RADIOCHEMISTRY AND RADIOPHARMACEUTICALS

Evaluation of Inorganic Adsorbents for the Rubidium-82 Generator: I. Hydrous SnO_2

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An Sr-82→Rb-82 generator based on the inorganic adsorbent hydrous tin oxide is described. K_D values for Sr(II) were determined as a function of pH, equilibration time, and Sr(II) carrier content. The K_D values for Rb(I) were determined as a function of salt concentration. Elution of a generator of 2-cc bed size with isotonic saline allows Rb-82 collection in 13 ml with radiochemical yields of 65%. Strontium breakthrough is less than 10^{-9}/ml for elution speeds of up to 60 ml/min.

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The measurement of regional myocardial blood flow is of the utmost importance for the complete evaluation of the effects of coronary disease and acute myocardial infarction. A safe, atraumatic measure of regional myocardial perfusion is therefore desired, one that could be performed well before clinical symptoms become severe enough to warrant cardiac catheterization. Ideally, sequential measurements should be possible in order to allow the study of the effects of medical and physiologic interventions, such as exercise. Currently, most such measurements are made by means of Tl-201 scintigraphy. However, the three-day half-life of Tl-201 precludes sequential injections, and its decay characteristics are such that its accuracy in the detection of significant coronary artery disease is marginal when used in conjunction with standard two-dimensional imaging.

Rubidium-82 has been investigated as a potential successor to Tl-201 (*1*,*2*). The positron-emitting Rb-82 ($T_{1/2}$ = 76.4 sec) (*3*) has been used to image the myocardium sequentially at various stress levels. The usefulness of rubidium-82 for the measurement of myocardial perfusion is presumably due to its concentration in the myocardial muscle by the same processes that enrich potassium in the heart. The idea that rubidium can actually substitute for potassium in biological systems was already put forward in 1882 by Ringer (*4*). Zipser et al. (*5*) determined its distribution in the human body, and Tyor and Eldridge (*6*) and Kilpatrick et al. (*7*) compared potassium-42 and rubidium-86 distribution in man and found differences only in their urinary excretion rates. Knoebel et al. (*8*), Budinger (*9*), and Freedberg et al. (*10*) showed that intravenously administered rubidium-86 left the blood of dogs and men within 5 min. This rapid clearance from the blood makes the use of the short-lived rubidium-82 feasible. The nuclide is obtained through a generator system via its parent strontium-82 ($T_{1/2}$ = 25.6 day). Such a generator system obviates the need for an in-house cyclotron and as such is a convenient source of radionuclides. Moreover, because of its short half-life, 10 mCi of Rb-82 results in a whole-body radiation dose of only 17 mrad (*11*).

Various column chromatographic procedures have been developed to separate Rb-82 from Sr-82 (*1*,*2*,*10*,*12–15*). Because of the daughter's short half-life, these procedures must effectively retain the radiotoxic Sr-82 while rapidly eluting Rb-82. For the same reason a rapid means of collecting and administering the eluate is necessary. This would preferably be realized by direct infusion of the eluate into the patient. Another reason

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for fast delivery of the Rb-82 is the rapid uptake of the nuclide into the heart muscle, leading to a time-activity distribution in the heart that is a reflection of the time-activity distribution at the injection site.

Previous Sr-82→Rb-82 generators had one or more undesirable features. They used nonphysiological eluents, they used radiolytically unstable organic adsorbents, or they exhibited a high Sr-82/Sr-85 breakthrough when eluted rapidly. This paper reports the development of a new Rb-82 generator system using hydrous SnO_2 as the inorganic adsorbent. Such a generator has one of the lowest Sr-82/Sr-85 breakthrough levels of all systems tested thus far (*16*), it can be eluted efficiently with isotonic saline of physiologic pH, and it delivers Rb-82 in a small enough volume to allow a full bolus injection in less than 20 sec.

