Radiopharmacy

Stability of Xenon-127 in Unit Dose Vials

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The stability of Xe-127 in unit dose vials—filled and stored under various conditions—was studied. Vials stored for 40 days retained between 50% and 98% of the original xenon, depending upon the type of rubber closure used. Puncturing the closures during vial filling had no effect upon retention, with two exceptions. Highest retention was found with synthetic rubber closures and vials stored under refrigeration. Natural rubber closures were unsatisfactory and carrier xenon had little effect upon retarding xenon loss. Vial activity sorbed to rubber closures varied between 1% and 6% and teflon-facing had no effect in retarding xenon loss.

Xenon-127 is gaining wider acceptance in nuclear medicine as the radiogas of choice for lung ventilation imaging. Its principal advantages are well documented (*1–3*); however, its availability for routine use awaits further investigation and FDA approval. Presently, investigators using Xe-127 obtain it in a multiple dose ampule and for convenience may package it into individual vials for patient use. While the 36.4 day half-life is well suited for unit dose packaging, two potential problems exist with this method. They are: xenon loss by permeation through the vial's rubber closure and egress at the rubber-glass interface; and xenon sorption by the rubber closure, which limits the amount that can be removed for patient use. Resolution of these problems is important from economic and radiation safety standpoints—particularly with the latter because shelf-life of Xe-127 far exceeds that of other xenon isotopes in use.

Numerous studies have been done describing the use of and problems associated with Xe-133. LeBlanc (*4*) found that leakage of Xe-133 in saline from plastic syringes was 0.5–1% per hour and 5–6% per day from multi-injection bottles, but did not identify the composition of the rubber closure. Keaney (*5*) reported on redistribution of Xe-133 in saline in carpules with 80% activity in rubber components after several days. Ponto (*6*) prepared an extensive report on radioactive gases describing many properties of xenon including adsorption by plastic syringes and various rubber O-rings used in xenon-saline transfer vessels. In addition, the report noted up to 40% adsorption of Xe-133 in the rubber stopper of single dose ampules.

Rubber closures used to seal single and multiple dose serum vials are available in many different designs and rubber composition. While many previous investigations reported on the problems with xenon-rubber interactions, I could find no detailed, quantitative study describing which commercial closures provided the least interaction with xenon.

The objective of my investigation was to determine the conditions that would minimize loss and maximize recovery of xenon from unit dose vials. Studies undertaken considered type of closure used, effect of closure puncture when filling vials, effect of storage temperature, and presence of stable xenon carrier.

Materials and Methods

Xenon-127 was obtained from Brookhaven National Laboratory in a 2–3-ml saline-type glass ampule containing 200 mCi of gas. Using a device developed in our laboratory (*7*), the gas was transferred from the ampule into an evacuated stock serum vial of predetermined volume. The activity concentration (mCi/ml) in the stock vial was calculated based upon its known volume and assay of ampule activity before and after transfer. Subsequently, 2-ml unit dose vials were filled with the desired activity of Xe-127 gas using a syringe-stopcock assembly and water reservoir. The required volume of xenon was removed from the stock vial with the syringe, replaced by an equal volume of water, and then transferred into the unit dose vial. Because xenon is poorly soluble in water, a constant activity concentration could be maintained in the stock vial while unit dose vials were being filled. Vials were sealed with different closures, consisting of the following rubber formulations: (a) standard V-32 stoppers in 86 white, natural rubber, and 461 black Viton® and 1,888 gray butyl,

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synthetic rubbers; (b) teflon-faced stoppers in 1,888 gray butyl and 541 red natural rubber; and (c) rubber disks, 0.075-in. thickness, in 535 red natural and 888 gray butyl, teflon-faced, and 461 black Viton. All closures were 13-mm diameter.

All vials were filled with 1 mCi of Xe-127. In a hospital laboratory it is easier to fill vials already stoppered; however, this requires puncturing the closure with a needle that may facilitate xenon loss during storage. To determine if such loss was significant, vials were filled by two methods. Vials filled by nonpuncture of closure were prepared by adding Xe-127 through a curved 22-gauge needle delivering xenon to the vial bottom, then stoppered and crimp sealed. Puncture-filled vials were stoppered first, sealed, and evacuated using a 27-gauge needle and syringe, removing a volume of air equal to the volume of xenon to be added, thus eliminating pressure build-up. Xenon-127 gas was then added to these vials through a 27-gauge needle in volumes of 0.1 to 0.3 ml.

