Technical note

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Neutron-activated ^{153}Sm-ion-exchange resin as a tracer for gastrointestinal scintigraphy

Chai-Hong Yeong[a,b], Basri Johan Jeet Abdullah[a,b], Kwan-Hoong Ng[a,b], Lip-Yong Chung[c], Khean-Lee Goh[d], Sazilah Ahmad Sarji[a,b] and Alan Christopher Perkins[e]

Nuclear medicine techniques are well established for the investigation of gastrointestinal (GI) motility and transit. Ion-exchange resins radiolabelled with ^{99m}Tc and ^{111}In are widely used as nonabsorbable radiopharmaceutical markers, with ^{111}In being preferred for whole-gut transit studies. This radionuclide, however, is not produced in many countries and may be expensive when obtained through international shipment. This study describes the use of neutron-activated ^{153}Sm-resin as an alternative tracer for use in GI scintigraphic investigation. A measure of 50 mg of stable samarium-152 chloride ($^{152}SmCl_3$) was incorporated into 100 mg of cation-exchange resin and irradiated in a neutron flux of $1 \times 10^{13}\,cm^{-2}\,s^{-1}$ for 100 s to achieve an activity of 5 MBq after 66 h. Aliquots of ^{111}In-radiolabelled resin (5 MBq) were prepared for comparison of labelling and stability. Radiolabelling efficiencies were obtained by washing resin with distilled water, and the activity lost was measured. The radiolabelled resins were immersed in simulated gastric and intestinal fluid environments, and the retention of $^{153}Sm^{3+}$ and $^{111}In^{3+}$ was measured over a 24 h period. At 66 h after production, 91.15 ± 12.42% of ^{153}Sm was bound to the resin after washing in distilled water, whereas radiolabelling with ^{111}In achieved 99.96 ± 0.02% efficiency. Both radiolabelled resins demonstrated almost 100% stability in simulated intestinal fluid and >90% stability in artificial gastric juice over 24 h. The performance of neutron-activated ^{153}Sm-resin is similar to that of ^{111}In-resin and can be used as an alternative tracer for GI transit studies when ^{111}In is not available. *Nucl Med Commun* 32:1256–1260 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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[a]University of Malaya Research Imaging Centre, [b]Departments of Biomedical Imaging, [c]Pharmacy, [d]Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia and [e]Radiological and Imaging Sciences and Nottingham Digestive Diseases Biomedical Research Unit, University of Nottingham, Nottingham, NG7 2UH, United Kingdom

Correspondence to Alan Christopher Perkins, PhD, CSci, FIPEM, ARCP, FRCR, Department of Medical Physics, Radiological and Imaging Sciences, A Floor, Medical School, Queen's Medical Centre, Nottingham, NG7 2UH
Tel: +44 (0)115 970 9192; fax: +44 (0)115 970 9301;
e-mail: Alan.Perkins@nottingham.ac.uk

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Introduction

Noninvasive imaging techniques are important clinical diagnostic tools in the investigation of gastrointestinal (GI) motility and transit. Several radiological and endoscopic techniques have been developed and are practised in clinical settings [1]. Among them, γ scintigraphy is one of the most favoured diagnostic methods because it combines quantitative assessment and visual information from sequential image data. Furthermore, this methodology does not involve dense contrast agents such as barium, which may alter the GI physiology during the examination.

A range of nonabsorbable radiopharmaceuticals have previously been used for gastrointestinal studies [2]. In 1989, Camilleri *et al.* [3] from Mayo Clinic, USA, successfully developed a method of indium-111 (III) chloride ($^{111}InCl_3$)-radiolabelled resin pellets for the assessment of gastric emptying and colonic transit. Amberlite IR-120 (H^+) cation resin pellets were successfully labelled with $^{111}InCl_3$, and this method has been widely practised in many centres, particularly for whole-gut transit studies [4–7]. This method, however, has certain limitations restricting its application to a broader population, mainly because of the requirement of an industrial cyclotron facility for the production of ^{111}In, which is not commonly available worldwide. As a consequence, the supply of ^{111}In to some countries can be relatively costly compared with other available radionuclides, especially when this involves international shipment with the added cost of lead shielding and agent charges to comply with different national radiation authorities.

In 1998, Mullan *et al.* [8] suggested a cheaper approach for radiolabelling activated charcoal with technetium-99m pertechnetate and technetium-99m-diethylene triamine pentaacetic acid, which are routinely available in most countries. Some later publications [9–11] described the use of ^{99m}Tc-radiolabelled ion-exchange resin pellets as an alternative for ^{111}In-radiolabelled resins; however, the short physical half-life of ^{99m}Tc (6.02 h) makes this radiotracer formulation only suitable for short time-course imaging studies such as oesophageal transit or gastric emptying. The investigation of whole-gut transit requires a radiotracer with a much longer physical half-life, preferably around 24–72 h.

