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THE PRODUCTION OF ^{81}Rb/^{81m}Kr GENERATORS WITH 60-MeV PROTONS AT BLIP*

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INTRODUCTION

The Rb-81/Kr-81m generator system is rapidly gaining acceptance in nuclear medicine for studies of regional lung ventilation in patients with suspected pulmonary emboli or obstructive pulmonary disease. The attractiveness of ^{81m}Kr for these applications is based on its desirable physical properties including a 13.1 s half-life, a high abundance (67%) of convenient 190 keV photons, and a 4.58 hr parent allowing practical distribution. The short half-life of this gas, relative to the transit time required to reach the alveoli, precludes its equilibration in the lungs. Instead the images reflect primarily the distribution of regional ventilation. The short half-life permits the administration of large amounts of activity for better imaging but still at low absorbed radiation dose. Multiple views or rapid sequential studies are also possible. Furthermore, there is no disposal problem after use.

Methods reported for preparing ^{81}Rb include the bombardment of NaBr with 50 MeV alpha particles[1], Cu_2Br_2 with 30 MeV alphas[2], enriched ^{82}Kr with 22 MeV deuterons[3] and protons[4], and natural krypton with protons[5]. A significant advantage of the krypton gas target over bromide salt targets is the much simpler processing involved. However, with low energy accelerators, isotopically enriched ^{82}Kr is often utilized due to the low abundance (11.6%) of the target isotope in naturally occuring krypton. Recovery and reuse of this expensive gas is then required. Typically when natural krypton is used very thick targets are necessary to compensate for the low abundance of ^{82}Kr.

METHOD

The Brookhaven LINAC Isotope Producer (BLIP) utilizes the excess beam capacity of a LINAC that injects 200 MeV protons into the 33 GeV Alternating Gradient Synchrotron which is used for high energy physics research. The LINAC provides a time averaged beam current of up to 60 μA for radioisotope production. By bombarding natural krypton gas with ∿63 MeV protons, ^{81}Rb is formed by (p,4n) reaction from high abundance ^{84}Kr (57%) as well as some additional contribution from ^{83}Kr (11.5%) and ^{82}Kr (11.6%) by (p,3n) and (p,2n) reactions, respectively. The 200 MeV proton beam from the LINAC is passed through an array of aluminum and copper degraders to reduce its energy. The variation of production rate with incident energy is shown in Figure 1. A small quantity of ^{77}Br can be a useful by-product of this irradiation.

The designs of the BLIP irradiation stations[6] require that the physical thickness of all targets be less than 2 cm axially. The high pressure gas target consists of a stainless steel frame, 6.5 cm in I.D. and 1.75 cm in thickness, onto both ends of which are welded 0.157-cm-thick type 304 stainless steel windows. The internal steel surfaces are polished. Reactants and products are introduced and removed through a stainless steel dip-tube and a needle valve welded to the rim of the chamber. The vessel is evacuated to approximately 10 μm Hg before filling with natural krypton to 180 psia, resulting in an effective krypton thickness of 0.07 g/cm^2. During the bombardment, both windows of the target are directly water cooled. The target processing is very straightforward and is substantially the same procedure followed by other producers using natural krypton targets. Following a one to five hour irradiation, the target is transported to a shielded hot cell facility and connected to processing equipment. The krypton is then released to waste by pumping. Ten milliliters of high purity water is then added to the target chamber, which is shaken vigorously for several minutes to dissolve the rubidium deposited on the inner metal surfaces. A single wash serves to rinse out more than 98% of the available rubidium activity. The solution is subsequently forced by air pressure through the AG50-x8 resin (Bio-rad Laboratories, CA) column of the generator, on which the rubidium is retained. The effluent, containing traces of bromine isotopes which are not absorbed, is collected in a waste container. An additional 5 ml of water is run through to wash the generator. The generator system is identical to that developed by Mayron et al.[7] except the metal column is replaced with a Nylon cylinder. This is to avoid leaching of metal from the column material, which would destroy the capacity of the resin to bind the rubidium ions. The generator itself is housed inside a 2-cm-thick lead cylinder through the top of which the polyethylene inlet and outlet lines protrude. After loading Rb-81, the shielded assembly is taken out of the processing hot-cell, inserted into a second 3.7-cm-thick lead shield and is ready for use. This processing takes less than 45 minutes and is amenable to automation.

