# RADIOLABELLING OF PHARMACEUTICAL DOSAGE FORMS BY NEUTRON ACTIVATION OF SAMARIUM-152.

M B Awang[a*], J G Hardy[a], S S Davis[a], I R Wilding[b] and S J Parry[c].

[a]Department of Pharmaceutical Sciences, University of Nottingham, Nottingham, NG7 2RD.

[b]Pharmaceutical Profiles Limited, 2 Faraday Building, Highfields Science Park, Nottingham, NG7 2QP.

[c]Centre for Analytical Research in the Environment, Silwood Park, Ascot, Berks SL5 7TE.

[*]Author to whom correspondence should be addressed.

## SUMMARY

Samarium-152 can be activated in a neutron flux for the labelling of pharmaceutical dosage forms for evaluation by gamma scintigraphy. The samarium is incorporated as samarium oxide powder which is available with $^{152}Sm$ in its natural isotopic abundance or isotopically enriched. The yield of $^{153}Sm$ was reduced considerably following the neutron activation of the non-isotopically enriched oxide. This can be attributed to the high neutron capture by $^{149}Sm$ present in the non-isotopically enriched oxide. In order to keep the mass of the added oxide powder to the minimum and also to reduce the neutron irradiation time, it is recommended that samarium oxide enriched with $^{152}Sm$ should be used routinely when radiolabelling pharmaceutical dosage forms.

Key Words: samarium oxide, neutron activation, self-shielding, radiolabelling, gamma scintigraphy.

0362-4803/93/100941-08$09.00

Received 15 April, 1993
Revised 10 May, 1993

## INTRODUCTION

Gamma scintigraphy has become the technique of choice for imaging in vivo the distribution of oral and inhaled pharmaceutical products administered to human subjects(1-4). There is a limited range of radionuclides available for such studies, principally $^{99}Tc^{m}$, $^{123}I$ and $^{111}In$. These short-lived radionuclides are used extensively in nuclear medicine. A major disadvantage of using these tracers for the radiolabelling of pharmaceutical dosage forms is that it may necessitate the handling of relatively high quantities of radioactivity during lengthy or complex formulation procedures. However, this problem can be overcome by the incorporation of a non-radioactive tracer into the formulations, with subsequent radiolabelling by neutron activation of the intact dosage forms(5-7).

Samarium-152, as the oxide, has been used in this way to radiolabel tablets(5-7) and multiparticulate formulations(8). Typically, each oral dosage form contains approximately 2 mg samarium oxide powder and is irradiated to yield approximately 1 MBq $^{153}Sm$ at the time of dosing, which is usually 24 hours after irradiation. Samarium oxide is water insoluble and is not absorbed from the gastrointestinal tract.

Neutron activation involves the bombardment of target material with neutrons to produce radionuclides. Suitable target nuclides should possess relatively large neutron capture cross-sections. They should also be available in isotopically enriched forms so as to minimise irradiation times and to reduce the quantity of material that need to be incorporated into the formulations. In addition, the product radionuclide should possess a suitable physical half-life, emit gamma radiation having energy suitable for scintigraphic imaging, and result in a low radiation absorbed dose to the subject. Samarium-152 (Table 1) fulfills these criteria, since it has a relatively high

neutron capture cross section and is available as an isotopically enriched oxide powder. The radioisotope $^{153}Sm$ has a physical half-life of 46.8 hours and emits gamma rays of 103 keV. The radiation dose to a subject from an oral dose of 1 MBq $^{153}Sm$-samarium oxide is approximately 0.7 mSv. Samarium-153 decays to the stable nuclide, $^{152}Eu$.

Table 1 Naturally Abundant and Enriched Samarium Oxides

| Nuclide | Abundance (%) | | Neutron Capture x-Section ($10^{-24}$ cm²) | Product Nuclide | Half-life |
|---|---|---|---|---|---|
| | Natural | Enriched | | | |
| Sm-144 | 3.1 | | 0.7 | Sm-145 | 340 days |
| Sm-147 | 15.1 | 0.1 | 57 | Sm-148 | 8 x $10^{15}$ y |
| Sm-148 | 11.3 | 0.2 | 4.7 | Sm-149 | stable |
| Sm-149 | 13.9 | 0.1 | 40,140 | Sm-150 | stable |
| Sm-150 | 7.4 | 0.2 | 104 | Sm-151 | 87 y |
| Sm-152 | 26.6 | 98.7 | 204 | Sm-153 | 46.8 h |
| Sm-154 | 22.6 | 0.7 | 5 | Sm-155 | 22.4 min |

Sources: Lederer(9)
Mughabghab(10)

Samarium-152 is present naturally in the oxide with an isotopic abundance of only 26.6%. Although the neutron capture cross-section of $^{152}Sm$ is 206 barns, naturally abundant samarium contains 13.3% $^{149}Sm$ which has a much greater cross-section of 40140 barns and may affect the generation of $^{152}Sm$ (Table 1). Neutron self-shielding is a phenomenon that occurs when an isotope in a sample competes for neutrons with the target nuclei

of interest. As a result the target nuclei will be exposed to a reduced neutron flux. This phenomenon considerably reduces the yield of the desired radionuclides.