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Samarium-153 (^{153}Sm) has a physical half-life of 46.3 h and emits γ radiation of 103 keV, which is well suited for γ scintigraphic imaging [12]. Neutron-activated ^{153}Sm has successfully been used in various drug delivery and pharmacology studies [13–16]. We have extensive experience with the production and use of ^{153}Sm as a tracer for studying the transit and release of oral dose forms such as enteric-coated matrix tablets [17,18]. ^{152}Sm is a rare-earth element that is commercially available in solid and aqueous forms. ^{153}Sm is produced by neutron activation of ^{152}Sm in a thermal nuclear reactor facility as a (n, γ) reaction. When such reactors are available, the production and use of ^{153}Sm become cost-competitive and more accessible.

This study describes a novel method for the incorporation of stable samarium-152 (III) chloride ($^{152}SmCl_3$) into cation-exchange resin beads, followed by neutron activation to produce a ^{153}Sm-radiolabelled formulation suitable for oral consumption and use in the study of gastrointestinal transit. The labelling stability of the ^{153}Sm product was compared with the more widely used ^{111}In-radiolabelled resin.

Materials and methods

Incorporation of $^{152}SmCl_3$ into cation-exchange resin

The stable nuclide samarium-152 (III) chloride hexahydrate ($^{152}SmCl_3 \cdot 6H_2O$, molecular weight 364.81 g/mol, assay purity $\geq$ 99%) and cation-exchange resin (Amberlite IR-120, H^+ form, 16–50 mesh, BDH Chemicals Ltd, UK) were purchased from Aldrich Chemical (Sigma-Aldrich Corporation, St. Louis, Missouri, USA). The cation-exchange resin was a styrene—divinylbenzene gel type with sulfonic acid (H_2SO_4) functionality. The mean size of the resin beads ranged from 0.62 to 0.83 mm according to the manufacturer's technical sheet. The total exchange capacity of the resin was $\geq$ 1.80 eq L^{-1} (H^+ form), and the moisture holding capacity was 53–58% (H^+ form).

For each ^{152}Sm-labelled formulation, 50 mg of $^{152}SmCl_3 \cdot 6H_2O$ was weighed and dissolved in 1 ml of pure distilled water. A measure of 100 mg of Amberlite IR-120 (H^+) ion-exchange resin was then added to the solution and mixed evenly. The mixture was dried in a laboratory oven for 12 h at a temperature of 70°C. The dried resin beads were then filled into an empty gelatin capsule and sent for neutron activation.

Neutron activation

The samples were sent to the nuclear reactor facility at Malaysian Nuclear Agency, Bangi, Malaysia, for neutron activation. This facility is a 250 kW open pool-type research reactor (Triga Mark II, General Atomics, California, USA) that uses a uranium zirconium hydride assembly with low-enriched uranium-235 (20 wt% ^{235}U) for the fuel source. Before irradiation, each capsule was heat-sealed into a polyethylene vial. Three vials were packed into a polyethylene ampoule (commonly known as the 'rabbit'). The ampoule was delivered to the reactor core by a pneumatic transport system. The capsules were irradiated in a neutron flux of 1×10^{13} cm^{-2} s^{-1} for 100 s to achieve a nominal radioactivity of 5 MBq at 66 h after neutron activation. Gamma spectroscopy was carried out to detect any radioactive impurities 24 and 48 h after neutron activation using a coaxial, p-type, germanium detector (Canberra, Meriden, USA) and γ spectrum analysis software (Genie 2000 Ver. 3.2, Canberra, Meriden, USA) . The safety requirement was that any net γ peak area not originating from ^{153}Sm should not exceed 0.3% of the ^{153}Sm main peak at 103 keV and that the total net peak areas not originating from ^{153}Sm should not exceed 1% of the ^{153}Sm main peak. The capsules were kept in a radioactive storage room until the study day to allow for decay of the unwanted short-lived activated by-products, primarily sodium-24 (^{24}Na) [15,16,19].

