The Influence of Carrier Strontium Level and Eluant Volume on the Performance of (Sr-82)-(Rb-82) Biomedical Generators

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Previous inconsistencies in the medical literature regarding the performance characteristics of (Sr-82)-(Rb-82) radionuclide generators have been partially resolved by further experimentation. The Chelex generator is dependent upon the presence of carrier strontium, and degrades appreciably below 0.5-mg column loadings. The Bio-Rex generator is not similarly affected, however. Chelex also exhibits a "self-cleaning" effect after initial loading, and this resin withstands generator deterioration produced by repetitive elution better than does Bio-Rex.

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Increasing interest in short-lived, positron-emitting radionuclides in nuclear medicine has led to recent investigations of Rb-82 for cardiovascular diagnosis (*1,2*). Produced through the decay of its 25-day Sr-82 precursor, Rb-82 is a 1.25-min alkali-metal activity that does not require a dedicated, on-site cyclotron for its utilization. The usefulness of this nuclide in medicine is, of course, dependent upon a practical ^{82}Sr-^{82}Rb generator system and source of supply.

The first Rb-82 biomedical generators reported in the literature were based upon the cation-exchange resin Bio-Rex 70, and, with an eluant of 3% NaCl solution, rubidium-strontium separation factors of 10^5 and Rb-82 elution yields of 62%, were measured (*3*). Subsequent work on the development of a generator based upon Chelex-100 resin indicated that separation factors of 10^7 and radiorubidium yields of 100% could be obtained with this system and an eluant of 0.1 *M* NH_4OH + 0.1 *M* NH_4Cl buffer (*4*).

More recent experimentation (*5,6*) with these ion-exchange resins, however, did not reproduce the earlier findings: Rb-82 yields were variable, while the observed separation factors were 10^7–10^8 with Bio-Rex and 10^4–10^5 with Chelex. Eluants employed in this latter work were 2% NaCl adjusted to pH 8.0 for the Bio-Rex generator, and the above-mentioned NH_4OH-NH_4Cl buffer solution (pH $\cong$ 9.3) for the Chelex system. The present investigation was initiated in an attempt to resolve these discrepancies and to provide further data relevant to two Rb-82 generator systems with high potential utility in nuclear medicine.

The principal foci of this study are the effects of carrier strontium content and eluant volume on generator performance, particularly radiostrontium breakthrough. Previous inconsistencies and erratic behavior in the history of radiochemistry have often been associated with carrier vs. carrier-free chemical effects (*7,8*), and this possibility was an obvious candidate for examination in the generator systems under consideration.

The production of medical radioisotopes at the Los Alamos Meson Physics Facility (LAMPF) uses very large targets as well as sizable volumes of processing media (kilograms and liters, respectively) in the normal course of a chemical recovery procedure. As a result, trace impurities present in the target

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material or chemical reagents—even at ppm concentrations—can translate into milligram amounts under these conditions. Significant syntheses of stable isotopes by nuclear mechanisms are also possible. Spallation reactions (*9,10*) induced by medium-energy protons are the nuclear interactions employed for radionuclide production at LAMPF, and the highly nonspecific nature of spallation ensures that stable nuclides are also included in the broad spectrum of product nuclei.

As an example of the quantities of nucleogenic, stable isotopes produced at LAMPF, a calculation has been executed for typical operating conditions. Spallation cross sections for stable isotopes are obtained from theoretical considerations (*11–14*). Input parameters for the computation were a target thickness of 2.3 cm, stable-product cross section of 10 mb, beam intensity of 500 μA, and irradiation time of 23 days. The resultant weight of stable spallation product was found to be of the order of 1 mg. Thus, along with the desired radionuclide, carrier quantities of stable isotopes can also be synthesized by nuclear processes during the course of the irradiation if the proton intensity is large enough.

