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A MULTIPLE-DOSE ^{133}Xe SOLUTION "GENERATOR": THE DISPOSABLE GLASS AMPULE EQUILIBRATION CHAMBER

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To have a continuously available supply of ^{133}Xe saline solution at low cost, a system based on the concept of dynamic equilibrium between a trapped bubble of ^{133}Xe gas and a small volume of periodically renewed saline has been designed. Unidirectional flow of saline within an all-glass vessel and the unique ampule design contribute to an extremely low xenon loss rate. High concentrations of xenon in saline are readily obtainable. The system consists of a glass ampule, a tap unit, shielding, and a fresh saline supply unit. The xenon concentrations per milliliter routinely obtained with this equilibrium chamber substantially exceed the ". . . up to 5 mCi Xe/ml" previously reported for glass ampule systems (1). No transfer vessel is required.

The use of ^{133}Xe saline solution as an injectable bolus is becoming increasingly important in the differential diagnosis of pulmonary disease and in the determination of regional perfusion in many organs. Various systems have been described for dispensing radioactive xenon gas (*2–4*) and for the production of injectable xenon saline solution (*2,5–8*). An inherent disadvantage in the design of these dispensers is the direct contact of xenon, either in the gaseous phase or in solution, with rubber components of the system. Such contact results in considerable xenon loss. The primary cause of this loss has been absorption into and diffusion through rubber fittings. Leakage in excess of 5% per day from intact rubber-stoppered glass vials (*9*) and loss of more than 80% of nominal dose by absorption into the rubber plungers of individual dose cartridges (*10*) have been documented.

Veall was the first to describe a system using a glass ampule and various attachments for the production of gaseous xenon or xenon saline solution (*2*). Later, Loken, et al used the Oak Ridge National Laboratory's glass ampule and a rubber and metal apparatus to produce xenon saline solution (*6*). Subsequently, Loken's group has used a stainless steel transfer vessel which completely crushes the gas-containing glass ampule in a chamber flooded with 500 ml of saline (*8*).

We have designed a new system with a maximum loss rate of 0.5% per day by (A) avoiding the use of conventional rubber, (B) minimizing the surface area of pliable seal, (C) maximizing the impervious glass surface area, (D) trapping the highly concentrated xenon bubble within an all-glass compartment, and (E) establishing a diffusion gradient which tends to minimize the xenon concentration adjacent to the pliable seal (the main point of potential xenon loss). This new system is based on two concepts, that of unidirectional flow of saline by volume displacement, and that of dynamic equilibrium between a trapped gas bubble and saline. This paper reports the design, operation, and evaluation of this low-cost glass ampule equilibration chamber for continuously dispensing radiopharmaceutical-quality xenon saline solution.

METHODS

The 5-in. long quartz glass ampule (Fig. 1) consists of a dispensing neck and an equilibration chamber which are separated by a conical glass seal. A filling tube projecting from the equilibration chamber allows suppliers to fill the chamber with ^{133}Xe gas.

New glass ampules are wrapped in gauze and autoclaved in our laboratory. After the neck is completely filled with bubble-free sterile saline, a sterile

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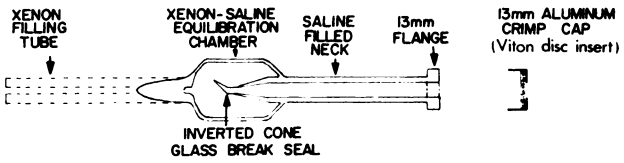

FIG. 1. Glass ^{133}Xe equilibration ampule.

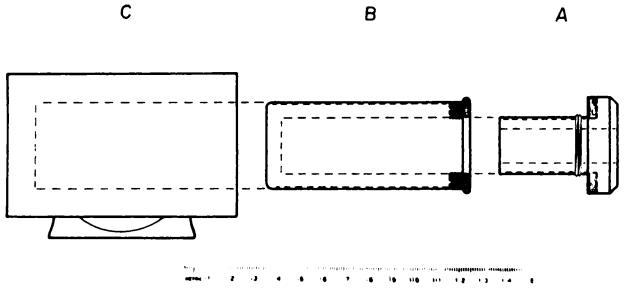

FIG. 2. Exploded view of equilibration ampule shield.

13-mm Viton® disk in an aluminum crimp seal is attached to the glass flange. The ampule is then sent to a commercial xenon supplier where the bulb is subjected to a high-vacuum and loaded with 1 curie of dry xenon gas at a pressure of 1.5–15 mmHg. The filling tube is heat-sealed and the ampule is shipped.

Upon receipt, the xenon-containing ampule is assayed in the laboratory dose calibrator and placed in the body of a portable shield (Fig. 2). The shield insert is screwed into place, the assembled device taken to a stationary shield located in a well-vented hood, and a permanent tap unit is inserted.

