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Production and first use of $^{153}SmCl_3$-ion exchange resin capsule formulation for assessing gastrointestinal motility

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ABSTRACT

We produced an enteric-coated gelatine capsule containing neutron-activated ^{153}Sm-labelled resin beads for use in gastrointestinal motility studies. *In vitro* test in simulated gastrointestinal environment and *in vivo* study on volunteers were performed. Scintigraphic images were acquired from ten volunteers over 24 h while blood and urine samples were collected to monitor the presence of ^{153}Sm. All the capsules remained intact in stomach. This proved to be a safe and practical oral capsule formulation for whole gut transit scintigraphy.

1. Introduction

There has been increasing interest in the measurement of whole gut motility for the examination of regional delayed gastrointestinal (GI) transit. Among all the diagnostic techniques, gamma scintigraphy is one of the most favoured diagnostic modalities used in the assessment of GI motility (Lin et al., 2005). Scintigraphic imaging is performed in conjunction with the oral administration of a non-absorbable radiotracer. Indium-111 (^{111}In) is a commonly used radiotracer for the study of whole gut motility because of its long physical half-life of 67.3 h. However, ^{111}In is not always available in some countries especially in Asia, and even when it is available, shipping from the country of production can be costly. A further issue with ^{111}In is that the radionuclide must be incorporated into a suitable non-absorbable formulation prior to use. This is often performed manually within the hospital radiopharmacy units and may result in personal radiation exposure to the individuals carrying out the procedure.

Neutron activated Samarium-153 (^{153}Sm) is a radionuclide that has been successfully used in various scintigraphic studies of drug delivery and pharmacology applications (Digenis and Sandefer, 1991; Marvola et al., 2008, 2004; Wilding et al., 1992). We have extensive experience with the production and use of ^{153}Sm as a radiotracer for oral dose formulation investigation in pharmacoscintigraphy (Perkins et al., 2001; Yeong et al., 2011a, 2011b). ^{153}Sm is derived from a rare earth element ^{152}Sm that is commercially available in oxide particle ($^{152}Sm_2O_3$) and acidic aqueous ($^{152}SmCl_3$) via neutron activation. The process requires a thermal nuclear reactor facility. The latest statistics from the International Atomic Energy Agency (IAEA) showed that there are currently 241 nuclear research reactors in operation over 58 countries. Although a relatively small number of these will be capable of producing clinical radionuclides a number of these reactors have the potential to the supply of ^{153}Sm as an alternative to ^{111}In. In terms of physical characteristics, ^{153}Sm has a relatively long physical half-life (46.3 h) and emits gamma radiation at 103 keV, which is well-suited for scintigraphic imaging (Tse et al., 1989). These features make ^{153}Sm an attractive alternative radiotracer to ^{111}In for scintigraphic imaging of GI motility.

We have previously reported the stability of ^{153}Sm binding with cation-exchange resin in simulated human GI environment.

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The retention of ^{153}Sm in resin was 100% in simulated intestinal fluid and >90% in artificial gastric juice over a period of 24 h (Yeong et al., 2011a, 2011b). In the present study, we aimed to produce a clinical oral enteric coated dose form containing a novel dispersible filling of neutron-activated ^{153}Sm-labelled ion-exchange resin for whole gut motility investigations. The performance of the formulations was tested *in vitro* in simulated GI environment and *in vivo* on healthy volunteers.

2. Materials and methods

2.1. Preparation of ^{152}Sm-labelled formulation

Samarium-152 (III) chloride hexahydrate ($^{152}SmCl_3 \cdot 6H_2O$, m.w. 364.81 g/mol, isotopic abundance 26.7%) with assay purity ≥99% and cation-exchange resin (Amberlite® IR-120, H^+ form, 16–50 mesh) were purchased from Aldrich Chemical Co. (Buchs, Switzerland). The cation-exchange resin was a styrene–divinylbenzene gel-type with sulphonic acid functionality.

For each capsule, 50 mg of $^{152}SmCl_3 \cdot 6H_2O$ was weighed and dissolved in 1 ml of distilled water. 100 mg of Amberlite® IR-120 (H^+) ion-exchange resin was then added into the solution and mixed thoroughly. The mixture was dried in a laboratory oven for 12 h at temperature of 70 °C. The dried resin beads were then filled into a medical-grade size 1 empty hard gelatine capsule (Halalgel Sdn. Bhd., Kedah, Malaysia). The capsule was further bulked up with lactose powder to make a final weight of approximately 350 mg, and then closed tight whilst trapping a dental floss of length approximately 10 cm between the cap and body.

