.2 M (pH 7.5).

The percentage of bound activity was determined by measuring the activity of both precipitate and supernatant solution in a dose calibrator system. From these data the percentage of FHMA labeled yield was calculated.

Physical characterization of the radiopharmaceuticals

Non-radioactive forms of the radiopharmaceuticals were prepared using tracer quantities of potassium perrhenate

in saline solution in volumes and concentrations corresponding to those of generator eluate.

The number, volume and area of the radiopharmaceuticals particles were analyzed with a laser diffraction particle size analyzer. Particles size were grouped in the following ranges, <2 μ m, 2–10 μ m, 10–40 μ m and >40 μ m.

Stability studies

In vitro and in vivo stability studies were performed for the ¹⁸⁸Re-Sn colloid, ¹⁸⁸Re-HA particles (Direct method) and for the ¹⁸⁸Re-Sn-FHMA.

In vitro stability studies

Each radiopharmaceutical was kept at room temperature or at 37 °C for 2 and 24 hr after labeling. Stability of ¹⁸⁸Re-Sn colloid, ¹⁸⁸Re-HA particles and ¹⁸⁸Re-Sn-FHMA was assessed in saline solution, ascorbic acid (pH 5)/human serum and saline solution/human serum, respectively. In every case the percentage of bound activity was measured.

In vivo stability studies

Urine samples were collected during the first 24 hr post-radiopharmaceutical administration.

Biodistribution in New Zealand adult male rabbits (4 kg weight) was performed. The animals were sacrificed with an overdose of sodium thiopental after 48 hr of intra-articular administration of ¹⁸⁸Re-Sn colloid, ¹⁸⁸Re-HA direct method and ¹⁸⁸Re-Sn-FHMA (1 mCi/mL).

Knee joint, thyroid, heart, urinary bladder, gall bladder, liver, spleen, lungs, stomach, intestines, kidney, muscle, bone, blood and urine samples were collected and radioactivity was measured in a scintillation counter.

Scintigraphic studies

The New Zealand rabbits were anesthetized by intramuscular administration of 50 mg/kg of ketamine and 10 mg/mL of xilazine. Scintigraphic images were acquired with a Sophy Camera DSX, with medium energy collimator, at 0, 24 and 48 hr after intra-articular administration of each radiopharmaceutical.

Table 1: Radiopharmaceutical stability during 24 hr after labeling as percentage

	¹⁸⁸ Re-Sn	¹⁸⁸ Re-Sn-FHMA	¹⁸⁸ Re-HA
Saline solution	100	90
Ascorbic acid	65
Human serum	86	69

Table 2: Radiopharmaceutical particles distribution according to size, volume and surface

Particle size	Number	¹⁸⁸ Re-Sn		Number	¹⁸⁸ Re-Sn-FHMA		Number	¹⁸⁸ Re-HA	
		Volume	Surface		Volume	Surface		Volume	Surface
< 2 um	90	8	31	95	2	22	98	7	53
2 to 10 um	9,9	63	61	4	34	42	1,8	10	19
10 to 40 um	0,1	29	8	1	64	36	0,2	83	28
>40 um	0	1	0	0	0	0	0	0	0

Results

Labeling procedures

¹⁸⁸Re-Sn colloid was obtained with a radiochemical purity over 95% and was stable for 24 hr, as was previously reported [11].

¹⁸⁸Re-HA was labeled according to Chinol M. procedure [1]. The first step which consisted in ¹⁸⁸Re-HEDP preparation, was successfully achieved (radiochemical purity over 99%). However in the second step the percentage of bound ¹⁸⁸Re-HA was not higher than 5%. In consequence a second technique called "direct method" was adopted, similar to that described by Kothari *et al* [9] with minor modifications. In this case the percentage of bound activity was 55% (n = 3).