The tap unit (Fig. 3) consists of a 20-gage 3½-in. spinal needle, a 0.45-micron Millex® filter, a plastic three-way stopcock, and a glass syringe containing 5 ml sterile saline. The disposable Millex filter and disposable Pharmaseal Laboratories plastic stopcock have satisfactorily replaced the metal components illustrated. The unit is primed to exclude air bubbles. The tap needle is then thrust through the Viton disk of the aluminum crimp seal, down the saline-filled ampule neck, through the glass inverted cone seal into the xenon-containing equilibration chamber which is thus filled with 5 ml saline. After this initial filling of the equilibration chamber, the direction of saline flow is always out through the tap needle as shown in Fig. 3.

After the xenon and saline have equilibrated for at least 30 min, patient doses may be displaced from the equilibration chamber into a dose syringe on the tap unit by injecting an equal volume of fresh saline through a separate saline supply unit. The fresh supply unit consists of a 20-ml saline-filled glass syringe attached in series to a BD #3134 automatic one-way valve and a bent ¾-in. long 23-gage needle (Fig. 3). This short needle is introduced through the Viton disk of the aluminum crimp seal into the ampule neck. Injection of fresh saline through the one-way valve into the ampule neck displaces the desired volume of xenon-equilibrated saline from the equilibration chamber out through the tap unit into the glass patient-dose syringe (Fig. 3).

The apparatus shown in Fig. 3 can be modified by using a scalp vein set instead of the short bent needle illustrated. The one-way valve can be eliminated if users are careful to flood the equilibration chamber with saline before inserting the fresh saline inflow needle. The flow of saline must always be through the short needle into the ampule neck, thus displacing saturated solution from the equilibration chamber out through the long needle. Both needles remain in place for the 2–3-week useful life of each device.

To determine the net xenon loss and to calculate the predicted dose per milliliter, we initially assay the glass ampule in our dose calibrator. This value is corrected by the decay constant to arrive at the amount of xenon available in the ampule bulb at the time when a dose is removed. After each dose is dispensed and assayed (with correction made for attenuation by the walls of the glass dose syringe), the remaining activity in the ampule is calculated. This process is carried on serially until useful doses (>10 mCi in 5 ml) can no longer be obtained. At that time, the remaining xenon gas can be removed (after eliminating the Millex filter) by injecting air into the neck and displacing the remaining gas bubble into a dose syringe. The ampule is then removed from its shielding and again placed in the dose cali-

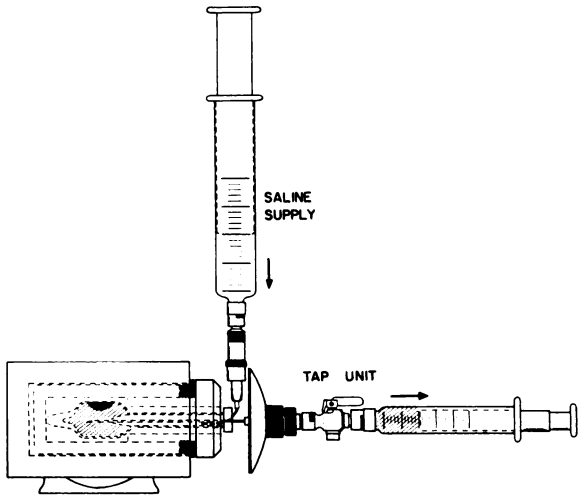

FIG. 3. Assembled system: Injection of fresh saline into ampule neck displaces saturated solution of ^{133}Xe-saline from chamber, out through filter of shielded tap unit into glass dose syringe.

brator. In addition, the tap unit is assayed. The measured activity remaining in the ampule and tap unit plus the measured activity in all dispensed doses is compared with the measured initial activity. Any discrepancy between the predicted remaining ampule activity and the measured remaining activity is expressed as a percent of initial activity divided by the number of days of "generator" use.

Xenon loss may be by diffusion through the Viton disk, by vaporization from the droplets of saline exposed when filled dose syringes are being disconnected from the tap unit and new saline-primed dose syringes attached, and by vaporization from the glass dose syringes before they are assayed.

Loss of xenon from this device has been minimal. Loss rates have varied between 0.05 and 0.50% per day. This very low xenon loss rate may be attributed to the inverted cone glass seal and the unidirectional saline flow which help to keep the ^{133}Xe bubble within glass walls and away from contact with Viton, the minimum exposed Viton surface (20 mm^2), and the 6-cm saline column separating the area of highest xenon concentration from the Viton seal. The ampule design minimizes radiopharmaceutical contact with broken glass and interaction with synthetic rubber seals. Exposed metal surface area is low, minimizing potential saline-metal corrosion.

Radiopharmaceutical quality has been enhanced through use of a glass container which allows easy visual check for contamination. Autoclaving of all internal glass surfaces assures initial sterility of the ampule.