2.2. Enteric coating

The gelatine capsule was designed to remain intact within the stomach but to disintegrate when it reaches the small intestine. In order to prevent capsule disintegration in the stomach, it was coated by immersion in an aqueous biocompatible polymer solution containing 13% Eudragit™ L100 (Evonik, Darmstadt, Germany) in a mixture of propan-2-ol and acetone (60:40). The capsule was immersed for 30 s then left to dry for 30 min. The coating procedure was repeated one more time and the capsule was finally suspended on the dental floss to dry for 24 h at room temperature (approximately 25 °C). On completion of the drying the dental floss was cut and the capsules were packed and sent to a reactor site for neutron activation.

2.3. Neutron activation

Neutron activation of the capsules was carried out at the nuclear reactor facility at Malaysian Nuclear Agency (Bangi, Selangor, Malaysia). This facility has a 250 kW open pool-type research reactor (Triga Mark II, General Atomics, California, USA), which utilises uranium zirconium hydride assembly with low-enriched uranium (20 wt% U-235) fuel source. Each capsule was heat-sealed into individual polyethylene vial and packed into a polyethylene ampoule (commonly known as a "rabbit"). The ampoule was then delivered to the reactor core by a pneumatic transport system (PTS). The capsule was irradiated in a neutron flux of 1×10^{13} cm^{-2} s^{-1} for 100 s to achieve nominal radioactivity of 5 MBq at 66 h after neutron activation, which was the intended diagnostic reference level (administered activity intended for clinical study). Gamma spectroscopy was carried out 24 h and 48 h after neutron activation using a coaxial, p-type, 40% relative efficiency germanium detector (Canberra, Meriden, USA) and gamma spectrum analysis software (Genie™ 2000 Ver. 3.2, Canberra, Meriden, USA) to detect any radioactive impurities. The safety requirement was that any net gamma 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 peaks areas not originating from ^{153}Sm should not exceed 1% of the ^{153}Sm main peak. The capsules were then kept in a radioactive storage room until the study day to allow for the decay of the unwanted activated by-products.

2.4. In vitro disintegration

From each batch, six activated capsules were randomly selected for *in vitro* disintegration testing using an US Pharmacopoeia compliant digital disintegration apparatus (LTD-2, Intech, Lasany International, Haryana, India). The disintegration test was performed using the basket method with a rotation rate of 100 rpm in 900 ml of artificial gastric fluid (pH 1.03, British Pharmacopoeia 2007) for 72 h, then the medium was changed to simulated intestinal fluid (pH 6.8, British Pharmacopoeia 2007) for an hour. The simulated gastric and intestinal fluids with enzyme composition were prepared according to the specification stated in the British Pharmacopoeia, 2007. The temperature of the medium remained at 37.0 ± 0.5 °C throughout the test. The disintegration of capsules was observed visually and the time of onset of disintegration was recorded. The acceptance criterion was that the capsules should remain intact in the gastric fluid and disintegrate in the intestinal fluid within 15 min.

2.5. Volunteer recruitment

The clinical protocol used for *in vivo* testing was approved by the Medical Ethics Committee of the University of Malaya Medical Centre, Kuala Lumpur, Malaysia (Protocol No. MEC 782.30). Ten healthy volunteers (6 females, 4 males, aged 33 ± 13 years old) were screened and recruited into the study. Females who were pregnant or suspected of being pregnant were strictly excluded. The volunteers were first interviewed using a questionnaire to ensure that they did not have symptoms of GI disorders or any history of GI disease. The volunteer's bowel status was verified by evaluating their bowel movements using the constipation scoring system of Agachan et al. (1996). Written informed consent was obtained from all volunteers. The volunteers were restricted from taking high fibre food for 3 day prior to the study. All volunteers abstained from alcohol and cigarette for 24 h, and fasted for at least 8 h prior to the ingestion of the capsule. Upon completion of the study, all volunteers were again given another questionnaire to determine if they experienced any adverse effects or any discomfort throughout the period of investigation.