Radiolabelling of ion-exchange resin with $^{111}InCl_3$

$^{111}InCl_3$ (molecular weight 221.18 g/mol, assay purity $\geq$ 99%) was purchased from General Electric Healthcare (The Grove Centre, Amersham, UK). A measure of 100 mg of Amberlite IR-120 (H^+) ion-exchange resin was weighed into a glass beaker. A volume of 5 MBq of $^{111}InCl_3$ solution was prepared and added to the ion-exchange resin. After mixing evenly using a glass rod, the radiolabelled compound was left to dry completely in a laboratory oven at a temperature of 70°C.

Specific activities

Both ^{153}Sm-radiolabelled and ^{111}In-radiolabelled resins were weighed and assayed for radioactivity to derive the specific activity. Labelling efficiencies were obtained by determining the activity bound to the resin after washing for 5 min with distilled water. Retention of the radioactivity bound to resins over time was measured as described below.

Stability of radiolabelled resins in simulated gastric and intestinal fluid

The stability of the activated ^{153}Sm-resin and the ^{111}In-radiolabelled resin was measured *in vitro* over a period of 24 h. Artificial gastric juice (pH 1.03) and simulated intestinal fluid (pH 6.8) with enzyme incorporation were prepared according to the recommendation in the British Pharmacopoeia, 2007.

The activated ^{153}Sm-resins were emptied from the capsule and transferred to glass tubes containing either 10 ml of artificial gastric juice or 10 ml of simulated intestinal fluid. The initial activities of all the samples were measured using a dose calibrator (CRC-12, Capintec Inc., New Jersey, USA) and recorded. The tubes were then placed on a tilt and mix roller (Movil Rod, J.P. Selecta, Espano) and rolled constantly at 50 rpm for 1 h. The tubes were then transferred to a multipurpose centrifuge (CR4–12, Jouan Inc, St. Herblain, France) and rotated at 1200 rpm for 5 min to separate the resin beads and fluid. After centrifugation, 1 ml of fluid was carefully

removed from the middle of the tube without disturbing the resin beads at the bottom using a micropipette. The same procedures of rolling and sampling were repeated every 2 h for 10 h, and a final sample was taken at 24 h. All the samples were then assayed using an automatic γ counter (2470 Wizard^2, PerkinElmer, Massachusetts, USA) for measurement of ^{153}Sm activity. The γ counter was precalibrated using a standard ^{153}Sm source from a secondary standard dosimetry laboratory (SSDL, Malaysian Nuclear Agency, Bangi, Malaysia). Background counting was carried out, followed by sample counting.

The procedures explained above were repeated six times for both ^{153}Sm-radiolabelled and ^{111}In-radiolabelled formulation in both simulated gastric and intestinal fluid.

Data analysis

The γ counting data were first corrected for background count rates before further analysis. The count rates collected from 1 ml samples were normalized according to the volume remaining in the test tube at the time of sampling. The data were then corrected for radioactive decay and expressed as a percentage to the initial activity. The retention of radioactivity was calculated using the following formula:

$$\text{Retained activity}\,(\%) = \frac{\text{Initial activity of resin} - \text{activity of sample}}{\text{Initial activity of resin}} \times 100\,\%$$

Results

Production of ^{153}Sm-resin by neutron activation was successfully achieved on 18 separate occasions. Assay of individual batches by γ spectroscopy showed that the main photopeaks measured were in the expected energy region of 69.0 ± 1.5 and 102.6 ± 1.5 keV, both were γ energies emitted by activated ^{153}Sm. A further peak at 1020.3 ± 1.5 keV was measured. This decayed with a physical half-life of 14.9 h and was consistent with the decay of activated ^{24}Na. The only other significant peaks produced were of low energy, at 40.3 and 46.1 keV, which were observed to decay with the same physical half-life as the main ^{153}Sm peak.

The mean ($n = 18$) specific activity of activated ^{153}Sm-resin was 0.056 ± 0.004 MBq mg^{-1} and that of ^{111}In-radiolabelled resin was 0.047 ± 0.006 MBq mg^{-1} when measured on the day of study 66 h following neutron activation. Both values were close to the target specific activity of 0.050 MBq mg^{-1} considered suitable for clinical use.

The radiolabelling efficiency of $^{111}InCl_3$ with Amberlite IR-120 (H^+) cation exchange resin was $99.96 \pm 0.02\%$. The retention of ^{153}Sm bound to the resin after washing with distilled water was $91.15 \pm 12.42\%$.

