

Production of the Positron Emitting Radioisotope ^{86}Y for Nuclear Medical Application

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The production of ^{86}Y via the $^{86}\text{Sr}(p,n)$ -reaction was studied. Samples of 96.3% enriched $^{86}\text{SrCO}_3$ were irradiated using a 4π water-cooled target system at nearly optimum proton energy ranges (14 → 10 MeV) at beam currents of 3–8 μA . Thick target yields calculated from the measured excitation functions were compared with results from production runs. A chemical separation procedure including the recovery of the enriched target material was developed. Activities of about 1.5 GBq (40 mCi) ^{86}Y per batch with high radionuclidic and radiochemical purity were achieved and [^{86}Y]citrate was prepared for pharmacokinetic studies using PET.

Introduction

^{90}Y ($T_{1/2} = 64.1$ h, $\beta^- = 100\%$, $E_{\beta^-} = 1.3$ MeV) is one of the widely used therapeutic nuclides. It is available in no-carrier-added concentration from the ^{90}Sr ($T_{1/2} = 28.5$ a)/ ^{90}Y generator system. It is used in targeted tumour therapy in the form of different chemical complex compounds, microspheres or monoclonal antibodies. However, ^{90}Y cannot be used for imaging. Consequently, a few recent reports described attempts to use γ -emitting yttrium isotopes (^{87}Y , ^{88}Y) to quantify the biodistribution of Y-pharmaceuticals in animals (Beyer *et al.*, 1992) as well as in humans (*cf* Buchali *et al.*, 1993; Kutzner *et al.*, 1992). The introduction of a positron emitting isotope seems to be the method of choice since quantitative regional kinetics can be studied by positron emission tomography (PET). The biokinetics of the yttrium-pharmaceutical is important for the optimization of therapy. Such data are still missing for the ^{90}Y compounds. In addition, new [^{90}Y]-radiopharmaceuticals could be designed, studying the correlation between the chemical and the radiopharmaceutical properties of various compounds by means of the positron labelled radiopharmaceutical and PET.

Among the neutron deficient isotopes ^{86}Y , a relatively long-lived positron emitter, appears to be most promising for such PET studies [*cf* Rösch and Beyer (1991a,b); Rösch *et al.* (1993)]. It has a half-life of 14.7 h and decays 33% by β^+ emission with a maximum positron energy of 1.2 MeV. Recently we measured nuclear data of the $^{86}\text{Sr}(p,xn)$ - and $^{86}\text{Rb}(^3\text{He},xn)$ -processes with a view to investigating production routes of ^{86}Y (Rösch *et al.*, 1993). From the point of production yield, and particularly the

level of radionuclidic impurities, the $^{86}\text{Sr}(p,n)^{86}\text{Y}$ reaction is the method of choice. Another advantage of the (p,n) route is that a small-sized cyclotron is adequate. On the other hand, this route requires highly enriched target material and consequently, quantitative recovery of ^{86}Sr is an important part of the ^{86}Y production process.

The aim of this work was:

- (i) to develop a production target;
- (ii) to measure experimental production yield and radioisotopic purity;
- (iii) to develop a chemical separation method; and
- (iv) to produce [^{86}Y]citrate for application in humans.

Experimental

Target material and reagents

Strontium carbonate was supplied by v/o Technobexport Moscow with an isotopic composition of ^{84}Sr (<0.002%), ^{86}Sr (96.3%), ^{87}Sr (1.02%), ^{88}Sr (2.68%). As described earlier (Rösch *et al.*, 1993) the chemical composition of this material was analysed by optical emission spectroscopy and diffractometric phase analysis, detecting a sum of metal impurities like Na, Mg, Si, Ca and Ba of <400 ppm and a chemical form of >99% carbonate.