¹⁸⁸Re-Sn-FHMA was first labeled according to the procedure used with ¹⁹⁵Dy described by Castro M and Portilla A [10]. The percentage of bound activity obtained with this procedure was 1.2%. A technique in two steps introducing tin as a reducing agent improved the labeling yields to 91.8% (n = 3).

Physical characterization of the radiopharmaceuticals

There are no significant differences between the radiopharmaceuticals formulated taking into account number and volume of the particles that are in the critical range (less than 2 micrometers and over 40 micrometers) as can be seen in Table 2. However differences arise when we study the surface area of each formulation analyzed.

Stability studies

In vitro stability studies

Stability studies for ¹⁸⁸Re-Sn were carried out in saline solution, showing that the radiopharmaceutical was stable for 24 hr at room temperature (Table 1).

For ¹⁸⁸Re-HA the stability studies were carried out in human serum and ascorbic acid, showing that the radiopharmaceutical was stable for 24 hr at 37°C (Table 1).

Stability studies for ¹⁸⁸Re-Sn-FHMA in saline solution and human serum were performed, showing that the radiopharmaceutical was stable for 24 hr at 37°C (Table 1).

In vivo stability studies

Renal elimination of ¹⁸⁸Re-Sn colloid and ¹⁸⁸Re-Sn-FHMA was detected by activity measurements in urine samples during the first 12 hr post-radiopharmaceutical injection.

Activities per gram of selected tissue/organs including the knee joint after 48 hr of the radiopharmaceutical intra-articular administration to New Zealand rabbits are shown in Table 3.

The percentage of activity retained in the knee joint for each radiopharmaceutical at 48 hr post injection was over 90% of residual activity in the whole body (Figure 1).

Nevertheless the percentage of injected activity in the knee joint after 48 hr for each radiopharmaceutical was significantly different. The ¹⁸⁸Re-Sn colloid had the highest percentage of retention in the knee joint (Figure 2).

Scintigraphic studies

The scintigraphic images of the rabbits, at 0, 24 and 48 hr post administration, indicate relevant activity only in the knee, and negligible activity in the rest of the organism for each formulation (Figure 3).

Discussion

The labeling procedures for ¹⁸⁸Re-HA and ¹⁸⁸Re-Sn-FHMA included multiple centrifugation and separation steps. In both cases modifications from previous techniques had to be adopted to improve the percentage of bound activity to the particles. For ¹⁸⁸Re-HA a two step procedure (used for Samarium-153 and Rhenium-186 labeled hydroxyapatite) [1] was discarded and a direct labeling technique was tried [9], that improved the percentage of bound activity from less than 5% to over 55%.

For the ferric hydroxide macroaggregates labeling a procedure originally developed for ¹⁹⁵Dy was followed. This method did not succeed for ¹⁸⁸Re (less than 2% of bound activity) because of the differences in reduction potentials of the two radionuclides. Therefore several reducing agents were tested and the best results were obtained with the two step procedure using tin to reduce the ¹⁸⁸ReO₄⁻ prior to the labeling (coating) of the ferric hydroxide macroaggregate (over 90% of bound activity was obtained).