To test the ability of different closures to retain xenon, puncture- and nonpuncture-filled vials were stored at ambient temperature for 40 days. At 3- to 4-day intervals, vials were radioassayed and corrected for decay to determine activity retained in them. Because Xe-127 contains small and uncertain amounts of 8-day Xe-129m and 12-day Xe-131m, the usual mathematical decay correction was replaced by this method: five 2-ml glass ampules were filled with the same mixture of xenon and then flame-sealed shut. These ampules were assayed along with the vials and served as controls, because no xenon could be lost through glass. The true fraction of original xenon activity retained in the stoppered vials was determined on each sampling date by dividing the observed fraction of activity remaining in vials by the average fractions remaining in ampules.

The fraction of xenon removed from vials and sorbed by rubber closures was determined by assaying vials at the end of 40 days storage, ventilating with 60 ml of air, reassaying, disassembling, and assaying closures separately.

To test effect of temperature on xenon retention during prolonged storage, vials sealed with 86 white and 1,888 gray butyl stoppers were stored at refrigerated (3.2 ± 0.5° C), ambient (23.4 ± 2.2° C), and elevated (37.1 ± 0.5° C) temperatures. Vials were assayed at 3- to 4-day intervals for 35 days and corrected for decay as before.

Effect of carrier xenon was determined using vials sealed with 86 white stoppers. Before adding Xe-127, each vial was stoppered, crimp sealed, vented with a 25-gauge needle, and flushed with several volumes of pure research grade Xe-131 (Air Products and Chemicals, Inc., Tamagua, PA). These vials were stored at ambient temperature for 35 days, assayed, and decay-corrected as previously described. Carrier-filled vials were compared to control noncarrier vials prepared identically, but flushed with air instead of stable xenon.

All radioactivity measurements were made using a dose calibrator with preset activity range and calibration factor and standardized before each measurement with a Cs-137 source. Five vials of xenon were used in all experimental conditions to obtain data. Equivocal comparisons were evaluated using the student's t-test ($P = 0.05$).

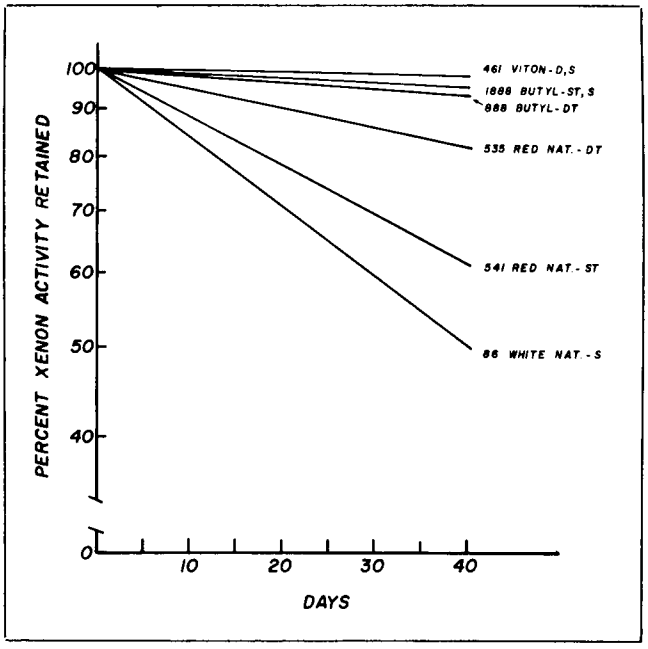

FIG. 1. Xenon retention in unit dose vials: D = disk; S = stopper; ST = teflon-faced stopper; and DT = teflon-faced disk.

Results and Discussion

Figure 1 illustrates retention of xenon in vials stored at ambient temperature for 40 days. While data presented reflect only puncture-filled vials, there was no significant difference found between puncture- and nonpuncture-filled vials, with two exceptions. Rate of xenon loss from puncture-filled vials sealed with 535 red rubber teflon-faced disks and 541 teflon-faced stoppers was significantly greater than nonpuncture-filled vials ($k\ day^{-1} = 0.0050$ and 0.0122 compared to 0.0044 and 0.0105, respectively). The most plausible reason for this difference is poor resealing ability of natural red rubber.