2.6. Clinical procedure

On the first study day (Day 1), the volunteers remained at the study site from 07.30 to 18.30 h, and returned the next morning (Day 2) at 08.00 h to complete the imaging at 24 h post-ingestion. To prevent any nutritional bias in the results, all volunteers were provided with standardized meals on Day 1 at 09.30, 12.30, 15.30 and 18.30 h. The total calorific intake of the day was approximately 2000 kcal, as recommended by the United Kingdom Committee on Medical Aspects of Food Policy. Upon arrival on Day 1, the volunteers gave 7 ml of blood and approximately 100 ml of urine. Further urine samples were collected every time the volunteers emptied their bladders up to 9 h. A final blood sample was collected at the end of study at 24 h.

2.7. Radioactive assay of the urine and blood samples

All urine and blood samples were assayed using an automatic gamma counter (2470 Wizard^2, PerkinElmer Inc., Massachusetts, USA) for the detection of any absorption and excretion of free ^{153}Sm. The gamma counter was pre-calibrated using a standard ^{153}Sm source and all sample count rates were background corrected. The radioactivity levels in the blood and urine were compared before and after administration of the ^{153}Sm-labelled capsule.

2.8. Imaging protocol

Upon arrival at the study site, two radioactive surface markers, each containing 0.37 MBq of ^{153}Sm, were positioned on the skin surface at the left and right lower costal margins on each volunteer. These markers were used as references for visualisation of *in vivo* activity distribution.

At 08.00 h, the volunteers swallowed one ^{153}Sm-labelled capsule with 250 ml of water. They were then positioned supine in a dual-detector gamma camera (BrightView, Philips, Eindhoven, The Netherlands) fitted with low energy high resolution (LEHR) collimators. Anterior and posterior static images were acquired using $103 \pm 10\%$ keV energy window for a duration of 2 min. Image acquisition was repeated every 30 min for 9 h, and a final image was acquired at 24 h post-ingestion.

The images were motion corrected and concatenated using dedicated nuclear medicine software (Extended Brilliance Workspace V3, Philips, Eindhoven, The Netherlands). The GI tract was segmented into seven regions: stomach (ST), jejunum (JJ), ileo-caecal junction (ICJ), ascending colon (AC), transverse colon (TC), descending colon (DC) and recto-sigmoid (RS). The sites and times of onset of capsules disintegration were recorded.

3. Results

3.1. Neutron activated ^{153}Sm-labelled capsule

The enteric-coated capsules had the mean weight of 395.4 ± 14.0 mg ($n=10$). The mean activity measured at time of administration was 4.44 ± 1.11 MBq per capsule, which corresponded to an effective does of approximately 3.1 mSv (Awang et al., 1993). Fig. 1 shows a photograph of the gelatine capsule after neutron activation.

The results of gamma spectroscopy analysis are shown in Table 1. These demonstrated that the main photopeak measured from the samples were in the expected energy region of 103.2 ± 1.5 keV. Additional peaks were detected in the region of 68.8 ± 1.5 keV and 97.0 ± 1.5 keV, which were recognised as the associated gamma energies emitted from the ^{153}Sm. Another significant peak was detected at 1368.6 ± 1.5 keV. 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, these being at 40.3 and 46.1 keV, which were observed to decay with the same physical half-life as the main ^{153}Sm peak. Sufficient time was given between activation and administration (66 h) to allow for the significant decay of the short lived activated impurities.

3.2. In vitro disintegration

The *in vitro* disintegration test showed that all the capsules remained intact in the artificial gastric juice for 72 h and started to disintegrate in less than 15 min when in the simulated intestinal fluid. The gelatine capsules were observed to disintegrate first into pieces and then dissolved completely in the simulated intestinal fluid. With the ^{153}Sm-labelled resins beads spread throughout the medium. This complied with the purpose of enteric coating for targeted disintegration of gelatine capsules.

Fig. 1. A photograph of an enteric-coated gelatine capsule following neutron activation.

3.3. Clinical study

Ingestion of the ^{153}Sm-labelled capsules and the imaging procedures were well tolerated by all ten volunteers with no adverse events reported.