RESULTS

The production rate of ^{81}Rb is typically 1.5 mCi/μAh. This is routinely measured by gamma ray spectroscopy of a known aliquot of the product solution. This production rate is sufficient to create up to several hundred millicuries per run if necessary, enough for several high activity ^{81}Rb/^{81m}Kr generators. Presently generators that deliver 10-20 mCi to the lungs are produced weekly for on-site use.

The radionuclidic composition of the product solution is summarized in Table 1. The only other important activity in the solution is Rb-82m (6.4 hr). Small amounts of Br-76 (16.1 hr), Br-77 (57 hr), Br-82 (35.5 hr), Rb-83 (86.2 d), and Rb-84 (33 d) were also present. The bromine impurities pose no problem since they are not trapped on the generator. Rb-82m and Rb-84 decay to stable Kr-82 and Kr-84 in the generator and do not interfere with Kr-81m studies. Since only traces of Rb-83 are present very little 1.86 hr Kr-83m is produced during

Table 1

Rubidium-81 Radionuclidic Purity

Radionuclide	Half-life	Relative activity (EOB)
Rb-81	4.58 h	100 %
Rb-82m	6.4 h	50 %
Rb-83	86.2 d	0.2 %
Rb-84	33. d	0.2 %
Br-75	101. m	1.2 %
Br-76	16.1 h	0.2 %
Br-77	57. h	0.5 %
Br-82	35.5 h	0.5 %

Table 2

^{81}Rb/^{81m}Kr Generator Parameters

Production Rate:		1.5 mCi/μAh
Recovery from target:		98%
Column loading efficiency:		98%
Elution yield:		∿85%
Breakthrough:	1×10^{-7}	(air)
	3×10^{-4}	(water)

the life time of the generator due to the large difference in half-life. Moreover, it can be washed from the generator in a pre-elution.

The relevant performance parameters of the generator are shown in Table 2. The elution yield is measured by pushing an air bolus through the generator into an evacuated multi-injection bottle placed in a Capintec dose calibrator and comparing this value with the amount of ^{81}Rb loaded on the column. The elution yield is relatively insensitive to flow rate. The ^{81}Rb breakthrough is determined by bubbling an air bolus of ^{81m}Kr through a water trap placed in the dose calibrator and then analyzing the water for ^{81}Rb by gamma ray spectroscopy. A millipore filter on the output line of the generator reduces the ^{81}Rb reaching the patient. When used for perfusion studies, the dextrose water solution can be analyzed for ^{81}Rb breakthrough. Because these measurements take some time, they are not routinely done on every generator. Instead a simple, reproducible measurement is used that gives relative activity from run to run. Distilled water is pushed at constant flow rate by syringe pump through the generator and into a bottle inside a dose calibrator. The flow rate has been adjusted to give a steady state radiation reading. This value is related to the actual ^{81m}Kr activity of the generator by an arbitrary factor and thus only yields a relative comparison of each generator. Of course, this effluent water can be checked for ^{81}Rb breakthrough.

With the advent of commercially available ^{81}Rb/^{81m}Kr generators, our high activity generator system is no longer distributed off-site but is produced weekly at Brookhaven primarily for studies emphasizing the early detection of non-embolic lung disease. For example, the inspiration of successive boluses of ^{81m}Kr each introduced at a different lung volume, in conjunction with ^{127}Xe equilibrated in the lungs of the same patient, allows quantitative assessment of the extent and regional distribution of lung airway closure. Airways normally close as residual volume is approached during maximum expiration. This traps air distal to the point of closure. Obstructive pulmonary diseases cause these airways to close prematurely, trapping an abnormally large volume of air. This can provide one of the earliest indications of lung impairment[8]. Krypton-81m is also being used in an investigation of the relationship between the degree of ventilation non-uniformity and overall pulmonary function impairment in patients with coal worker's pneumoconiosis. The point-by-point values of ^{81m}Kr activity were corrected for lung volume by dividing them by the corresponding ^{127}Xe activities at equilibrium. This gives a result approximately proportional to ventilation per unit lung volume ($\dot{V}/V_A$). The differences between $\dot{V}/V_A$ values for neighboring pixels were used to establish a non-uniformity index ($\dot{U}$I). Significant differences were found between values of UI for normals and patients with coal worker's pneumoconiosis[9].