MATERIALS AND METHODS

Hydrated SnO_2, carrier-containing Sr-85, and Rb-86 were obtained commercially. Strontium-82 was made by 800-MeV proton irradiation of molybdenum metal. The material typically contained Sr-85 and Sr-83 as radionuclidic impurities. Minor radiocontaminants included Mn-52, Mn-54, Co-56, Co-58, and Y-88. The Sr-85 level was three to five times that of Sr-82, while the Sr-83 level was low but variable. Very low levels of Rb-83 were present in the first few generator eluates as a result of the decay of Sr-83.

Distribution coefficients. Distribution coefficients K_D for the equilibration of Sr(II) and Rb(I) between $SnO_2 \cdot H_2O$ and various mobile phases were determined by batch equilibration as described previously (*16,17*). $SnO_2 \cdot H_2O$ (200 mg) was washed free of fines and preequilibrated three times with the appropriate mobile phase before 5 g of the mobile phase, containing the radionuclide, was added to it. The reaction mixtures were stirred, and the K_D values measured as a function of time, pH, Sr(II) concentration, Ca(II) concentration, and NaCl concentration. The pH of the equilibration mixtures was adjusted with either NaOH, HCl, or $Na_2HPO_4 \cdot 7H_2O$. The K_D values were calculated as

$$K_D = \frac{\text{activity/gram of solid phase}}{\text{activity/gram of liquid phase}}.$$

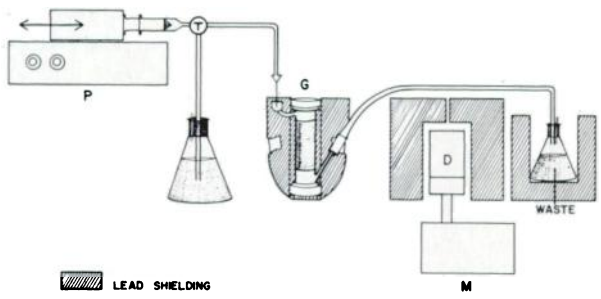

FIG. 1. Experimental arrangement for the measurement of the Rb-82 elution profile. P: pump (peristaltic or syringe pump); G: generator; D: Ge(Li) or NaI(Tl) detector; M: multichannel analyzer.

Column Experiments. These were carried out using experimental generators of 2.6 cm length with adsorbent bed volumes of either 0.5, 1, or 2 cc. Elutions were performed under positive pressure exerted by a peristaltic pump, syringe pump, or by means of 30-ml evacuated vials. No difference in column performance was observed depending on whether the column was stored wet or dry between elutions. The Rb-82 bolus size was defined as the FWHM of the elution profile, where the half-maximum on the downward slope was taken between the maximum activity in the peak and the steady-state Rb-82 activity eluted off after the bolus. The measurements were carried out by using the detection and analysis equipment shown in Fig. 1. The eluate from generator G was pumped by syringe pump P through a plastic tube passing in front of a shielded and collimated Ge(Li) detector D, coupled to multichannel analyzer M. Data were collected in the multiscaler mode, using a 0.1-sec dwell time in each channel of the analyzer and a 400- to 600-keV window. The bolus position and width were used to calculate N, the number of theoretical chromatographic plates in the columns. The formula $N = 8\,(V_{max}/\Delta V)^2$ was used, where V_{max} corresponds to the volume element containing the maximum Rb-82 activity and ΔV represents the volume interval that contains 84% of the eluted activity (*18*). The Rb-82 yield was measured by eluting the generator with enough eluent to ensure complete collection of the Rb-82 bolus, by counting the eluate on a calibrated Ge(Li) detector and by correcting for Rb-82 decay between the end of elution and the time of the radioactive measurement.

Alternatively, the yield was measured using the following method:. A Rb-82 generator was measured before elution and again during elution when the activity from the 777-keV gamma had reached steady state.

Strontium-82 breakthrough from the hydrated SnO_2 columns was studied as a function of eluent composition, total eluent volume, and elution rate. Breakthrough was measured by NaI(Tl) scintillation counting of 50-ml eluate fractions, and results are expressed as the fraction of the total loaded strontium activity that elutes in each milliliter of eluate, and was studied as a function of both elution speed and total eluate volume.