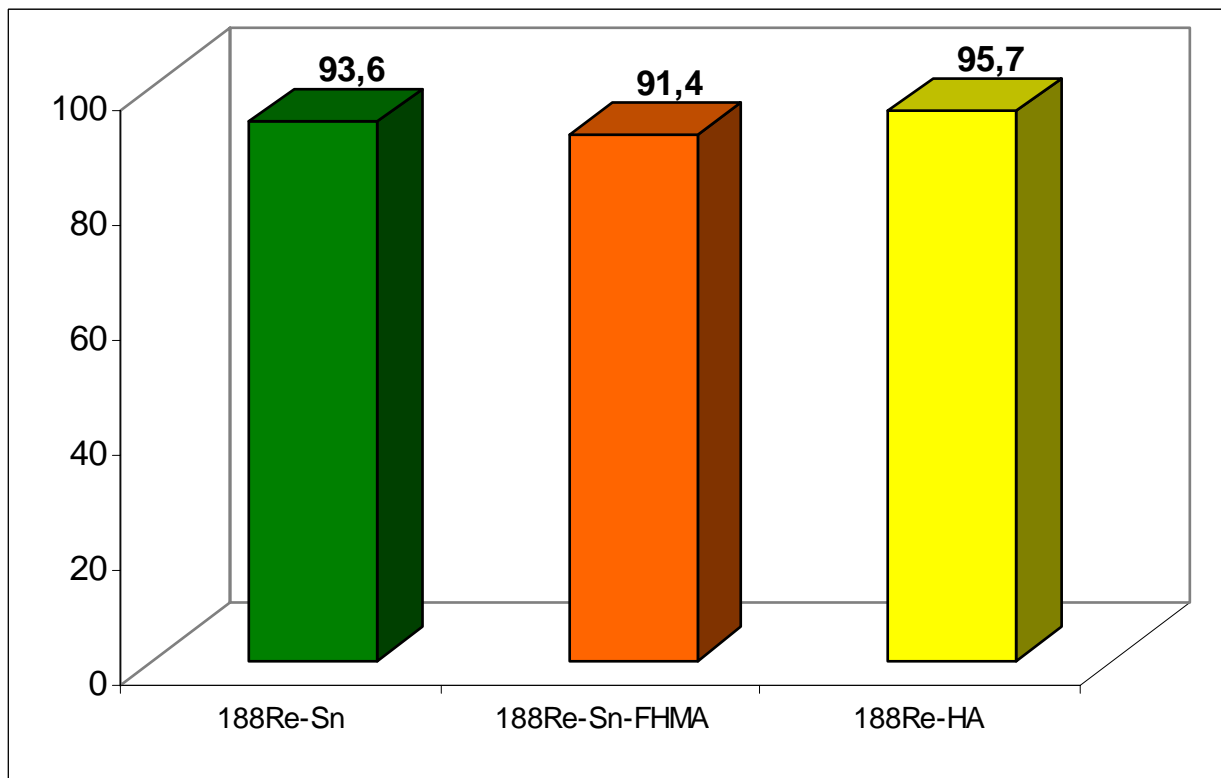


Figure 1
Percentage of residual whole body activity in the knee joint at 48 hr post-administration.

Table 3: Radiopharmaceutical biodistribution at 48 hr after injection

Organ	Activity per gram of organ		
	¹⁸⁸ Re-Sn	¹⁸⁸ Re-Sn-FHMA	¹⁸⁸ Re-HA
Thyroid	9,58E-04	6,03E-04	3,31E-04
Lungs	9,18E-04	1,55E-03	8,68E-05
Kidneys	4,39E-04	2,64E-02	3,07E-03
Liver	1,62E-03	2,46E-03	1,68E-04
Spleen	1,53E-04	3,43E-03	9,33E-05
Stomach	3,64E-04	1,98E-04	3,52E-05
Muscle	5,64E-05	2,27E-04	1,62E-04
Bone	3,98E-03	2,62E-04	1,15E-04
Intestines	3,20E-03	3,54E-03	5,76E-04
Heart	3,39E-04	3,17E-04	4,83E-05
Blood	2,67E-04	9,75E-04	2,43E-04
Urine	2,34E-03	1,16E-02	6,52E-03
Urinary bladder	2,56E-03	4,66E-04	1,64E-03
Gall bladder	6,25E-03	5,36E-03	2,08E-04
Joint (knee)	1,01E+00	9,99E-01	6,21E-01