Samarium oxide, enriched to more than 98% with respect to $^{152}Sm$ isotope is available but expensive, typically costing 150 times more than the non-enriched material. In the present study, experiments were designed to investigate the feasibility of radiolabelling pharmaceutical dosage forms using naturally abundant samarium and to investigate the influence of other isotopes of samarium on the neutron activation of $^{152}Sm$.

## MATERIALS AND METHODS

Samarium in its natural isotopic abundance was obtained as the oxide powder with a volume mean diameter of 7.57 μm (chemical purity 99.99%, REActon, Cheshire) and as nitrate (Koch-Lite, Buckingham). Enriched samarium oxide powder, of volume mean diameter 4.80 μm, containing 98.7% as $^{152}Sm$ isotope was provided by Pharmaceutical Profiles, Nottingham. Spray-dried lactose powder was manufactured by Lactochem (Saltney, U.K.).

Four sets of samples containing samarium compounds were irradiated at the Imperial College Reactor, Ascot, using a nominal neutron flux of $1 \times 10^{12}$ n/cm²/s. The weights of samarium samples used were expressed in terms of their of $^{152}Sm$ contents. All samples were sealed in polyethylene irradiation capsules and were subsequently irradiated for 2 minutes.

Five samples of isotopically enriched samarium oxide were irradiated. The $^{152}Sm$ contents ranged from 5.02 to 61.1 mg. The same experiments were carried out using naturally abundant samarium with $^{152}Sm$ contents ranging from 1.17 to 16.08 mg.

The effect of diluting the oxide powder was investigated by mixing with lactose powder. Naturally abundant samarium oxide powder with the $^{152}Sm$ contents ranging up to 16.31 mg was mixed

with lactose so that the total mass of each mixture was 200 mg. The mixtures were rotated using a Turbula T2C mixer (Glencreston Ltd, Stanmore) for about 10 minutes.

Solutions of samarium nitrate were also irradiated to study systems containing completely dispersed samarium atoms. The solutions contained up to 16.02 mg $^{152}Sm$ dissolved in 1 ml water.

Following irradiation, each sample was analysed for $^{153}Sm$ using a high resolution lithium-drifted germanium detector (Princeton Gamma-Tech LGC14, USA). The detector has a relative efficiency of 14.1% and a FWHM at 1.33 MeV $^{60}Co$ of 1.95 keV; and is connected to a computer based analyser system for data acquisition and processing with the manufacturer's software. The activity detected was corrected for radioactive decay.

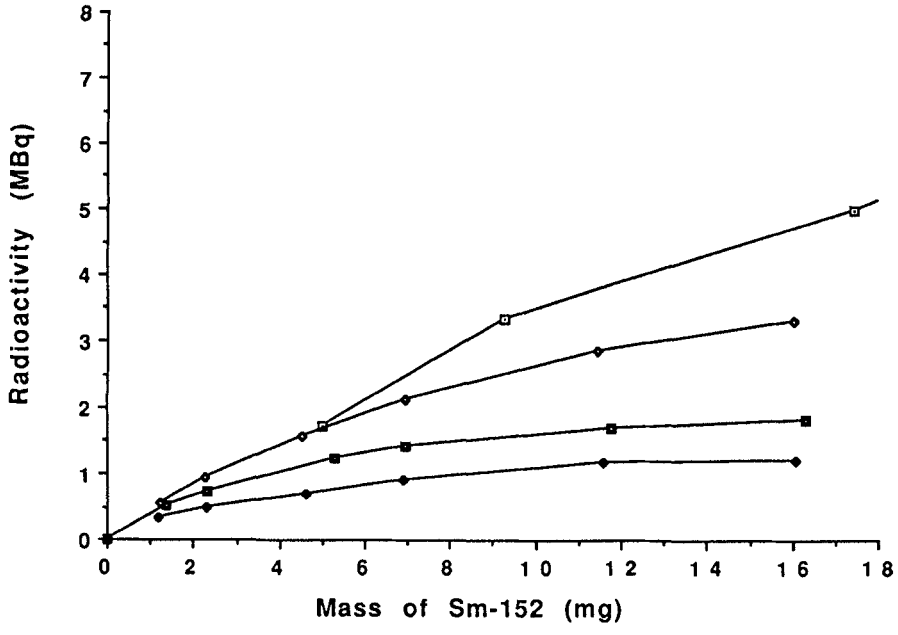
## RESULTS

There was a considerable reduction in the amount of $^{153}Sm$ generated using natural abundance oxide compared to the activation of the isotopically enriched material (Figure 1).

Using enriched samarium oxide, approximately 1.7 MBq of $^{153}Sm$ was generated following 2 minutes of irradiation of a 5 mg sample in a nominal neutron flux of 1 x $10^{12}$ n/cm²/s. There is a linear relationship between activity achieved and the mass of $^{152}Sm$ irradiated up to about 10 mg $^{152}Sm$.