With these types of considerations foremost in mind, then, the present study was undertaken as a careful comparison of the Bio-Rex and Chelex generator systems from a strictly radiochemical viewpoint. A conscientious effort was made to keep constant the various ion-exchange properties that affect system performance (such as column dimensions, flow rate, resin size, etc.) so that direct comparisons between Bio-Rex and Chelex could be made. Note that the experimental configuration employed in this work has no particular clinical significance since it was designed purely from considerations of the radiochemistry involved. In addition, there is no reason to expect the results of this study to agree precisely with those of the previous studies (*3–6*) since the generator elution conditions are not exactly the same.

EXPERIMENTAL

Isotope production. Radiostrontium (*Sr) for this study was produced by irradiating a Mo target with 800-MeV protons at the Nuclear Chemistry Area B targeting station at LAMPF. The Mo was 0.5 cm in thickness and of reduced density (80%) to aid in dissolution, and the total integrated beam intensity on the target was approximately 12 μA-hr. Following proton bombardment, the Mo was processed (*15*) to isolate a purified *Sr fraction. At the start of the generator experimentation, the above procedures resulted in the availability of 0.3 mCi each of Sr-82 and Sr-85, for a total *Sr content of 0.6 mCi.

The estimated quantity of stable strontium generated during the irradiation has been computed. A theoretical calculation for 800-MeV protons on Mo resulted in a total cross section (cumulative yield) of 107 mb for the four stable strontium isotopes, and this gave a value of 0.1 μg of stable strontium as the spallogenic contribution under the present bombardment conditions. The Mo metal used for the target was assayed for strontium by spectrochemical methods with negative results (limit of detection = 3 ppm), and all processing materials used in the radiochemical procedure were of reagent-grade quality or better. It was thus reasonable to believe that the maximum amount of stable strontium present with the *Sr before beginning the generator studies was of the order of 0.1 μg.

Generator chemical procedures. The ion-exchange materials used in this work were Chelex-100 and Bio-Rex 70 analytical-grade resins*. Both were 100–200 mesh and originally in the sodium form. The columns were glass, had an i.d. of 1.5 cm, and were filled to a height of 4 cm with the appropriate resin. Generators were prepared by adjusting the *Sr solution with NH_4OH to pH 8 for a Bio-Rex column, or to pH 9–10 for a Chelex column, and then passing the solution through the resin at a flow rate of 1–2 ml/min.

Following column loading, the generator was successively milked with eluants of either 2% NaCl solution adjusted to pH 8.0 in the case of Bio-Rex, or a 0.1 *M* NH_4OH + 0.1 *M* NH_4Cl buffer (pH ~ 9.3) in the case of Chelex. A regulated column overpressure (with compressed air) was used to maintain the generator elution rate constant at 0.5 ml/sec, and 40-ml volumes of eluant were sampled for subsequent radioactivity analyses. The choice of 40-ml eluant volumes was arbitrary and was based upon considerations of generator geometry and performance; 40 ml was a convenient eluant reservoir volume and, although an excessive amount with respect to Rb-82 milking, it served to increase the *Sr content of any given activity determination. The *Sr breakthrough from both Bio-Rex and Chelex generators is typically extremely small, so that the tactic of enhanced elution volumes allowed significant savings in radioactivity counting times over what would otherwise have been required. In fact, 40 ml was 2 or 3 times the volume that would be employed in a clinical situation for a bolus injection from a generator of the above specifications.

After a suitable number of elutions of a given generator, the *Sr was stripped from the resin with a small volume of 1 *M* HCl and then prepared for placement on a fresh column. Stable strontium concentrations were adjusted by adding an appropriate quantity of standardized $SrCO_3$ carrier solution before generator loading.

Radioactivity analysis. All radioactivity determinations were made by gamma-ray spectrometry using a high-efficiency, high-resolution Ge(Li) detector. The details of spectral acquisition, reduction, and interpretation have been described in previous work (*4,15*).

RESULTS AND DISCUSSION

The influence of carrier strontium on initial *Sr generator breakthrough is shown in Table 1. Breakthrough from Bio-Rex resin was measured to be 10^{-8}–10^{-7} over the entire carrier range, while that from Chelex varied between 10^{-8} and 10^{-5}. Above 0.5 mg of stable strontium, however, both materials demonstrated approximately equivalent *Sr breakthroughs of 10^{-8}–10^{-7}.