α -Hydroxyisobutyrate (α -HIB) and sodium citrate were obtained commercially from Merck as analytical grade materials. Neutral solutions of α -HIB were obtained using NH_4OH as solvent; pH of the 1 M α -HIB stock solution was 5.4. Aqueous isotonic solutions of sodium citrate, pH 7.4, were prepared from Na_3Cit (7.5 mg/mL).

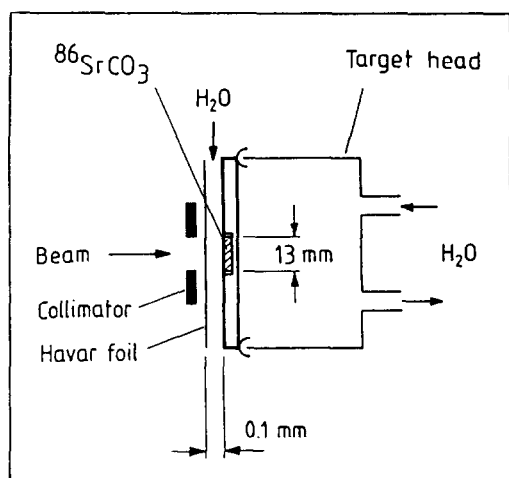


Fig. 1. Simplified sketch of the target system used.

Production target

About 220 mg $^{86}\text{SrCO}_3$ was used as target material. The powder was pressed into a tablet of 13 mm dia. The tablet was then placed into a cylindrical groove in a target holder, which is essentially the same as used earlier for production of ^{123}I via the $^{124}\text{Te}(p,2n)$ - or $^{123}\text{Te}(p,n)$ -reaction [cf Michael *et al.* (1981); Scholten *et al.* (1989)]. In brief, it consists of a $20 \times 40 \times 3$ mm rectangular piece of Al, having in the middle of its upper surface a circular hole 16 mm dia. and 2.1 mm deep, in which the tablet is put. An Al foil of chosen thickness, corresponding to a calculated proton energy degradation, is placed on the surface of the $^{86}\text{SrCO}_3$ pellet. Finally, the upper surface of the target holder is closed by a $50 \mu\text{m}$ thick Al foil having exactly the same dimensions as the upper surface of the target holder.

The target was then placed in a 4π -water cooled target head [cf Michael *et al.* (1981)]. A simplified sketch of the target system used is shown in Fig. 1. The present system differs from that used in ^{123}I production in two respects:

- the target holder is made of Al instead of Pt;
- unlike $^{123,124}\text{TeO}_2$ the $^{86}\text{SrCO}_3$ is not in contact with the cooling water.

The proton loses some energy in the Harvar foil ($50 \mu\text{m}$ thick), cooling water (0.1 mm thick), Al foil ($50 \mu\text{m}$ thick), Al absorbers ($100 \mu\text{m}$ thick) and $^{86}\text{SrCO}_3$ (130 mg/cm^2), and deposits the rest energy in the beam stop. The optimum production energy range calculated from the excitation function was $E_p = 14 \rightarrow 10$ MeV (Rösch *et al.*, 1993). In practice, it was slightly different.

Irradiations

Targets were irradiated at the Jülich compact cyclotron CV28 using different beam currents. In early experiments natural SrCO_3 targets were irradiated for 0.5 h with beam intensity increasing from

1 to $10 \mu\text{A}$. The ^{86}Y yield increased proportionally to the beam current and the target material was found to withstand beam currents of up to $10 \mu\text{A}$. Production runs using highly enriched $^{86}\text{SrCO}_3$ were performed at proton beam currents of 6.0 and $8.0 \mu\text{A}$ for 1–3 h.

Chemical separations

In studies on $^{87\text{m},\text{g}}\text{Y}$ formed in strontium targets via the $^{88}\text{Sr}(p,2n)$ nuclear reaction, radioyttrium was separated first by means of coprecipitation with iron(III) (Allen and van Pinajian, 1965) or precipitation with yttrium(III) hydroxide (Hillmann *et al.*, 1966; Homma *et al.*, 1980) and then adsorbed on di(2-ethylhexyl)-phosphoric acid coated PTFE granules matrix (Levin *et al.*, 1969, 1972).