Considerably lower yields, however, were obtained when naturally abundant samarium oxide samples were irradiated. For a sample containing 5 mg of $^{152}Sm$, the yield produced was half of that obtained with the enriched oxide under the same irradiation condition.

Dispersing the naturally abundant samarium oxide with lactose increased the yield of $^{153}Sm$. With 5 mg of $^{152}Sm$, the neutron activation achieved was 70% of that of the enriched material. While complete dispersion of samarium atoms in 1 ml




LEGEND FOR FIGURE 1

Figure 1. Samarium-153 produced following neutron activation of samarium oxide powder: enriched with the samarium-152 isotope —□—; of natural isotopic abundance —◆—; of the non-enriched oxide dispersed in lactose powder —■—; and of non-enriched samarium dissolved in aqueous solution —◇—.

water generated the highest radioactivity among the naturally abundant target materials, it was considerably much less than that obtained using the isotopically enriched oxide powder.

## DISCUSSION

There was considerable reduction in the yield of $^{153}Sm$ resulting from the presence of the other isotopes of samarium, principally samarium-149 which has a large neutron capture cross-section.

In pharmaceutical dosage forms, the oxide powder is dispersed amongst the other excipients of the formulation. This

dispersion reduces the extent of self-shielding and this was simulated in the experiments using lactose as diluent.

It would be expected that on dispersion, the finer the particle size of the oxide the less the self-shielding effect. For a completely dispersed formulation, as demonstrated by the result from the solution studies, there is still a considerable reduction in their yield, compared to using isotopically enriched $^{152}Sm$ starting material.

At the higher masses, a reduction of yield also occurred with the isotopically enriched samarium oxide, presumably a result of the samarium-149 impurity present.

When preparing pharmaceutical dosage forms, it is desirable to keep the mass of the added tracer to a minimum. Therefore, an advantage of using isotopically enriched samarium oxide is that the mass of tracer required can be minimised. Typically, a batch for irradiation could contain 10-20 doses, i.e. containing up to 40 mg samarium oxide. Thus, unacceptable irradiation times may be required if the non-enriched tracer were used. This may result in unacceptable damage to the compound or pharmaceutical formulation.

## CONCLUSION

This study has demonstrated that a significant degree of self-shielding can occur when samarium oxide in its natural isotopic abundance is irradiated. This results in a reduction in the yield of $^{153}Sm$. It is therefore recommended that material enriched with the $^{152}Sm$ is used for the radiolabelling of pharmaceutical dosage forms for in vivo scintigraphic imaging studies.

## REFERENCES

1. Casey,D.L., Beihn,R.M., Digenis,G.A. and Shambhu,M.B.(1976) Method for monitoring hard gelatin capsule disintegration time in

humans using external scintigraphy, J. Pharm. Sc. 65,1412-1413.

2. Daly,P.B., Davis,S.S., Frier,M., Hardy,J.G., Kennerly,J.W. and Wilson,C.G.(1982) Scintigraphic assessment of the in vivo dissolution rate of sustained release tablet, Int. J. Pharm. 10, 17-24.

3. Davis,S.S. and Hardy,J.G.(1988) Drug delivery in the gastrointestinal tract, in An illustrated guide to gastro-intestinal motility, Eds. D. Kumar and S. Gustavsson, John Wiley & Sons, New York, pp 265-271.

4. Davis,S.S. Hardy,J.G., Newman, S.P., Wilding,I.R.(1992) Gamma scintigraphy in the evaluation of pharmaceutical dosage forms, Eur. J. Nucl. Med. 19, 971-986.

5. Parr,A, Jay,M., Digenis,G.A. and Beihn,R.M.(1985) Radio-labelling of intact tablets by neutron activation for in vivo scintigraphic studies, J. Pharm. Sc. 74, 590.

6. Digenis,G.A. and Sandefer,E.(1991) Gamma scintigraphy and neutron activation techniques in the in vivo assessment of orally administered dosage form, Critical Rev. in Therap. Drug Carrier System 7, 309-345.

7. Hardy,J.G., Lamont,G.L., Evans,D.F., Haga,A.K. and Gamst,O.N.(1991) Evaluation of an enteric-coated naproxen pellet-formulation, Aliment. Pharmacol. Ther. 5, 69-75.

8. Digenis, G.A., Sandefer, E.P., Parr,A.F., Beihn,R., McClain,C., Scheinthal,B.M., Sellasie,G., Iyar.U., Nesbitt,R.U., and Randinitis,E.(1990) Gastrointestinal behaviour of orally administered radiolabelled erythromycin pellets in man as determined by gamma scintigraphy, Clin. Pharmacol. 30, 621-631.

9. Lederer, C.M. and Shirley, V.S. (1978), Table of Isotopes, John Wiley & Sons, New York.

10. Mughabghab, S.F., Devadeenam,M. and Holden, N.E. (1984), Neutron cross sections, Volume I, Academic Press, New York.