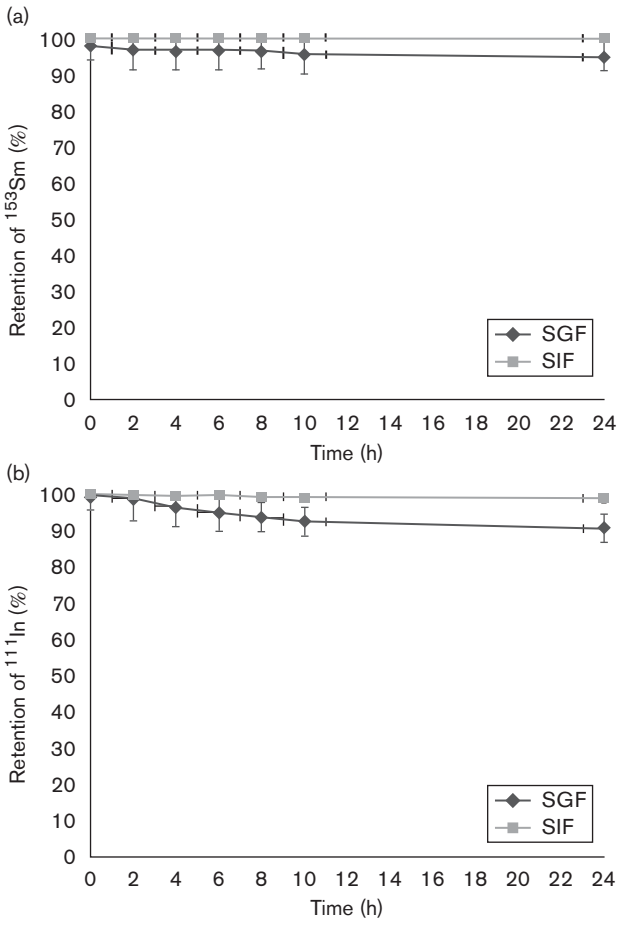
The percentages of $^{153}Sm^{3+}$ and $^{111}In^{3+}$ ion retention in the radiolabelled resin compounds tested in simulated gastric and intestinal fluid versus time are demonstrated in Fig. 1.

Discussion

This study demonstrates the production and stability of ^{153}Sm-radiolabelled cation-exchange resin compared with the established method of radiolabelling resin with ^{111}In. Amberlite IR-120 (H^+) cation-exchange resin has been shown in this study to be a suitable insoluble polymer that can be bound to $^{152}Sm^{3+}$ ions through ion-exchange reaction and activated to a radioactive tracer for scintigraphic imaging.

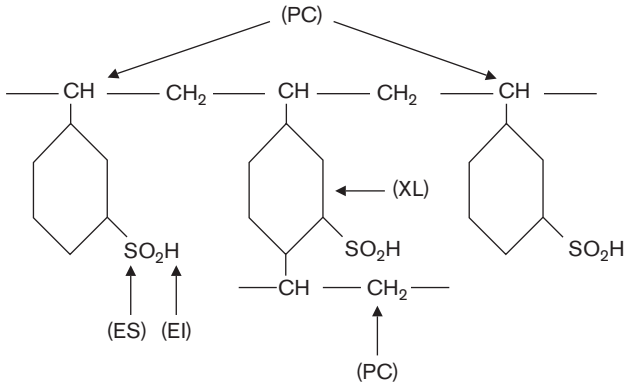
Amberlite IR-120 (H^+) resin is a gel-type strongly acidic cation exchange resin of the sulphonated polystyrene type. The name 'Amberlite' was given because of its physical appearance of amber spherical beads. The chemical structure of the resin is shown in Fig. 2.

Fig. 1



Percentages of (a) $^{153}Sm^{3+}$ and (b) $^{111}In^{3+}$ ion retention in the radiolabelled resin compounds versus time (error bars show 1 standard deviation for $n = 6$). SGF: simulated gastric fluid; SIF: simulated intestinal fluid.

Fig. 2



Chemical structural formula of Amberlite IR-120 (H^+) sulphonic strong acidic cation resin. PC, polymer chain; XL, cross-link; ES, exchange site; EI, exchangeable ion.

For radiolabelling resin with ^{153}Sm, two possible approaches can be taken. ^{153}Sm can be activated in aqueous form as radioactive samarium-153 (III) chloride ($^{153}SmCl_3$) and incorporated to the resin in the same way as $^{111}InCl_3$. The alternative approach is incorporation of stable samarium $^{152}SmCl_3$ into the resin for subsequent neutron activation. In this study, the latter approach was used mainly for the purpose of radiation safety. This had the advantage of eliminating the manipulation of ^{111}In liquid and drying of the resin during the radiolabelling procedure at the hospital site.