Specific activity of the ^{133}Xe gas ranges from 14 to 140 curies/ml at STP. The usual specific activity is 25 curies/ml. Using methylparaben preserved saline which is usually saturated with dissolved atmospheric gases, we commonly achieve initial concentrations of over 100 mCi ^{133}Xe in each milliliter of saline. Concentrations are lower if the system contains gross air bubbles. One can compensate for radioactive decay by using degassed (boiled and cooled in a vacuum) or cold saline to increase ^{133}Xe concentration.

DISCUSSION

The yield in terms of millicuries of xenon activity per milliliter of saline depends upon specific activity, solubility, partial pressure, and temperature. The solubility of xenon gas in saline at room temperature and pressure is around 0.1 ml gas/ml saline. If xenon gas is supplied at 25 curies/ml, 1 curie representing 0.04 ml gas could be dissolved in 0.4 ml of degassed saline. The total volume of the equilibration chamber and ampule neck is 7 ml. Concentrations of 143 mCi/ml represent complete solution of 1 curie of gas in 7 ml of saline.

Ladefoged and Andersen have demonstrated that xenon follows Henry's law over the pressure range of 0–760 mmHg (*11*). Thus the effect of competing partial pressures of dissolved atmospheric gases must be considered. Saline in multiple-dose vials is commonly saturated with atmospheric gases. The degree of saturation can be estimated by measuring the partial pressure of oxygen in saline using a blood gas machine. Saline solution free of atmospheric gases can be prepared by boiling which also removes volatile preservatives.

The effect of competing partial pressures is not severe unless gross air bubbles are present in the system. Even at a specific activity of only 10 curies/ml gas, 1 curie could be completely dissolved in saline having a competing partial pressure of 650 mmHg.

The amount of gas dissolved is equal to the solubility multiplied by the partial pressure. If the solubility is 0.1 ml gas/ml saline, and the partial pressure is 110/760, this 0.1 ml gas can be dissolved in 7 ml of saline. When saline containing atmospheric gases is used, a gas bubble is always present in the equilibration chamber. This results from atmospheric gases being pulled out of solution by initial contact with a chamber which had been at only 10 mmHg pressure. The presence of this gas bubble allows use of the Ostwald solubility coefficient for the ratio of the volume concentration in air to the volume concentration in saline. An equilibrium is established in which xenon from the bubble equilibrates with each milliliter of fresh saline.

The effect of temperature on the solubility of xenon in saline has been well documented (*12*). The Ostwald solubility coefficient for xenon in saline at 37°C is 0.0780 ml gas (760 mmHg)/ml saline, whereas, at 25°C, solubility increases to 0.0976 ml gas/ml saline (*10,11*). Thus the net mCi/ml can be increased by cooling the saline.

Proper calibration of xenon ampules is difficult due to the relatively weak 81-keV gamma and 31-keV x-rays. The effect of attenuation by the walls of the calibration equipment should be considered. Calibration with a ^{197}Hg standard should be performed over the range of activities actually used.

Measurement of individual patient doses in glass syringes just before use requires additional correction for physical shielding by the 0.06-in. thickness of the glass syringe barrel. Our experiments demonstrate that the glass walls of the BD Multifit® 5-ml glass syringes result in attenuation such that 16.4% must be added to the observed activity to arrive at the actual activity within the syringe. The BD Multi-

fit 10-ml glass syringes result in 19.0% attenuation. Each laboratory should perform this dose attenuation measurement on its individual dose calibration equipment. To determine experimentally our syringe correction factor, we fill an empty 2.5-ml Wyeth Tubex® individual glass dose vial with xenon saline solution. This tubex is assayed alone and then assayed inside a series of 5- and 10-ml glass syringes with plungers in place. The decrease in apparent measured activity is due to absorption by the glass syringe walls.

For each ampule, the dose per milliliter as a percent of remaining ampule activity is fairly constant because of the dynamic equilibrium between gas and liquid phases. The small volume of saline in the bulb promotes rapid equilibration. Nonetheless, an equilibration period of several hours is necessary for the maximum concentration of xenon in saline to be available. Immediately after tapping, xenon concentration is approximately 1% of total ampule activity per milliliter saline; at 30 min, concentration rises to half of the equilibrium value. By 60 min, the concentration is ¾ of the full equilibrium value obtainable at 3 hr. At equilibrium, approximately 10% of the current ampule activity is available in each milliliter of saline.

If xenon gas is supplied at a specific activity of 25 curies/ml at STP, the initial xenon solution activity is usually above 100 mCi/ml using room temperature air-saturated saline. These previously unavailable very high concentrations may prove to be an asset in organ blood flow studies. Saline stabilized with methylparaben is preferred if organ blood flow studies are to be done because of the vasodilator effect of benzyl alcohol (*13*).

If xenon as a gas is desired, it can be readily obtained by exposing a small volume of xenon saline solution to a large volume of air within a glass syringe.

ACKNOWLEDGMENT

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