All activities were corrected to the sacrifice time

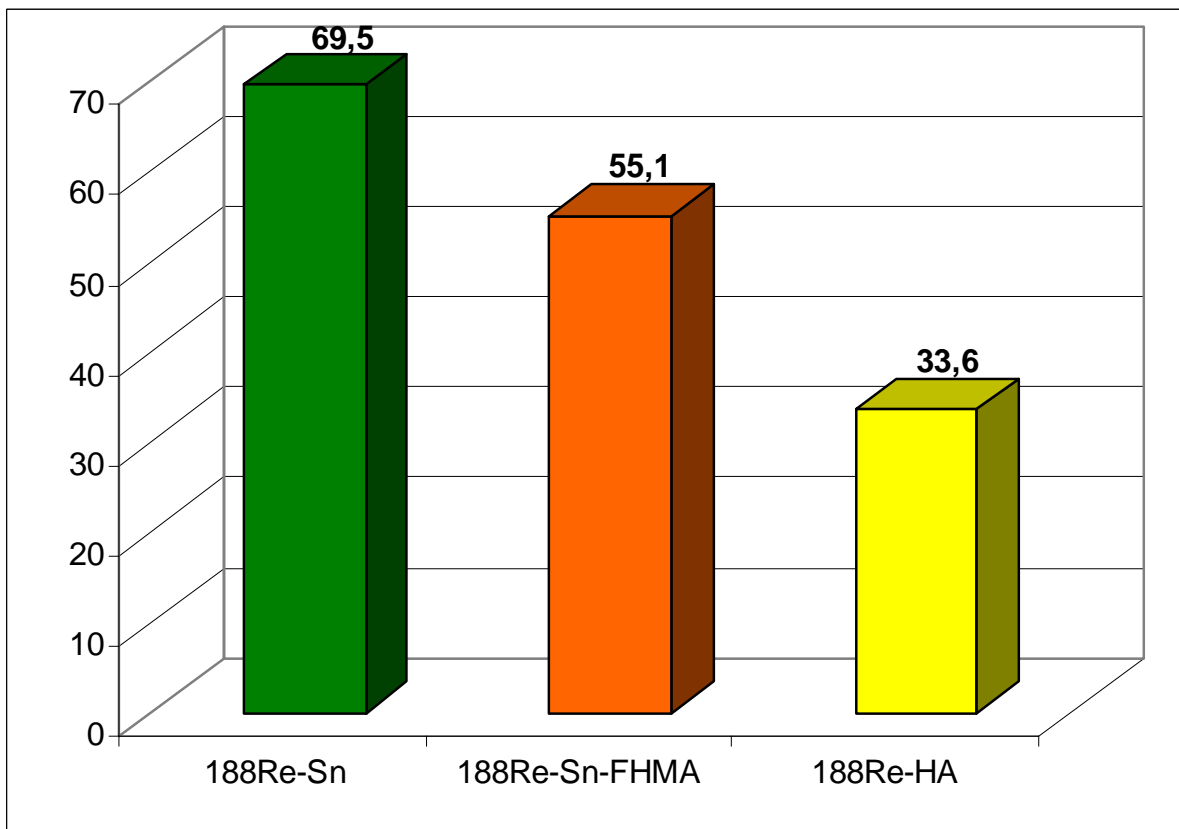


Figure 2
Percentage of injected activity in the knee joint at 48 hr post-administration.

The labeling procedures for both ¹⁸⁸Re-HA and ¹⁸⁸Re-Sn-FHMA was time consuming and difficult to perform in a nuclear medicine facility in sterile conditions. On the other hand the ¹⁸⁸Re-Sn colloid is easily labeled in sterile conditions with high radiochemical purity (over 95%) and was stable for a 48 hr period.

It has been well established in previous works [8] that radiopharmaceutical particle size must be small enough to be phagocyted by the superficial cells of the sinovium (<40 μm) but not so small as to facilitate fast biological clearance by diffusion from the joint (>2 μm). For each of the radiopharmaceuticals tested, the activity remaining in the knee joint at 48 hr represented over 90% of the activity detected in the whole body, with no significant levels being detected in other tissues or organs, including liver and spleen.

Therefore any radiopharmaceutical not remaining in the knee joint must be rapidly excreted. This was confirmed by activity renal clearance during the first 12 hr, probably associated with very small particles, much less than 2 μm.