For the target system presented here a radiochemical separation of radioyttrium had to be adapted, separating the no-carrier-added ^{86}Y from the target material as well as from the disturbing isotopes ^{83}Rb and ^{85}Sr . Additionally, the whole procedure should guarantee the recovery of the highly enriched ^{86}Sr target material. A combination of coprecipitation and cation-exchange techniques was used. A flow sheet of the radiochemical separation procedure is shown in Fig. 2.

The target material was dissolved in a few drops of concentrated hydrochloric acid. The solution was diluted with 10 mL water, containing 2 mg La(III) as a carrier. The $\text{La}(\text{OH})_3$ was then precipitated by adding some drops of concentrated ammonia. The ^{86}Y was coprecipitated almost quantitatively. After centrifugation the precipitate was purified. The precipitate was then dissolved in 1–2 drops conc. HCl and this solution was diluted with 10 mL water.

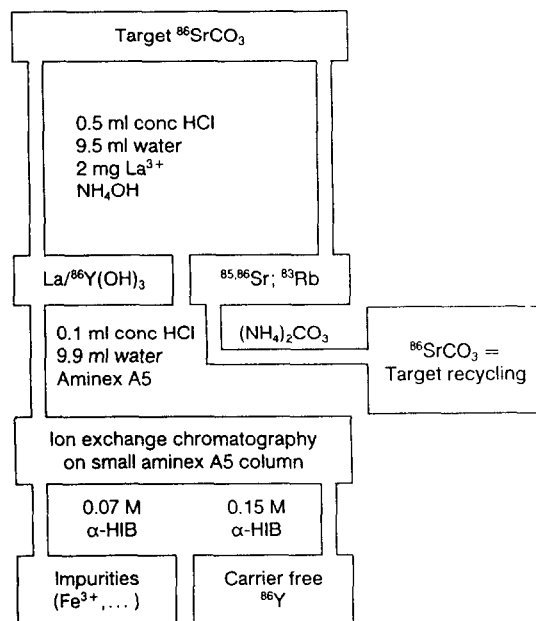


Fig. 2. Flow sheet of radiochemical separation procedure.

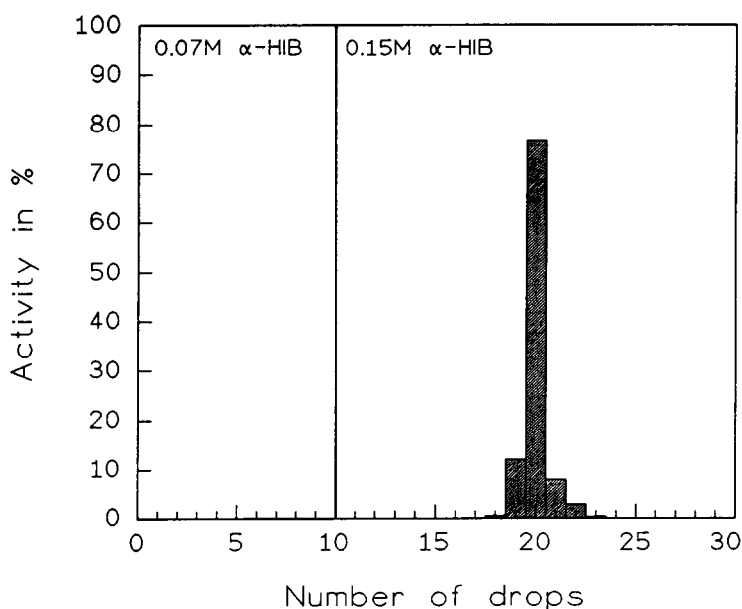


Fig. 3. Elution chromatogram of no-carrier-added ^{86}Y (α -HIB on Aminex A5 cation exchange resin column; 4 mm dia., 40 mm length).