RESULTS

Distribution coefficients. The K_D values for Sr(II) on $SnO_2 \cdot H_2O$ are shown in Tables 1 and 2. The values increased with time and with NaCl concentration. The adsorption capacity of the SnO_2 for Sr(II) was not saturated at 2×10^{-5} *M* Sr(II) or 5×10^{-4} *M* Ca(II). The K_D values for Sr-82 varied between pH 2 and 7.2 but were essentially constant between pH 7.2 and 11.4 (Table 2).

TABLE 1. DISTRIBUTION COEFFICIENTS OF Sr(II) BETWEEN HYDROUS SnO_2 AND VARIOUS LIQUID PHASES AS A FUNCTION OF EQUILIBRATION TIME

Liquid phase†	K_D* Equilibration time 1 min	3 min	5 min
H_2O	50 ± 2	74 ± 2	95 ± 2
0.017 *M* NaCl	71 ± 2	480 ± 2	1,700 ± 150
0.05 *M* NaCl	51 ± 2	420 ± 40	1,800 ± 200
0.10 *M* NaCl	76 ± 2	620 ± 50	1,600 ± 160
0.15 *M* NaCl	81 ± 2	380 ± 30	2,100 ± 200
0.05 *M* NaCl + 20 μ*M* Sr(II)	81 ± 2	950 ± 90	3,200 ± 400
0.05 *M* NaCl + 20 μ*M* Sr(II) + 0.5 m*M* Ca(II)	68 ± 2	1,050 ± 100	3,800 ± 400
0.15 *M* NaCl + 20 μ*M* Sr(II)	47 ± 2	540 ± 40	1,800 ± 200
0.15 *M* NaCl + 20 μ*M* Sr(II) + 0.5 m*M* Ca(II)	62 ± 2	720 ± 50	2,700 ± 300

* Error limits represent one standard deviation.
† n = 6.

The K_D values for Rb(I) are four orders of magnitude less than the corresponding values for Sr(II) (Table 3), indicating that numerous collections of Rb-82 should be possible before Sr-82 breakthrough levels become unacceptable. No significant difference in K_D(Rb) was found in 0.15 *M* NaCl as the pH was varied between 5 and 10.

Column experiments. The Sr(II) breakthrough from SnO_2·H_2O columns of 1-cc and 2-cc bed sizes, when eluted with isotonic saline at 10 ml/min, were 10^{-8}/ml and less than 10^{-9}/ml, respectively. The breakthrough values remained constant for at least 20 l of eluent. Cobalt, manganese, and yttrium radiocontaminants were not seen at detection limits of 0.2 nCi/ml, nor was any stable tin found at a detection limit of 0.1 μg/ml. The Sr(II) breakthrough from 1.0-cc columns increased with increasing elution speed. The increase was approximately threefold when the elution rate went from 10–50 ml/min. With a 2-cc SnO_2 column, the Sr(II) breakthrough/ml remained less than 10^{-9} for elution speeds between 10 ml/min and 60 ml/min. With isotonic saline as the eluent, the bolus sizes for 1.0-cc and 2.0-cc SnO_2 columns were 9 ml and 17 ml, respectively. Basic Al_2O_3 columns with a 1.0-cc bed volume have a 15-ml bolus. It was found that the Rb-82 bolus size was dependent on the period elapsed since the previous elution. After an overnight rest of the generator, the first Rb-82 bolus from a 1-ml hydrated SnO_2 column was ~5 ml. From the second bolus onwards the volumes average 9 ml. Increasing the NaCl concentration in the eluent from 0.15 *M* to 0.22 *M* to 0.30 *M* decreased the Rb-82 bolus size with a 1-cc SnO_2 column from 9 ml to 8 ml to 7 ml, respectively. The chemical yield of Rb varied between 88% and 95% with a 2-cc SnO_2·H_2O column eluted with 0.15 *M* NaCl. Radiochemical yields for Rb-82 at 12 ml/min elution speeds varied from 60% for 2-ml columns to 70% for 1-ml columns. These values were decay corrected to end of elution and will increase with increasing elution flow rates.