The ^{153}Sm-labelled resins were clearly visualised in all the scintigraphic images as a single hot-spot when the capsule was intact, and the activity was seen to disperse when the capsule disintegrated. Fig. 2 shows the example of sequential static images at 2 h interval and a final image at 24 h post-ingestion from a volunteer subject. Visualisation of transit of the radiotracer along the GI tract and the site of capsule disintegration was aided by concatenating all the static images into a dynamic display. Table 2 summarises the sites and times of onset of capsules disintegration in each subject. Fig. 3 demonstrates the dynamic of spatial and temporal distribution of the radiolabelled resin in each individual subject, indicated by the colour-coded boxes. Imaging showed that 6 out of 10 capsules disintegrated at the ileo-caecal junction and 3 capsules disintegrated at the jejunum. The mean time of the onset of disintegration was 3.7 ± 0.8 h post-ingestion. In one subject onset of disintegration of the capsule occurred between 9 and 24 h post-ingestion and was therefore not observed from the acquired images. In this case the capsule travelled to the ileo-caecal junction within 1.5 h and was observed to remain at the transverse colon from 2.5 to 9.0 h without disintegration. Dispersion of tracer within the descending and recto-sigmoid colon was observed at 24 h post-ingestion in all subjects.

No significant levels of radioactivity above background were detected in the urine and blood samples from all volunteers. No significant differences of radioactivity levels were found before and after ingestion of the capsules.

Table 1
Gamma spectroscopy result at 24 and 48 h after neutron activation ($n=30$).

Radio-nuclide	Peak energy ($\pm$1.5 keV)	24 h Post-activation		48 h Post-activation	
		Net peak area	Activity (MBq)	Net peak area	Activity (MBq)
Scattered energies	40.2	138 ± 26	0.020 ± 0.004	97 ± 12	0.013 ± 0.003
	46.0	130 ± 19	0.019 ± 0.003	81 ± 11	0.012 ± 0.001
Sm-153	68.8	97 ± 12	0.014 ± 0.002	77 ± 9	0.011 ± 0.001
	97.0	9 ± 5	0.001 ± 0.001	4 ± 1	0.000 ± 0.000
	103.2	$57{,}670 \pm 1327$	8.350 ± 0.026	$47{,}730 \pm 987$	0.898 ± 0.019
Na-24	1368.6	172 ± 56	0.025 ± 0.010	56 ± 9	0.007 ± 0.001

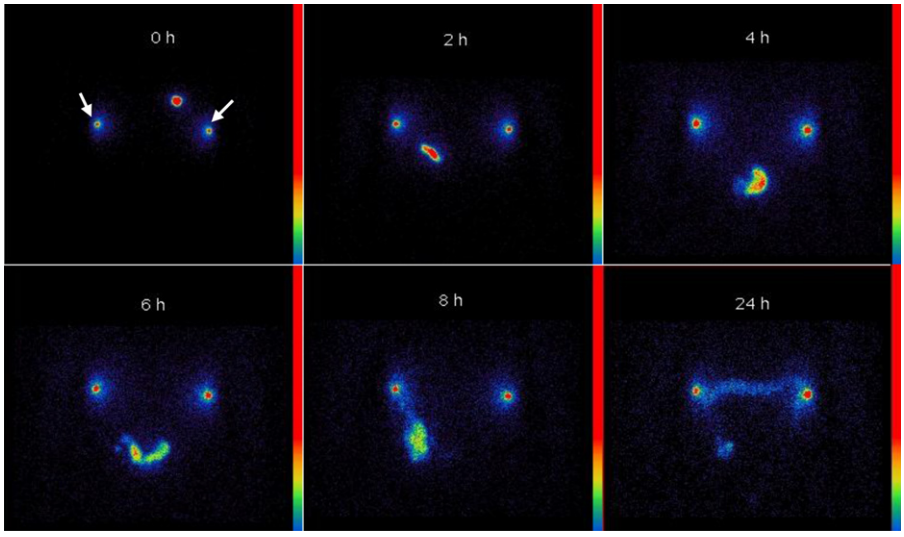

Fig. 2. Static scintigraphic images at two hours interval and a final image at 24 h post-ingestion. The capsule started to disintegrate at 4 h post-ingestion at the ileo-caecal junction. The white arrows point to the anatomical markers.