However the percentage of injected activity in the knee joint was significantly different for the preparations tested. The ¹⁸⁸Re-Sn colloid had the highest retention (69.5%) followed by ¹⁸⁸Re-Sn-FHMA (55.1%) and finally ¹⁸⁸Re-HA particles (33.6%) (Figure 2).

Both ¹⁸⁸Re-Sn colloid and ¹⁸⁸Re-HA particle results were in agreement with the distribution percentage according to the surface area criteria (Table 2). It can be seen for the tin colloid that the greatest percentage surface area corresponds to the 2 to 10 micrometers range. ¹⁸⁸Re-HA had the biggest loss of the injected activity because 53% of the

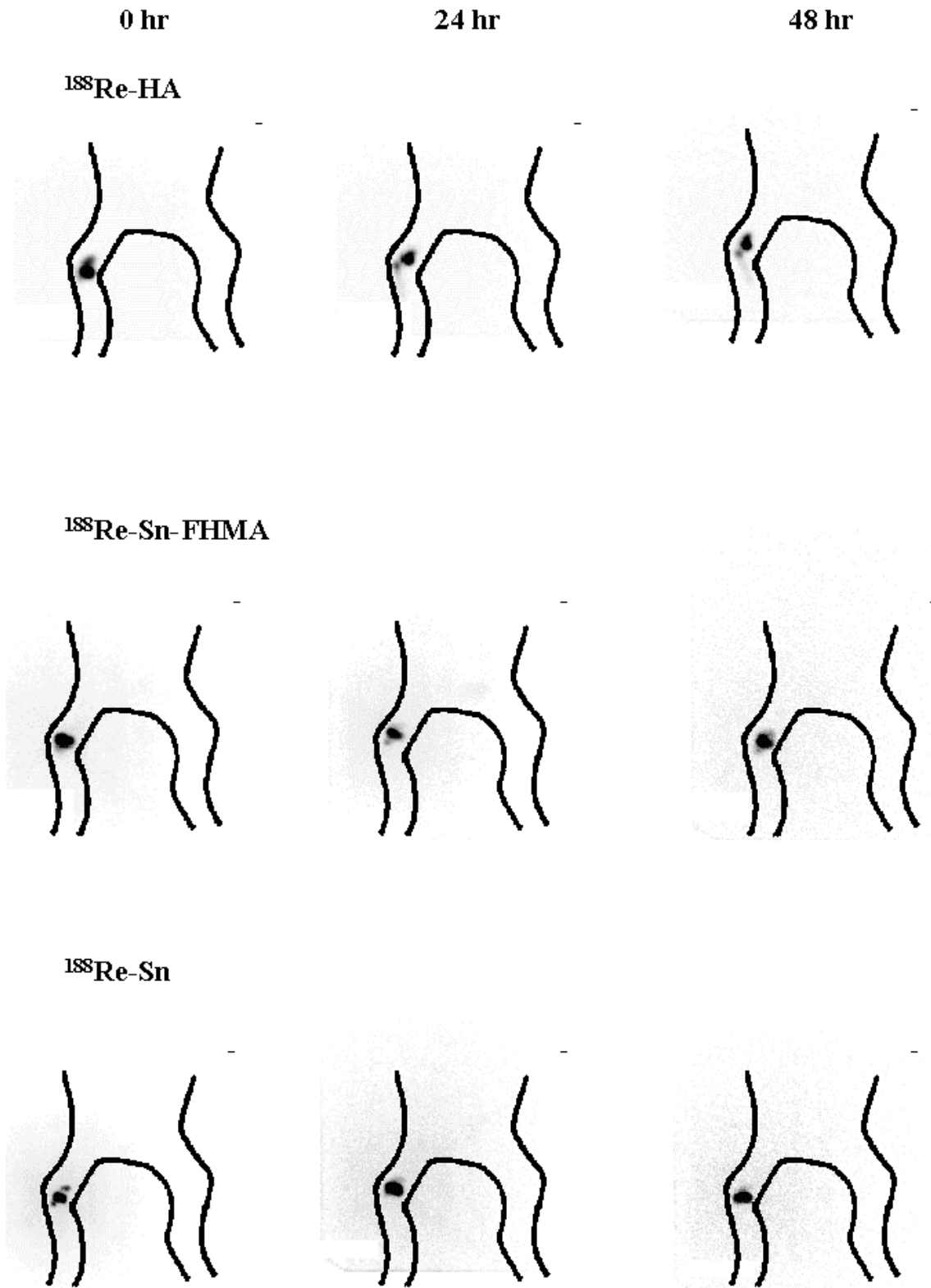


Figure 3
Scintigraphic images at 0, 24 and 48 hr for $^{188}\text{Re-Sn}$, $^{188}\text{Re-Sn-FHMA}$ and $^{188}\text{Re-HA}$.

surface area corresponds to particles of less than 2 μm which could leak from the joint.

Nevertheless apparently anomalous values were obtained for $^{188}\text{Re-Sn-FHMA}$ distribution (surface area criteria, Table 2) where only 22% of the particle surface corresponds to the range lower than 2 μm and the residual activity in the knee was 55% instead of 80%. The ferric hydroxide radiopharmaceutical is actually a macroaggregate coated by a tin colloid as it was observed by electronic microscopy of HSA microspheres labeled with ^{188}Re [12]. The macroaggregate labeling (coating) may be achieved by a combination of the reduction of $^{188}\text{ReO}_4^-$ by tin and a particle surface related co precipitation effect of a ferric hydroxide macroaggregate with a tin colloid. The dissociation of $^{188}\text{Re-Sn}$ from the ferric hydroxide macroaggregate could happen in a certain range, and as a consequence we postulated that the fraction smaller than 2 μm could leak from the joint. So actually the leakage of $^{188}\text{Re-Sn-FHMA}$ would be by ferric hydroxide macroaggregates smaller than 2 micrometers and the $^{188}\text{Re-Sn}$ colloid dissociated with a size of less than 2 μm .