Xenon loss from all vials followed first order kinetics and a wide variation was evident between rubber formulations in their ability to retard xenon loss. In particular, synthetic Viton and butyl rubbers, which retained greater than 90% of original activity, were superior to red and white natural rubber formulations.

It appeared that teflon-facing had no effect on retarding xenon loss. Consider the following. There was no significant xenon-retention difference between the teflon-faced (butyl-ST) and non-teflon-faced (butyl-S) 1,888 butyl stoppers (94% compared to 95%). The butyl-ST and red natural-ST teflon-faced stoppers were identical except for rubber type, as were the butyl-DT and red natural-DT teflon-faced disks, yet large differences in xenon retention were observed (94% compared to 62% and 93% compared to 82%, respectively.)

TABLE 1. Xenon Recovery From Unit Dose Vials After 40 Days of Storage.

Closure Type	Vial Xenon (mean ± s.d.) Retained %	Fraction Removed	Fraction Sorbed by Closure	Recovery %
461 Viton-D	97.5±0.2	0.992±0.000	0.008±0.000	96.8±0.2
461 Viton-S	97.5±0.2	0.984±0.004	0.016±0.004	95.9±0.7
1,888 Butyl-ST	94.4±1.1	0.953±0.007	0.047±0.008	90.0±1.7
888 Butyl-DT	93.2±0.4	0.970±0.004	0.030±0.004	90.4±0.6
1,888 Butyl-S	95.3±0.3	0.944±0.003	0.056±0.003	89.9±0.5
535 Red Natural-DT	82.0±1.4	0.990±0.001	0.010±0.001	81.2±1.4
541 Red Natural-ST	61.6±3.7	0.984±0.004	0.016±0.004	60.6±3.6
86 White Natural-S	50.7±1.9	0.946±0.004	0.054±0.004	47.9±1.8

Xenon Recovery

Table 1 summarizes the overall recovery of Xe-127 from puncture-filled vials after 40 days' storage at ambient temperature. The amount of xenon that could be recovered for patient use was determined by multiplying percent retained in the vial by the fraction that could be removed by ventilation, the latter being inversely related to xenon sorbed by closures. Xenon sorption varied from about 1 to 6% of vial activity depending upon type of closure. Overall, stopper-type closures sorbed more xenon than disk-type closures. This is reasonable because stoppers protrude into the vial opening exposing more surface area, whereas disks merely lie over the vial opening. No significant difference in closure sorption was found between punctured and nonpunctured closures.

The primary factor influencing overall recovery of xenon appears to be type of rubber used, with synthetic rubbers clearly superior to natural rubbers. Among the synthetics, Viton was superior to butyl rubber. The only disadvantage of Viton is cost; Viton closures cost about $1.00 each in minimum lots of 1,000 whereas butyl closures cost about 6¢ each.

Temperature Effect

Figure 2 demonstrates the effect of storage temperature on xenon retention by two types of closure. The 86 white stopper was chosen because with it, xenon exhibited the greatest loss; additionally, any temperature effect was expected to be most dramatic. The 1,888 butyl stopper was chosen because it was the one used in our clinic and would also offer a comparison between natural and synthetic rubber. The most dramatic effect is seen with the 86 white stopper, where the rate of xenon loss under refrigeration was 75% less than the rate of loss at ambient temperature and 90% less than the rate of loss at elevated temperature; for the butyl stopper these results were 33%, and 50% respectively. While the temperature effect observed was not as pronounced with butyl rubber, refrigeration of xenon vials appears to offer a ready means of retarding loss during prolonged storage.