Table 2
Capsule emptying time from the stomach, time and site of onset of capsule disintegration and site of activity remained at 24 h post-ingestion.

Subject ID	Stomach emptying time (h)	Onset of disintegration		Sites of activity at 24 h
		Time (h)	Site	
1	2.0	3.0	ICJ	AC, TC
2	1.5	3.0	ICJ	RS
3	1.0	N/A	N/A	DC, RS
4	5.0	5.0	JJ	DC, RS
5	1.5	3.0	ICJ	DC
6	1.0	3.0	ICJ	RS
7	1.5	4.0	ICJ	DC
8	2.0	4.5	JJ	TC
9	2.0	4.5	JJ	RS
10	2.0	3.5	ICJ	RS
Mean	2.0	3.7		
S.D.	1.1	0.8		
Minimum	1.0	3.0		
Maximum	5.0	5.0		
1st Quartile	1.5	3.0		
Median	1.8	3.5		
3rd Quartile	2.0	4.5		

AC: ascending colon, DC: descending colon, ICJ: ileo-caecal junction, JJ: jejunum, RS: recto-sigmoid, TC: transverse colon, N/A: data not available.

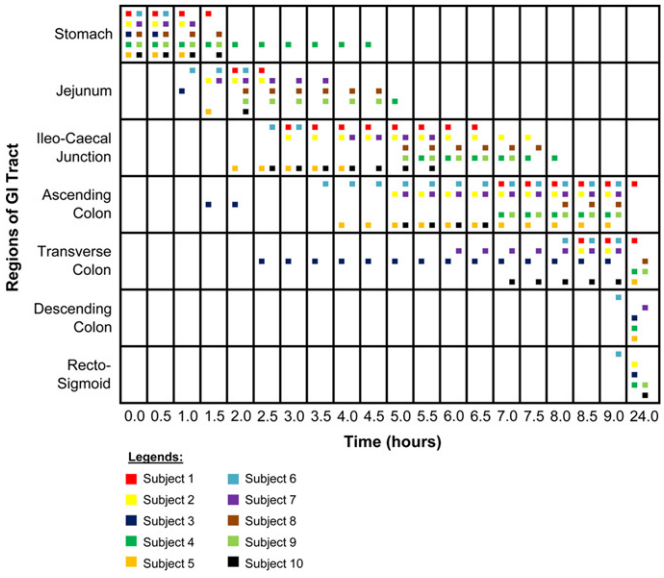

Fig. 3. Localisation of the formulations in the gastrointestinal tract. The colour-coded boxes represent the location of the ^{153}Sm formulation with time for each individual subject. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

4. Discussion

^{111}In-labelled non-absorbable materials are widely used as the preferred tracer for the scintigraphic investigation of whole gut transit. This radionuclide is considered to have suitable physical characteristics of gamma emission, physical half-life and acceptable radiation dosimetry for widespread clinical use. However ^{111}In is produced in relatively few countries where industrial cyclotrons are available.

The production of ^{153}Sm, in this context, requires access to a thermal research reactor. Where available, the cost of using a reactor will be offset by a reduction of the cost of international shipping of radioactive materials. Furthermore, labelling of ion-exchange resin with $^{152}SmCl_3$ does not involve radiation exposure to the hospital personnel and the preparation of the ^{152}Sm-labelled enteric capsule formulation can be carried out in a routine laboratory facility.

The *in vitro* disintegration results confirmed the effectiveness of enteric-coating used in our manufacturing process. Eudragit™ poly(meth) acrylate has been widely used for the coating of oral pharmaceuticals and has proven to be effective for GI targeted delivery system (Akhgari et al., 2006; Cheng et al., 2004; Cole et al., 2002; Ibekwe et al., 2006; Khan et al., 2000, 1999; Kotagale et al., 2009; Moustafine et al., 2008). The coating solution was easily prepared prior to use. Each enteric dip coating took less than 2 min excluding the drying time and no special tools were required. In contrast to ^{111}In-radiolabelled formulation, the encapsulated ^{152}Sm-labelled formulation including enteric coating can be pre-manufactured in batches before studies. The products can be stored within appropriate time frame and sent for neutron activation at least 48 h prior to administration.