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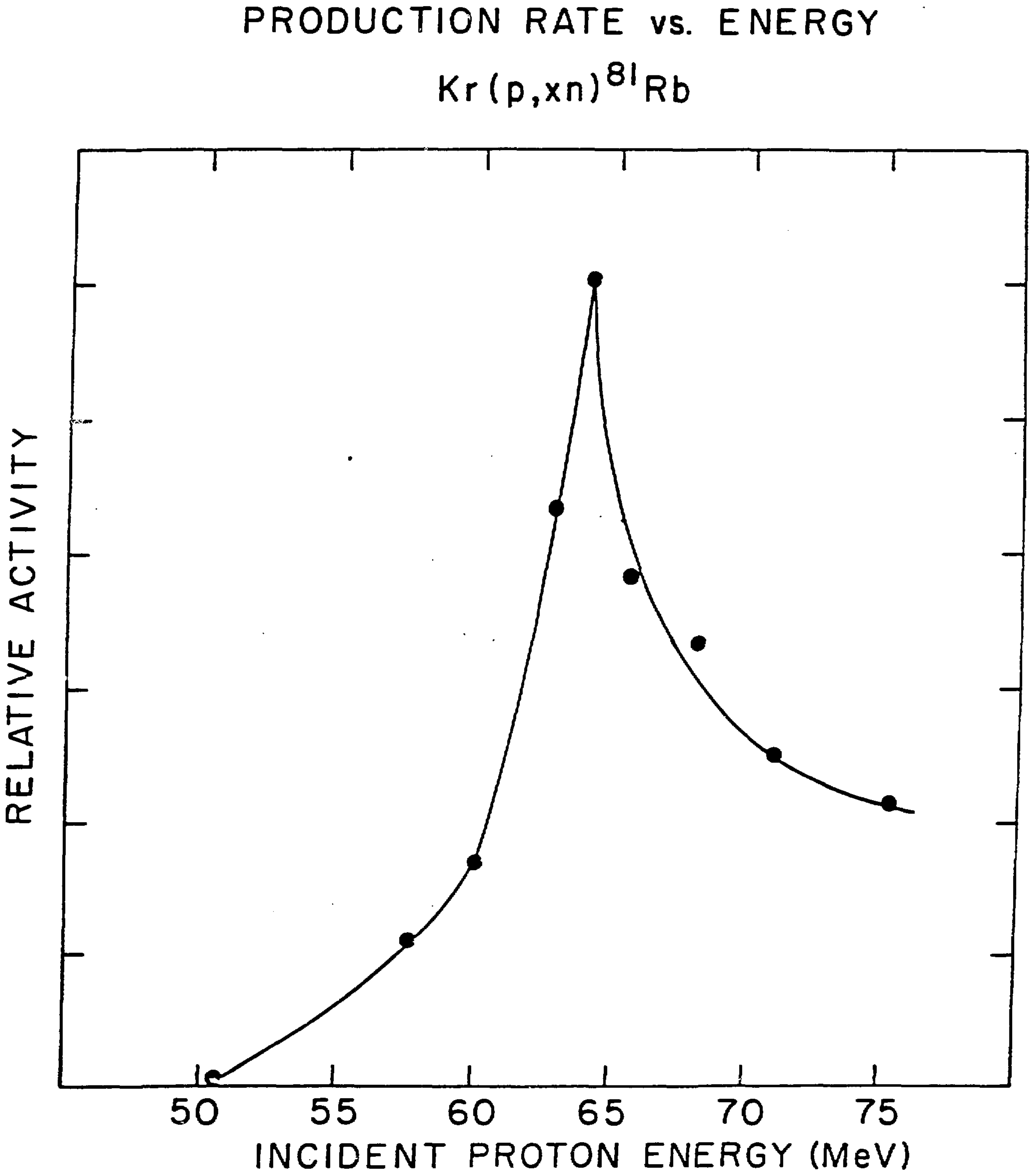

Figure 1. ^{81}Rb relative production rate vs. energy for a 0.07 g/cm^2 Kr target.