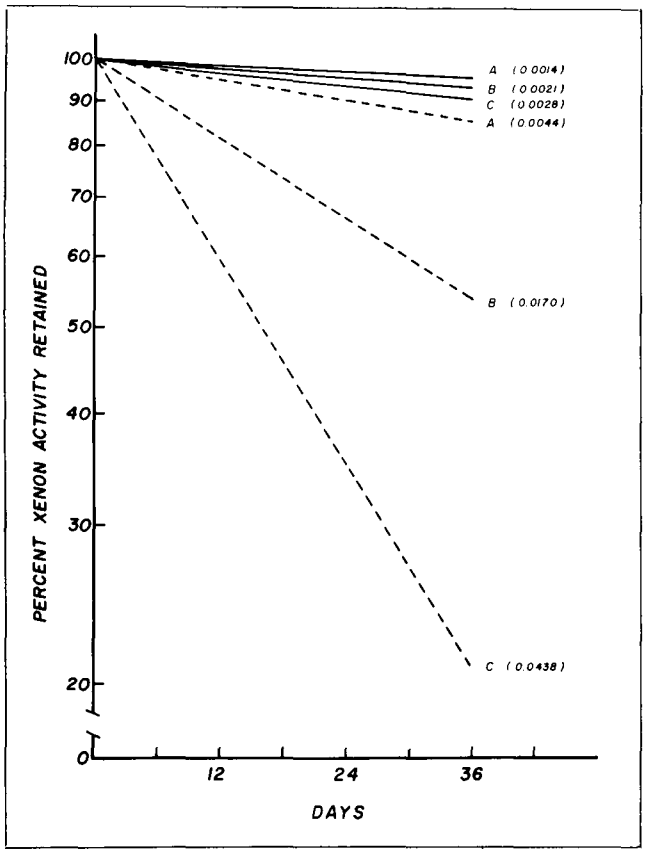

FIG. 2. Temperature effect on xenon retention in unit dose vials. 1,888 gray butyl-S = solid lines. 86 white-S = dashed lines; rate constant (k day^{-1}) for xenon loss is in parenthesis. A = refrigerator; B = ambient temperature; and C = elevated temperature.

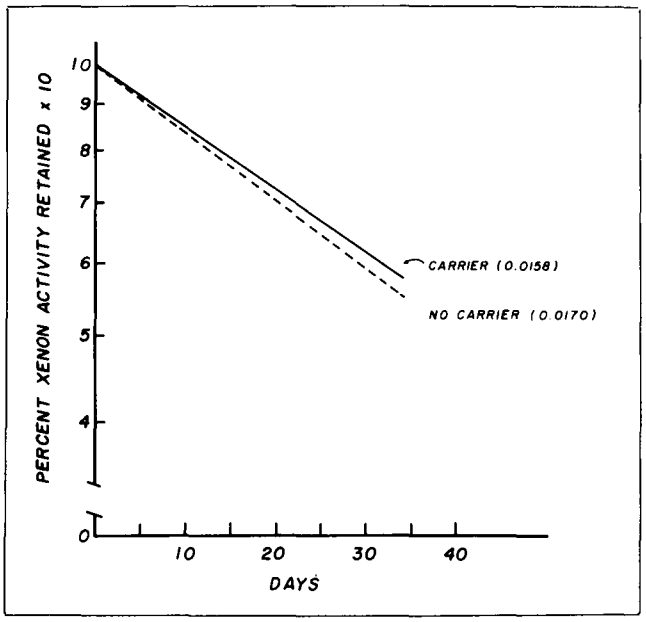

FIG. 3. Carrier effect on xenon retention in unit dose vials with 86 white stopper at ambient temperature; rate constant (k day^{-1}) for xenon loss is in parenthesis.

Carrier Effect

Figure 3 shows the effect of stable carrier xenon in retarding Xe-127 loss from vials sealed with 86 white stoppers. Results indicate that the rate of xenon loss with carrier was only 7% less than the rate of loss without carrier added. This nominal difference was probably due to the fact that carrier xenon was already present, as it was added at Brookhaven during target processing to improve recovery. Thus, additonal carrier added during unit dose packaging would be of little consequence in retarding xenon loss.

Application

The information gained from the foregoing experiments shows that recovery of xenon gas stored in rubber stoppered vials was significantly affected by closure composition and storage temperature, but not by puncture-filling of vials or use of stable xenon carrier. I recommend that Viton or butyl rubber stoppers be used for hospital packaging of xenon gas followed by storage at 2–8°C. While these recommendations are important for all xenon isotopes, they are most significant for those with long half-lives that will be stored for several weeks before use.

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