All uncertainties given in this work are one standard deviation and are merely propagated errors reflecting radioactivity counting statistics. No attempt was made to estimate other potential sources of error, and the listed uncertainties therefore represent only minimum values associated with these experiments.

At carrier levels of 1.0 and 20 mg, *Sr breakthrough was studied as a function of increasing eluant volume resulting from successive generator elutions. Figures 1 and 2 present the results of the study at 20-mg column loadings for the Bio-Rex and Chelex generators, respectively. Bio-Rex achieved minimum *Sr breakthrough immediately after generator loading, and it remained stable for 200 ml of elution before breakthrough began to increase. Chelex resin, on the other hand, required about 200–300 ml of eluant after initial loading to attain minimum breakthrough, but this generator was then quite steady over elutions of several liters in total volume. These general characteristics of the two resins were observed at all carrier levels. Decreasing the column loading to 1.0 mg gave qualitatively similar results with the following differences: the plateau region for Bio-Rex breakthrough was extended to approximately 300 ml, and Chelex was milked for 8 l without any apparent increase in *Sr breakthrough.

During the experimentation at the 1-mg carrier level, several elutions were analyzed for the Rb-82 generator yield. The mean value of data from three independent milkings indicated that 100% (range 93–105%) of the radiorubidium was removed from the Chelex column, while 100% (range 92–107%) was also removed from Bio-Rex. The former result is in agreement with previous work (*4*).

Because of patient discomfort and damage to vein endothelium induced by the pH 9 NH_4OH-NH_4Cl solution, a few substitute eluants were studied with

TABLE 1. EFFECT OF CARRIER Sr LEVEL ON BREAKTHROUGH FROM FRESH GENERATORS

Stable Sr Content	*Sr breakthrough (plateau region)	
	Bio-Rex	Chelex
"Carrier-Free" ($\leq$ 0.1 µg)	$<(1.0 \pm 0.6) \times 10^{-7}$	$(5.0 \pm 0.4) \times 10^{-7}$
5.1 µg	$(6.7 \pm 2) \times 10^{-8}$	$(3.2 \pm 0.1) \times 10^{-6}$
51 µg	$(2.1 \pm 0.3) \times 10^{-7}$	$(4.5 \pm 0.2) \times 10^{-6}$
200 µg	$(1.0 \pm 1) \times 10^{-7}$	$(9.3 \pm 0.3) \times 10^{-6}$
510 µg	$(1.5 \pm 0.8) \times 10^{-7}$	$(5.8 \pm 2) \times 10^{-8}$
1.0 mg	$(3.4 \pm 1) \times 10^{-8}$	$(1.2 \pm 0.2) \times 10^{-7}$
5.1 mg	$(1.1 \pm 0.1) \times 10^{-7}$	$(1.6 \pm 0.2) \times 10^{-7}$
10 mg	$(1.5 \pm 0.3) \times 10^{-7}$	$(4.9 \pm 2) \times 10^{-8}$
20 mg	$(1.1 \pm 0.1) \times 10^{-7}$	$(1.3 \pm 0.5) \times 10^{-7}$

the Chelex system. Solutions of pH 8 distilled water and pH 8 0.05% NaCl, while not adversely affecting the *Sr breakthrough properties, were found to be unsuccessful in eluting Rb-82 from the generator. This result implies that a minimum ionic strength is required of a solution for its application as an effective generator eluant. The NH_4OH-NH_4Cl buffer normally used for elution was adjusted to pH 8 with