Following neutron activation, gamma spectroscopy of the enteric-coated capsules containing ^{153}Sm-radiolabelled resin indicated that the capsules and enteric coating material did not produce any significant radioactive by-products other than ^{24}Na. ^{24}Na has a short physical half-life of 14.9 h therefore a storage of 48 h as suggested by other researches (Ahrabi et al., 2000, 1999; Fani et al., 2002; Marvola et al., 2008, 2004) will allow sufficient decay of the radioactive impurities.

The scintigraphic images obtained with ^{153}Sm were of acceptable quality and were comparable to those commonly acquired using ^{111}In in other clinical patients. The ^{153}Sm-labelled resins were clearly seen in all the images recorded up to 24 h post-ingestion. The gross pattern of tracer distribution in the GI tract could be seen by concatenating the sequential images in dynamic display or summing up all the images into one display frame.

The administered activity of 5 MBq used in this study was based on the amount of activity routinely used clinically for whole gut transit studies using ^{111}In-radiolabelled capsule formulations at the Nottingham University Hospitals, UK. There is currently a lack of established data on radiation dosimetry for oral ingestion of ^{153}Sm-labelled resin formulations for clinical GI transit imaging. Most ^{153}Sm-labelled formulation imaging has been carried out for drug delivery research. Published data for this formulation showed that 1 MBq of ^{153}Sm ingested orally give an effective dose of 0.7 mSv (Ahrabi et al., 2000, 1999a,b; Awang et al., 1993; Fani et al., 2002; Marvola et al., 2008, 2004). However further investigations need to be carried out using a standard GI model to verify the internal radiation dose arising from the formulation recommended in this study. In comparison, ^{111}In has a more well-established radiation dosimetry data. The dose reference level (DRL) recommended by the Administration of Radioactive Substances Advisory Committee (ARSAC), United Kingdom for oral ingestion of ^{111}In-radiolabelled non-absorbable materials in a standard adult is 1.7 mSv from the administered activity of 5 MBq.

One of the disadvantages of ^{153}Sm for diagnostic use is the emission of several beta energies associated with its decay [E_{max}=632 (34%), 702 (44%), 805 (21%) keV]. Although these beta energies are useful for therapeutic applications, the administered activity used for imaging in this study was greatly lower, 5 MBq versus 29.6 MBq per kg therapeutic activity. Therefore the biological effect of beta radiation in this study was considered acceptable. Even though the whole body effective dose received from ^{153}Sm is about twice the dose from ^{111}In (1.7 mSv versus 3.1 mSv) it is considerably lower when compared to the use of X-ray imaging of radiopaque markers, which generally gives an effective dose of approximately 0.7 mSv per radiograph for the lower abdomen (Mettler et al., 2008). Where In-111 is not routinely available, X-ray imaging of colonic transit could result in a total dose of up to 5 mSv depending on the number of X-ray exposures taken. Samarium therefore offers a valuable alternative with the advantage of the quantification of transit that nuclear medicine studies can provide.

Following neutron activation, it is essential that the radiolabel remains intact with the resin and is not absorbed in the GI tract. Our previous studies have demonstrated that the radiolabel was firmly bound to the resin over a period of 24 h (Yeong et al., 2011a, 2011b). Assay of activity in serum and urine of the subjects in the present study confirmed that no ^{153}Sm was absorbed through the gastric mucosa to the vascular space over a period of 9 h.

A limitation of this study was that imaging was only carried out up to 24 h post-ingestion. In routine clinical use imaging would normally be required on a daily basis for up to 72 h and possibly over 7 day in patients with chronic constipation or obstruction. We will be undertaking further studies to evaluate the full clinical value of this formulation for patient investigations over extended periods.

5. Conclusion

We have demonstrated the clinical use of neutron activated ^{153}Sm-labelled resin within an enteric coated capsule as a viable alternative radiotracer to ^{111}In for the assessment of GI motility. The advantages of using ^{153}Sm compared to ^{111}In include alternative manufacturing availability worldwide, minimisation of radiation exposure to radiopharmacy staff and capsule manufacturing in standard pharmacy unit. Administration of 5 MBq ^{153}Sm resulted in good image quality and there was no evidence of release or absorption of the radiolabel up to the limit of observation at 9 h. This study prepares the way for the further assessment of this methodology for clinical gut motility studies.

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