The effective number of theoretical plates for Rb(I) on the column changed with elution speed. A 1-cc hy-

TABLE 2. K_D VALUES FOR Sr(II) ON SnO_2 AS A FUNCTION OF pH*

Liquid phase*	K_D†
0.15 *M* NaCl, pH 2.0	105 (90–120)
0.15 *M* NaCl, pH 5.0	1,300 (1,260–1,320)
0.15 *M* NaCl, pH 7.2	53,000 (47,000–58,000)
0.15 *M* NaCl, pH 7.6	48,000 (42,000–54,000)
0.15 *M* NaCl, pH 9.4	55,000 (50,000–60,000)
0.15 *M* NaCl, pH 10.5	66,000 (58,000–74,000)
0.15 *M* NaCl, pH 11.4	56,000 (50,000–62,000)

* pH adjusted with NaOH, phosphate buffers, or HCl; 60-min equilibration time
† Mean and range.

TABLE 3. K_D VALUES FOR Rb(I) ON SnO_2

Liquid phase*	K_D†
H_2O	≥20
0.01 *N* NaCl	≥20
0.10 *N* NaCl	3.9 ± 0.5
0.15 *N* NaCl	2.5 ± 1
0.20 *N* NaCl	1.8 ± 0.2
0.23 *N* NaCl	1.9 ± 0.2
0.30 *N* NaCl	1.5 ± 0.2

* n = 6.
† Sixty minutes equilibration time; error limits represent one standard deviation.

TABLE 4. SUMMARY OF EXISTING Rb-82 GENERATORS INCORPORATING NaCl ELUENT

Adsorbent	Column bed size (ml)	Eluent	pH	Elution speed (ml/min)	Rb-82 yield %	Bolus size (ml)	Sr-82 breakthrough (fraction/ml)	Reference
Bio-Rex 70	5	NaCl 2%	8	30–60	70	12	10^{-5}–10^{-8}	(*2*)
	5	NaCl 3%	8	30–60	90	12	10^{-5}–10^{-8}	(*2*)
Chelex 100	2.25	NaCl 2%	—	60–90	90	20	5×10^{-7}–5×10^{-5}	(*14*)
Al_2O_3	1	NaCl 0.9%	8–9	72	25	10	5×10^{-6}-	(*26*)
	2.25	NaCl 2%	8–9	30	76	20	5×10^{-6}–5.10^{-8}	(*14*)
ZrO_2	2.75	NaCl 0.9%	7.5	300	56	20	—	(*15*)
SnO_2	1	NaCl 0.9%	7	12	65		5×10^{-8}	This work
	2	NaCl 0.9%	7	30	65	17	$<10^{-9}$	This work

drous SnO_2 column was calculated to have 6.6, 4.2, 2.9, and 2.4 plates when the Rb-82 was eluted at 12, 50, 100, and 125 ml/min, respectively.

DISCUSSION

Inorganic ions have been separated from one another using hydrous SnO_2. Kraus (*19*) described a separation of Ba(II) from Cs(I) on SnO_2. Donaldson and coworkers (*20–22*) described cation and anion exchange behavior of Sn(IV) materials. Girardi et al. (*23*) and Brandone et al. (*24*) studied the adsorption of 50 elements onto hydrous SnO_2 from HCl, $HClO_4$, HF, and HNO_3. They noted partial adsorption of Sr(II) only from 14 *N* HNO_3. Their adsorption studies, carried out by passing the eluent through the SnO_2 bed at 1.5–2 ml/min, may not reflect equilibrium K_D values.

Hydrous SnO_2, as obtained commercially, is a glassy material with amphoteric properties. It behaves as a cation exchanger in the basic pH region but loses its cation adsorption capacity as well as some exchange capacity when the pH is lowered. Above pH 7, however, the K_D for Sr(II) between SnO_2 and aqueous NaCl is rather constant. This contrasts with basic Al_2O_3, for which the K_D for Sr(II) depends very strongly on the pH of the eluent (*25*). The adsorption rate of Sr(II) onto hydrous SnO_2 is highly dependent on the salinity of the eluent, but the equilibrium binding is independent of NaCl concentration above 0.02 *M*. Calcium or strontium carrier in small concentrations does not influence the rate of Sr(II) adsorption by SnO_2. This is important because of possible Ca(II) addition during the chemical purification of the Sr-82 from its target material and the formation of stable strontium by the spallation reaction (*13*) used for the Sr-82 production. Strontium can also be introduced inadvertently as impurities in the target material and the reagents used.