As the resin and gelatin capsules were also directly irradiated during neutron activation, it was necessary to consider contamination with other activated products, particularly within the resin itself. Gamma spectroscopy demonstrated that the main product was ^{153}Sm and, as expected, there was evidence of short-lived ^{24}Na. The other low-energy peaks at 40.3 and 46.1 keV were considered to be low energy scatter from the ^{153}Sm photopeak, which they decayed at the same physical half-life as ^{153}Sm.

For clinical use, the radiolabelled resin can be administered within the gelatin capsule, or it can be emptied from the capsule for incorporation into a suitable meal or oral formulation. Before clinical use it is important that the stability of the resins be tested *in vitro* over time in a simulated GI environment. A review of the literature found little data on the stability of the resin formulations commonly used for GI investigation. One of our main concerns was that the molecular structure of the resins might be altered by the acidic condition in the stomach, hence releasing free $^{153}Sm^{3+}$ or $^{111}In^{3+}$ ions that may be absorbed through the intestinal tract. This study therefore tested the stability of the ^{153}Sm-resin and compared the results with ^{111}In-resin.

The radiolabelling efficiency of $^{111}InCl_3$ with resin was almost 100%. This indicated that all the $^{111}In^{3+}$ ions were bound with the resin. However, the retention of ^{153}Sm on the resin beads was not as high as ^{111}In after washing with distilled water. The mean percentage retention was 91%; however, the standard deviation was relatively large, with some capsules having retention of 80% or lower. Any unbound activity could result in an increased absorbed dose to the patient. Further optimization of labelling may be achieved by increasing the amount of resin beads to prevent saturation. An additional suggestion would be adding the washing step with distilled water after labelling ion-exchange resins with ^{152}Sm to eliminate any unbound ^{152}Sm from the formulation.

In our experiments, both ^{153}Sm-radiolabelled and ^{111}In-radiolabelled resins showed similar stability in the tested mediums. Retention of both radionuclides in intestinal fluid was almost 100% in all samples collected over 24 h. The percentage retention decreased when both radiolabelled resins were tested in artificial gastric juice. Approximately 5% of $^{153}Sm^{3+}$ ions were unbound immediately after immersing the radiolabelled resins into the gastric fluid. However, the stability of the ^{153}Sm-radiolabelled compound remained almost constant from 2 to 24 h at approximately 95%. The $^{111}In^{3+}$ ions showed 100% retention at the first sampling (0 h) but released slowly and gradually from the resins from 0–24 h.

When considering the radiation burden, the effective dose to subjects administered with ^{153}Sm is 0.7 mSv per MBq [20] which is over twice that from ^{111}In at 0.3 mSv per MBq [21]. For routine use, studies of whole-gut transit may be undertaken with the order of 5 MB ^{153}Sm, resulting in an effective dose of 3.5 mSv. This is considered acceptable, and, although this is a disadvantage of samarium-153, it is still low when compared with the use of X-ray procedures that may be used in countries where indium is not routinely available.

The neutron activation of ^{152}Sm to ^{153}Sm requires a thermal research reactor. The latest statistics (as of June 2011) from the International Atomic Energy Agency showed that there are currently 241 nuclear research reactors in operation over 58 countries. The broad availability of the reactors makes the supply of ^{153}Sm relatively easier to be accessed worldwide. The main cost of the ^{153}Sm product is the cost of neutron activation. The cost of raw materials, i.e., nonradioactive ^{152}Sm and cation-exchange resin, are minimal, at about 0.50€ per sample. Commercial neutron activation services at a European research reactor typically costs about 100€ per sample, on the basis of our previous experience [18]. The cost for ^{153}Sm obtained from MNA in this study was similar. In comparison, the price of In-indium-111 chloride is approximately 350€ per 37 MBq within the United Kingdom. This equates to approximately 50€ for 5 MBq-administered activity per patient. However, the cost of transportation for international shipping of radioactivity would double the product price, depending on

the country of delivery. ^{153}Sm may therefore be a competitive alternative if a local research reactor is available, especially for the countries in Asia—Oceania.

In conclusion, we have developed and demonstrated an effective method for radiolabelling resin beads with $^{153}SmCl_3$. The proposed manufacturing method has the advantage of reduced radiation exposure to staff. Moreover, the imaging characteristics of both radionuclides are equivalent, although the effective dose to patients is twice that from ^{111}In-radiolabelled resin. This is acceptable for diagnostic use and provides a viable alternative radiolabel for nonabsorbable resin markers intended for gastrointestinal scintigraphy. Further studies are required to validate the in-vivo performance of ^{153}Sm-radiolabelled resin formulations for assessing GI motility and transit in clinical use.

Acknowledgements

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Conflicts of Interest

There are no conflicts of interest.

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