To separate the no-carrier-added ^{86}Y from the La-carrier, cation-exchange chromatography was applied using α -HIB, pH 5.4, as eluent, and Aminex A5 as resin on a small column (4 mm i.d., 40 mm length). Aminex A5 was stored in diluted NH_4OH and preconditioned by elution with water just before the experiments. The upper part of the packed resin, representing about 1 cm column length, was transferred to the 10 mL aqueous ^{86}Y -solution. After about 10 min the resin was isolated by means of centrifugation (absorption efficiency of >95%) and transferred carefully back on to the column head. Next, elution started with a flow rate of the eluent of 10 drops per minute. Possible impurities like Fe(III) were separated first by means of 0.07 M α -HIB. The ^{86}Y was eluted with 0.14 M α -HIB within a few drops. Traces of rubidium and strontium, if present, and the La-carrier remained quantitatively on the column. A typical elution chromatogram is shown in Fig. 3. The overall separation yields are ca 90%. The whole procedure takes about 1 h.

Results

Production yields

To compare theoretical and experimental thick target yields several $^{86}\text{SrCO}_3$ samples of various thicknesses were irradiated. After chemical processing the yield of ^{86}Y was determined via γ -ray spectrometry. The results are summarized in Table 1. For ^{86}Y production, targets consisting of 220 mg $^{86}\text{SrCO}_3$ (i.e. 130 mg/cm²) are irradiated for 1–3 h at 6–8 μA proton beam current. After chemical processing the batch yield of ^{86}Y amounts to 1.5 GBq (40 mCi).

Radionuclidic purity

As shown by nuclear data measurements (Rösch *et al.*, 1993) the major impurities associated with ^{86}Y in the $^{86}\text{Sr}(p,n)$ -process are the yttrium isotopes ^{86}m , 85 , ^{85}m , 87 , ^{87}m and 88 as well as ^{83}Rb and ^{85}Sr . The rubidium and strontium isotopes are separated during the chemical processing but the isotopes of yttrium are not separated from each other.

Table 1. Theoretical and experimental yields of ^{86}Y from a 96.3% enriched $^{86}\text{SrCO}_3$ thick target

Target energy range (MeV)	Theoretical thick target yield MBq(mCi)/ μAh	Experimental Batch yield MBq(mCi)	Experimental thick target yield MBq(mCi)/ μAh	Experimental yield as % of theoretical thick target yield (%)
13.8 → 10.4 ^a	196 (5.3)	31 (0.83)	155 (4.2)	78
12.0 → 8.0 ^b	126 (3.4)	1369 (37)	86 (2.3)	61
12.0 → 8.0 ^c	126 (3.4)	1184 (32)	74 (2.0)	58

^aIrradiation parameters: $t = 1.0\text{h}$, $I = 0.2\mu\text{A}$.

^bIrradiation parameters: $t = 3.0\text{h}$, $I = 6.0\mu\text{A}$.

^cIrradiation parameters: $t = 2.0\text{h}$, $I = 8.0\mu\text{A}$ (proton energy ranges entail an error of 0.2MeV).

Table 2. Radionuclidic impurities of ^{86}Y from a 96.3% enriched $^{86}\text{SrCO}_3$ thick target

Irradiation parameter ^a			Radionuclidic impurities in % of ^{86}Y activities					
I_p (μA)	t_b (h)	t_w (h)	^{86m}Y $T_{1/2}$ 48 min	^{85}Y 2.68 h	^{85m}Y 4.86 h	^{87}Y 3.35 d	^{87m}Y 12.9 h	^{88}Y 106.6 d
0.05	0.25	0	280	<0.1	<0.1	0.4–0.5	1.5–3.0	0.02–0.03
0.2	1.0	1–2		<0.1	<0.1	0.32	1.5	0.03
6.0	3.0	13	<0.1	<0.1	<0.1	0.75	1.9	<0.1
8.0	2.0	3	5.7	<0.1	<0.1	0.2	1.4	0.06

^a I_p is intensity of proton beam; t_b irradiation time; t_w waiting time after EOB.