We found that the range from 2 to 10 micrometers was the optimum because the particles were phagocytosed and remained in the target area for at least 48 hr.

From the point of view of the radiological security of the patient, the best radiopharmaceutical is that one with a greater percentage of the injected dose retained in the joint because a smaller activity amount had to be injected to obtain the desired radiation dose. This fact takes into account radioprotection principles for the patient in order to minimize absorbed dose. The three formulations tested had rapid renal clearance and showed negligible retention in other tissues or organs other than the knee. Therefore $^{188}\text{Re-Sn}$ which had the greatest retention in the knee (69.1%) was the radiopharmaceutical that could give the desired effect with the lowest absorbed dose in the patient's whole body.

Conclusions

$^{188}\text{Re-Sn}$ could be selected as the best formulation for synovectomy therapy taking into account ease of labeling procedure, kit formulation, minimum facilities required, suitable physical and biological characteristics and the lowest absorbed dose for the patient. Because of this the highest benefit/risk relation was found for $^{188}\text{Re-Sn}$ in comparison with $^{188}\text{Re-Sn-FHMA}$ and $^{188}\text{Re-HA}$.

Competing interests

None declared.

Authors' contributions

ES planned the study, coordinated it and drafted the manuscript.

MCU participated in the design of the radiopharmaceutical, carried out pharmaceutical experiments and drafted the manuscript.

PZ carried out pharmaceutical experiments and also drafted the manuscript.

VT carried out pharmaceutical experiments.

AP carried out the scintigraphic studies.

VM carried out pharmaceutical experiments.

AM performed the Coulter Analyzer determinations.

MF performed the experimental animal studies.

JG was responsible for scintigraphic studies.

All authors read and approved the final manuscript.

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