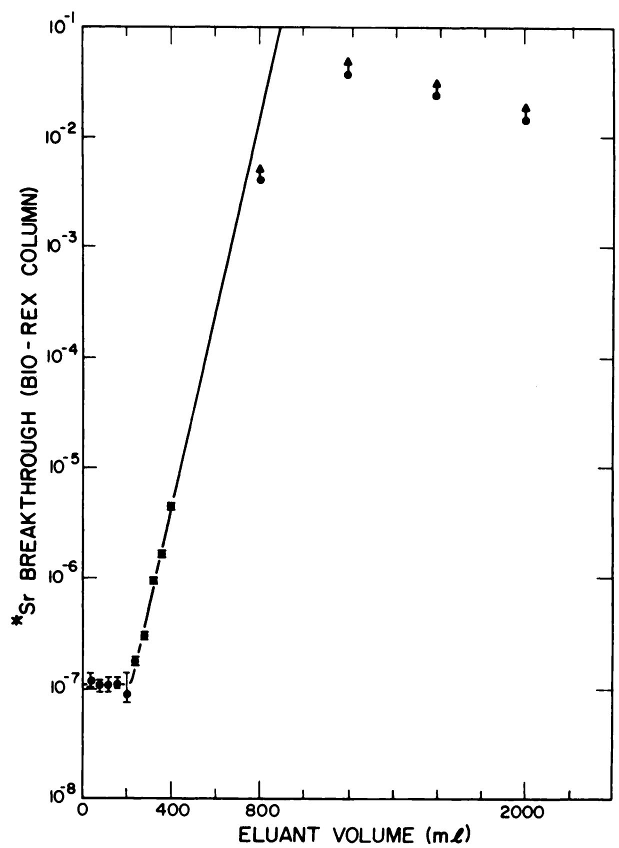

FIG. 1. Radiostrontium breakthrough from Bio-Rex 70 generator as a function of eluant volume (carrier Sr level = 20 mg).

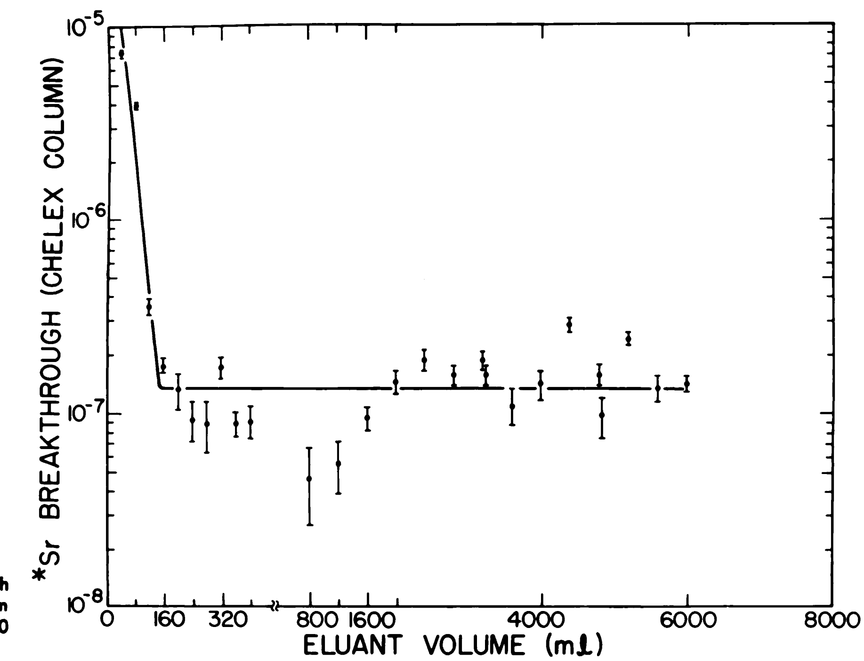

FIG. 2. Radiostrontium breakthrough from Chelex-100 generator as a function of eluant volume (carrier Sr level = 20 mg).

con. HCl, and a Chelex column was then washed with this solution. Quantitative Rb-82 yields were again obtained, but *Sr breakthrough was degraded by an order of magnitude to 10^{-6}. It seems, therefore, that the superior procedure for the Chelex generator is to milk the column at a high pH and perform a postelution neutralization before infusion.

Another relevant observation was that the Bio-Rex generators required greater column overpressures than the Chelex generators, by factors of 4–6, to produce the desired elution rate. This was true despite the fact that column dimensions and resin size were identical in both systems. Moreover, it was extremely difficult and sometimes impossible to get reasonable flow rates through narrow-diameter Bio-Rex columns. This characteristic could present a serious obstacle toward the future miniaturization of the Bio-Rex generator for continuous infusion studies.