The radioisotopes $^{87,87m}\text{Y}$ and ^{88}Y are formed from target strontium nuclei other than ^{86}Sr . Their amounts thus depend on the levels of ^{87}Sr and ^{88}Sr in the enriched ^{86}Sr sample. The components ^{86m}Y and $^{85,85m}\text{Y}$, on the other hand, are formed from ^{86}Sr . Above 14 MeV the percentage of $^{85,85m}\text{Y}$ increases with the increasing proton energy due to the onset of the $^{86}\text{Sr}(p,2n)$ -process.

The ^{86m}Y impurity is of special importance. It is formed together with ^{86}Y and is the dominant activity at EOB. The ratio of the activities $^{86m}\text{Y}/^{86g+m}\text{Y}$ formed is energy dependent (Rösch *et al.*, 1993), but the relative amounts of ^{86m}Y and ^{86}Y change rapidly after EOB due to the short half-life of ^{86m}Y . The isotopic composition of the nuclear reaction products is summarized in Table 2. For example, a 15 min irradiation of $^{86}\text{SrCO}_3$ in the proton energy range of $E_p = 14 \rightarrow 10$ MeV will result in 280% ^{86m}Y activity at EOB, whereas at a lower energy region of $10 \rightarrow 6$ MeV the ^{86m}Y activity amounts to 185%. The ^{86m}Y activity of course decreases significantly after some hours "waiting" time. Under routine conditions of ^{86}Y production, i.e. separation and preparation of [^{86}Y]-radiopharmaceuticals within 4 h, for example, ^{86m}Y impurities decreases by a factor of 100.

Preparation of [^{86}Y]citrate and quality control

For the synthesis of [^{86}Y]-pharmaceuticals, the α -HIB must be removed. This is possible by careful heating of the ^{86}Y fraction in a small teflon (PTFE) device using a quartz lamp as a heat source. The organic eluent is destroyed and volatilized quantitatively, if one drop of a concentrated mineral acid (HClO_4 for example) is added. To the remaining ^{86}Y reagents necessary for the synthesis of the [^{86}Y]compound are given. It should be noted that the reactions proceed under minimized volume conditions, i.e. only a few drops of the reagent solvents are needed and the overall volume of the product fraction is in the order of 1 mL or less. For preparation of [^{86}Y]citrate, an analogue of the common radiotherapeutic compound [^{90}Y]citrate, 0.5 mL of isotonic sodium citrate solution (pH 7.4) was added to the ^{86}Y immediately in the PTFE device. This solution can be transferred to a vial and further diluted as desired with isotonic sodium citrate or saline solution (in a $\text{Na}_3\text{Cit}:\text{NaCl}$ ratio of about 1:2).

All reagent solutions used for the synthesis were subjected to sterile filtration prior to use. The sterility of the product solution was assured by filtration

through a 0.22 μm Millipore filter. In general, 5–15% of the ^{86}Y activity was found to remain on the sterile filter.

The radionuclidic quality control was done by γ -ray spectrometry (for levels of impurities *cf* Table 2). The pharmaceutical quality control was carried out in a pharmaceutical laboratory and the products found to be pyrogen free.

Recovery of the target material

The enriched ^{86}Sr can be recovered almost completely in its original chemical form. For this purpose, the first fraction containing an alkaline solution of the target material ^{86}Sr (and radioisotopes ^{85}Sr and ^{83}Rb) is used. ^{86}Sr is precipitated as carbonate by adding freshly prepared saturated $(\text{NH}_4)_2\text{CO}_3$ solution. The $^{86}\text{SrCO}_3$ is separated by centrifugation, washed with dilute $(\text{NH}_4)_2\text{CO}_3$ and water and dried with acetone. Recovery yields are >90%.

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