Salinity has an influence on Rb-82 elution. Because of competition between Na(I) and Rb(I) for the SnO_2 adsorption sites, Rb-82 is eluted faster with more concentrated salt solutions. The smaller boluses obtained for Rb-82 after an extended resting period of the generator might be due to the slow concentration of Na(I) onto the SnO_2 particles. Many generator systems using NaCl solutions as eluents have been proposed for the separation of Rb-82 from Sr-82 (Table 4). The fractional breakthrough levels that these generators attain must be much lower than those of the Mo-99→Tc-99 generators (typically 10^{-4}/ml) because of the toxicity of Sr-82 and its radiocontaminant, Sr-85. The organic adsorbents have not been widely used because of their radiolytic instability.

The superiority of the hydrous SnO_2 over either Al_2O_3 or ZrO_2 at physiological pH is evident from the K_D values of Sr(II) between 0.9% NaCl solutions of pH 7.2 and these adsorbents. After 60 min of equilibration, the K_D for Sr(II) reached 53,000, 1,200, and 1,050 for hydrous SnO_2, basic Al_2O_3, and ZrO_2, respectively (*25*). Consequently, much lower breakthrough values for Sr(II) are possible with the hydrous SnO_2. The most widely employed generator system to date used an Al_2O_3 adsorbent and a 2% NaCl eluent adjusted to pH 8–9. The high pH was necessary to minimize Sr(II) breakthrough. The hypertonic eluent would preferably be diluted prior to i.v. administration, which further dilutes the Rb-82 bolus and will necessitate higher patient infusion rates.

In contrast, the SnO_2 generator can be eluted with the same isotonic NaCl solutions currently used with the Mo-99→Tc-99m generators. With such an eluent, Sr-82 breakthrough was typically 10 to 100 times less than with currently available Rb-82 generators (Table 4). Comparable breakthrough values can be obtained with a Chelex-based generator (*13*), eluted with a pH 9.3 solution of 0.1 *M* NH_4OH and NH_4Cl. The Rb-82 was eluted from $SnO_2 \cdot H_2O$ in high yield and in a much sharper bolus than that found with Al_2O_3-based generators. If required, the Rb-82 temporal bolus could be further shortened by increasing the elution speed, which would also serve to increase the radiochemical yield. An

increase in elution speed would be particularly advantageous were the generator to be used in a direct infusion mode.

The characteristics of the $SnO_2 \cdot H_2O$-based Rb-82 generator were found invariant with total elution volume. This was predicted by comparing the K_D values for Sr(II) and Rb(I) in 0.15 *M* NaCl. The ratio of K_D Sr(II) to K_D Rb(I) gives an approximation of how many collections of Rb-82 are possible before the Sr(II) breakthrough becomes unacceptable. SnO_2-based Rb-82 generators have been eluted with 20 l of eluent without experiencing any increase in Sr-82 breakthrough. A breakthrough of less than 10^{-9}/ml from a generator with 2-cc bed volume containing 30 mCi Sr-82 and 70 mCi Sr-85 would result in a total Sr-82 and Sr-85 activity of less than 0.6 nCi and less than 1.4 nCi, respectively, in a 20-ml injectate. According to a private communication by Hoop to Yano et al. (*2*), these activities would deliver less than 0.3 mrad to total bone, less than 0.3 mrad to red marrow, and less than 0.03 mrad to the total body. The projected maximum use of the Rb-82 generator—20 elutions per day of 50 cc each for one month—predicts a total eluent volume of 20 l. This volume is within the predicted and observed capabilities of the $SnO_2 \cdot H_2O$-based Rb-82 generator.

In conclusion, $SnO_2 \cdot H_2O$ is an effective, radiolytically inert adsorbent for separating Rb(I) from Sr(II).

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