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PRODUCTION OF A PHARMACEUTICALLY ACCEPTABLE SALINE SOLUTION CONTAINING A RADIOACTIVE GAS AND USE THEREOF

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ABSTRACT OF THE DISCLOSURE

A process for production of saline solutions containing a radioactive gas by dissolving the gas in the saline solution in the absence of air.

This invention relates to a novel process for the production of a pharmaceutically acceptable saline solution containing a radioactive gas and use thereof. In one aspect, this invention relates to a novel process for preparing saline solutions containing a radioactive gas which are useful in radiopharmaceutical diagnostic applications. In a further aspect, this invention relates to saline solutions containing a radioactive gas, the unit dosages of which, when administered from the same vial, contain essentially the same concentrations of radioactive gas.

Recent medical investigation has shown that certain radioactive gases are extremely useful tools for diagnosis. High purity radioactive xenon-133 is used primarily as a radioisotope in a variety of medical research and diagnosis. It is well suited for studies of the rate of blood flow in the various parts of the body as well as for perfusion studies of the lungs. For instance, H. Lysgaard and H. Lefevre have reported in Acta Obstet. Gynec. Scand 44:401–7, 1965, the measurement with xenon-133 of the myometrial blood flow in the fetus. Additionally, N. A. Lassen, J. Lindbjerg and O. Munck have reported in the Lancet, 686, 1964, the measurement of blood flow through skeletal muscle by intramuscular injection of xenon-133. The use of xenon-133 has also been employed in studying the ventilation and perfusion of the lung as reported by D. V. Bates, W. C. Ball, Jr., and A. C. Bryan at the October 1963 symposium held at Oak Ridge Institute of Nuclear Studies in an article entitled "Dynamic Studies with Radioisotopes."

In most instances by the conventional methods currently employed, the radioactive isotope is administered as a gas dissolved in a saline solution. One of the major problems encountered in this technique is that the gas comes out of solution very readily, and hence when multiple doses are withdrawn from the same vial, a significant portion of the gas escapes from the saline into the supernatent gas space, decreasing the concentration of the radioactive gas in the remaining saline. Consequently, subsequent doses from the same vial contain appreciably lower radioactive xenon than previous doses.

Heretofore, the preparation of xenon-133 saline solutions, has been effected by a variety of means. For instance, one technique for preparing the solutions is described in the International Journal of Applied Radiation and Isotopes, vol. 16, 385–387, 1965. However, it is indicated that by this technique, each successive saline vial prepared by this method has a lower concentration of xenon-133 than the previous one. Hence, to date none of the work reported in the literature on xenon-133 solutions currently available on the market disclose or provide systems wherein concentration gradients are not encountered, particularly, in when multiple doses are administered from the same vial.

It is therefore an object of this invention to provide a novel process for producing pharmaceutically acceptable saline solutions containing a radioactive gas. A further object of this invention is to provide a novel process wherein saline solutions of a constant concentration of radioactive gas can be prepared. Another object, is to provide a novel process for the withdrawal of multiple dosage units of the saline solution wherein the radioactive gas concentration is essentially the same. These and other objects will readily become apparent to those skilled in the art in the light of the teachings herein set forth.

In one embodiment, the present invention is directed to a novel process for the preparation of pharmaceutically acceptable saline solutions containing a constant concentration of a radioactive gas. The process comprises the steps of:

(a) admitting a radioactive gas into a sterile, closed evacuated dissolution zone;
(b) condensing said radioactive gas in said dissolution zone in the presence of sufficient sodium chloride to prepare an isotonic solution;
(c) admitting into said dissolution zone degassed pharmaceutically acceptable water until said zone is entirely filled producing an isotonic solution containing dissolved radioactive gas;
(d) admitting into said dissolution zone insoluble, low density, non-toxic, non-pyrogenic, silicone oil to displace said solution;
(e) dispensing said solution into sealable sterile unit cartridges until no air space remains.

Operating the process in accordance with the teachings of this invention provides a pharmaceutically acceptable saline solution containing a constant concentration of a radioactive gas. In contrast to previous known methods, the gas concentration of units withdrawn from the dissolution zone into the dispensing zone are essentially the same. For example, a method currently employed today, is to inject saline solution into the dissolution zone to replace the solution withdrawn. This obviously results in a concentration gradient from the first to subsequent withdrawn portions.

The process of this invention is particularly applicable to the radioactive inert gases, such as the isotopes of xenon and krypton. Illustrative gases include, among others, xenon-133, krypton-85, and the like. It has been observed that these gases readily evolve from pharmaceutically acceptable solutions.