CONCLUSION

Experiments designed to allow a direct comparison between Bio-Rex 70 and Chelex-100 (Sr-82)-(Rb-82) biomedical generators have been performed using approximately 0.5 mCi of *Sr activity. The results indicate that the systems are equally good in eluting Rb-82 and that 100% radiorubidium yields can be obtained. With generators loaded with 0.5–20 mg of stable strontium, both resins are roughly equivalent in hindering initial *Sr breakthrough. Strontium behavior, however, is carrier-dependent on Chelex-100, with breakthrough increasing by two orders of magnitude below 0.5-mg column loadings. A similar dependency has been noted previously for the retention of scandium by this material (*16*). Bio-Rex 70, on the other hand, exhibits no such carrier dependence.

The Chelex generator also demonstrated a "self-cleaning" effect at all carrier concentrations after initial loading. That is, the first several elutions of a freshly prepared generator contain larger quantities of *Sr than are obtained in the normal equilibrium configuration of the column. Analogous behavior has been observed in the (Mo-99)-(Tc-99m) alumina generator (*17–19*), although the underlying mechanisms responsible for this phenomenon are likely to be different in these dissimilar systems.

Both Bio-Rex and Chelex generators are currently being used in clinical situations, and periodic increases in *Sr breakthrough, unrelated to the self-cleaning effect, have been noticed with both resins (personal communications: R. A. Beh, and H. Krizek and P. V. Harper). The increases have occurred, however, after the investigators allowed the generators to remain dormant for long periods of time (e.g., overnight), and these observations can possibly be attributed to the use of unbuffered eluants and/or large quantities of *Sr activities. [For example, at the University of Chicago the Chelex generator loaded with tens to hundreds of millicuries of *Sr is eluted with 0.1 *M* NaOH-0.2 *M* NaCl solution (*20*)]. The retention characteristics of Bio-Rex and Chelex resins are strongly dependent on pH, and employment of a suitably buffered eluant might eliminate the rise in breakthrough following generator inactivity. Radiolysis effects resulting from the clinical activity levels are another possible explanation, but this variable has not yet been studied in a systematic way in these generators. Indeed, high radiation doses may give rise to additional observations not seen in the present work.

Chelex-100 has been observed to resist generator degradation resulting from sequential elutions better than does Bio-Rex 70. The practical consequence of this is that the Chelex generator would have to be reconstituted at the hospital less often than the Bio-Rex system.

The above findings serve as a reasonable explanation for much of the discrepancy that has appeared in the literature. In its initial development (*4*), the Chelex generator used a minimum of 0.8 mg of carrier strontium, an amount above the threshold required for good system performance as determined by the present work. Subsequent investigations (*5,6*), on the other hand, used Sr-82 supplied by Los Alamos and produced by some initial, relatively low-intensity irradiations. In processing the targets from these bombardments, considerable effort was expended in maintaining the *Sr solution as carrier-free as possible. This required the omission of the final HZO ion-exchange step (*15*) from the hot-cell procedure and the substitution of various other purification techniques for specific contaminants. Consequently, no carrier strontium was intentionally added to the *Sr employed in those experiments, nor were the proton irradiations intense enough to synthesize appreciable stable strontium by nuclear spallation. The work with this activity was thus conducted in the carrier-free mode.

In conclusion, neither Bio-Rex nor Chelex resin appears to be an absolutely ideal material for (Sr-82)-(Rb-82) biomedical generators. Chelex demonstrates an initial self-cleaning effect and a carrier dependence, while Bio-Rex degrades relatively rapidly with increasing eluant volume and requires greater column overpressures for elution. Both materials, however, will deliver large Rb-82 yields with extremely small *Sr contamination under the appropriate experimental conditions. As discussed in a previous paper (*4*), this area of research is ripe for further exploration to develop an improved clinical generator using the results to date as a basis. Perhaps a mixed Bio-Rex/Chelex column or a tandem arrangement of the two materials would provide a generator with the advantages of both resins without the weaknesses of either.

FOOTNOTE

* Obtained from Bio-Rad Laboratories, Richmond, Calif.

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