In a preferred aspect of this embodiment of the invention, the saline solutions containing the radioactive gas is prepared as follows.

A sealed ampoule containing xenon-133 is attached to a system containing a dissolution bulb, a water reservoir and a silicone oil reservoir. The dissolution bulb contains the correct weight of sodium chloride so that when the dissolution bulb is filled with water a 0.9 percent solution of sodium chloride in water is obtained. The whole apparatus is evacuated of air to a residual pressure of less than 10^{-2} millimeters of mercury. This evacuation process not only removes air from the dissolution bulb and connecting tubing, but also removes dissolved air from the water. The evacuated system is then isolated from the vacuum pump. The dissolution bulb is cooled, such as for example, in liquid nitrogen and the break seal of the ampoule is broken, and radioactive gas is condensed into the dissolution bulb. The evacuated ampoule is then closed off from the dissolution bulb and degassed water is admitted to the dissolution bulb. The water is stirred and the sodium chloride and radioactive gas is allowed to dissolve in the water.

During the dissolution process the dissolution bulb is normally isolated from the water reservoir but is opened

momentarily from time to time to connect the water reservoir so that at the end of the dissolution process no gas space is left in the dissolution bulb.

To dispense the radioactive gas in saline solution, silicone oil which is immiscible, insoluble and less dense than the solution is admitted to the dissolution bulb so that the solution is displaced without creating any gas space.

The particular silicone oil employed is not necessarily critical. However, it preferably should be low density, non-toxic and non-pyrogenic. Illustrative silicone oils are those of the formula $R_3SiO(R_2SiO)_x SiR_3$ wherein R is alkyl and the oils have viscosities within the range of from 7 to 100 centistokes, and higher.

In a further embodiment, the present invention is directed to a novel process for the administration of dosage units containing essentially the same concentration of the radioactive gas from the same vial. As hereinbefore indicated, a major disadvantage previously encountered, was a concentration gradient in successive unit doses due either to gas evolution or saline dilution. However, this embodiment of the instant invention provides a novel method for administering unit doses of essentially the same concentration.

As set forth above, the saline solution can be dispersed from the dissolution zone into sealable unit vials until no air space remains. All of the vials so filled from the same run have essentially the same concentration of radioactive gas. Moreover, it is possible by the process of this invention to employ a technique wherein several doses can be withdrawn from the same vial having essentially the same concentration.

This is conveniently accomplished by the use of a sealed, sterile cartridge completely filled with the radioactive gas saline solution, an aspirator, and a syringe. For example, a 1.8 cubic centimeter cartridge (63 millimeters in length) containing the gas saline solution is inserted piston end first into the syringe barrel of a short size aspirator, such as the Carpule Aspirator from which the needle end has been removed. Thereafter the needle of a 1 cubic centimeter disposable plastic syringe, such as the B–D tuberculin syringe, which has been flushed with saline solution to remove all air bubbles is inserted through the barrel end of the aspirator puncturing the septum of the cartridge. By applying pressure on the piston rod of the aspirator, the piston of cartridge moves inwardly forcing the saline solution into the plastic syringe spaces filling the syringe to the desired level. Operating in this manner avoids the creation of any gas spaces and permits mult-doses of the same concentration to be obtained.

The following example is illustrative:

Preparation of xenon-133 in isotonic saline solution

Clean, dry, and sterilize the whole apparatus. Dry sterilized sodium chloride by heating in oven at 110° C. for 8 hours. Cool sodium chloride in a sterile desiccator. Weigh the correct amount of sodium chloride to make 0.9% sodium chloride solution when dissolved in a volume of water equal to the volume of the dissolution bulb. Transfer the sterile sodium chloride into the dissolution bulb. Place a clean, dry sterile Teflon or glass covered magnetic stirring bar into the dissolution bulb. Put 500 ml. of sterile pyrogen-free water and a clean, dry, sterile Teflon coated magnetic stirring bar into a sterilized water reservoir. Assemble the apparatus and attach the silicone oil reservoir and vacuum system to the apparatus. Carefully place an iron bar to contact the break seal of the 133 Xe glass ampoule, and attach ampoule to the apparatus. Cool the cold trap of the vacuum system with liquid nitrogen. Evacuate air from all parts of the system. Test for and eliminate leaks. Degass the water in the water reservoir by evacuating the space above the water many times, stirring and heating the water, until the vacuum gauge indicates the base pressure of the pump, whether or not the tube to the water reservoir is open or closed. The water is then considered completely degassed. Fill the cold finger in the dissolution bulb with liquid nitrogen. Break the seal on the 133 Xe ampoule with iron bar and allow the xenon to condense on cold finger. Measure the radioactivity in the vicinity of cold finger to ascertain that essentially all the radioactive xenon has been transferred from the ampoule to the dissolution bulb. Isolate glass ampoule from the system by turning appropriate stopcock. Remove liquid nitrogen from cold finger. Allow cold finger to warm up to room temperature, thereby evaporating the radioactive xenon-133 into the dissolution bulb. Open appropriate water reservoir stopcock to permit degassed water to flow from water reservoir to dissolution bulb. Close water reservoir stopcock and stir the solution in dissolution bulb until no gas bubble is visible. Occasionally open water reservoir stopcock to dissolution bulb to insure no gas space is present in dissolution bulb. Stirring may be continued overnight. Place cartridge or vial under dispensing stopcock of dissolution bulb. Open silicon-oil reservoir stopcock to dissolution bulb. Open dispensing stopcock to dissolution bulb. Discard first 5 ml., then fill cartridges or vials completely. Stopper, cap and crimp each cartridge or vial quickly without introducing any gas space into the cartridge or vial. Dispense all the 133 Xe in saline solution into cartridges or vials and measure the radioactivity of each using a gamma ionization chamber. Calculate the millicuries of 133 Xe in each cartridge or vial as of the time of measurement. After dispensing, remove Xe ampoule and blow compressed air through entire apparatus to displace all of the silicone oil into a polyethylene bottle for storage as radioactive waste.

Although the invention has been illustrated by the preceding example, it is not to be construed as being limited to the materials employed therein, but rather, the invention encompasses the generic area as hereinbefore disclosed. Various modifications and embodiments of this invention can be made without departing from the spirit and scope thereof.

What is claimed is:

1. A process for the preparation of a pharmaceutically acceptable saline solution containing a constant concentration of a radioactive gas which comprises the steps of:
   (a) admitting a radioactive gas into a sterile, closed evacuated dissolution zone;
   (b) condensing said radioactive gas in said dissolution zone in the presence of sufficient sodium chloride to prepare an isotonic solution;
   (c) admitting into said dissolution zone degassed pharmaceutically acceptable water until said zone is entirely filled producing an isotonic solution containing dissolved radioactive gas;
   (d) admitting into said dissolution zone insoluble, low density, non-toxic, non-pyrogenic, silicone oil to displace said solution from said dissolution zone through a conduit into empty sealable sterile unit cartridge until no air space remains in said cartridges.

2. The process of claim 1 wherein said radioactive gas is xenon-133.

3. The process of claim 1 wherein said radioactive gas is krypton-85.

4. The process of claim 1 wherein said saline solution containing said radioactive gas is sterile.

5. A process for the preparation of a pharmaceutically acceptable saline solution containing a constant concentration of a radioactive gas which comprises the steps of:
   (a) admitting a radioactive gas into a sterile, closed evacuated dissolution zone;
   (b) condensing said radioactive gas in said dissolution zone in the presence of sufficient sodium chloride to prepare an isotonic solution;
   (c) admitting into said dissolution zone degassed pharmaceutically acceptable water until said zone is en-

tirely filled producing an isotonic solution containing dissolved radioactive gas;

(d) admitting into said dissolution zone insoluble, low density, non-toxic, non-pyrogenic, silicone oil to displace said solution from said dissolution zone through a conduit into empty sealable sterile unit cartridges having a movable piston until no air space remains in said cartridges;

(e) inserting said unit cartridge into an aspirator, inserting a saline-rinsed needle-syringe system into septum of said unit cartridge and filling said needle-syringe system with said saline solution containing said radioactive gas without introducing a gas bubble in either the said unit cartridge or said needle-syringe system by applying pressure with the aspirator on the movable piston of said cartridge.

6. The process of claim **5** wherein said saline solution containing said radioactive gas is dispensed from same said unit cartridge into more than one said needle-syringe system without introducing a glass bubble in any of the filled said needle-syringe systems or the said unit cartridge.

7. The process of claim **5** wherein said saline solution containing said radioactive gas is dispensed into a number of said needle-syringe systems from the same said unit cartridge with essentially the same concentration of said radioactive gas.

8. The process of claim **1** wherein said sodium chloride is not present and said degassed pharmaceutically accepted water is degassed pharmaceutically accepted saline solution.

9. The process of claim **5** wherein said sodium chloride is not present and said degassed pharmaceutically accepted water degassed pharmaceutically accepted saline solution.

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HOUSTON S. BELL, JR., Primary Examiner

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