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METHOD OF MAKING A RADIOACTIVE COMPOSITION

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This invention relates to absorbable radioactive compositions; in particular, it relates to radioactive salts adsorbed on an absorbable gelatin sponge.

In clinical practice it is highly desirable to implant certain substantially water-insoluble radioactive sources within the body proximate to areas or organs which are diseased or afflicted with tumor growth. Such substantially water-insoluble radioactive sources will desirably not dissolve in the blood serum and other body fluids until the radioactive energy therein is expended. Particular types of afflictions and tumors are preferably treated with radioactive sources having particularly energy emissions and half-lives. A radioactive substance such as radioactive phosphorus is often selected by the clinician to treat afflictions such as pleuro and peritoneal effusions caused by neoplastic involvement of those surfaces. It is also used to treat tumors such as pituitary tumors. The radioactive phosphorus is usually provided in the form of its phosphate and various phosphate salts are implanted either within the pleuro and peritoneal cavities or proximate to the pituitary gland.

The art has encountered many expected difficulties both in the handling and the implantation of such phosphate salts within the body. Aside from the contamination hazards involved in the handling of radioactive materials, other problems include the form in which such radioactive phosphates are implanted. It is the practice of the art to prepare substantially water-insoluble salts of phosphates so that the solid phosphate form is retained within the body at least over the time when such phosphates expend their radioactive energy. Representative insoluble salts of phosphate are the chromic phosphate and zirconyl phosphates.

It would be highly desirable to provide a radioactive composition wherein insoluble radioactive salts are adsorbed and whereby both the carrier and salt are eventually absorbed following the expenditure of the radioactive energy in the salt form.

It is an object of this invention to provide an adsorbable carrier for substantially water-insoluble radioactive salts.

It is another object of this invention to provide a method for preparing substantially water-insoluble radioactive salts on an absorbable carrier.

It is a still further object of this invention to provide a radioactive composition which can be easily cut into desired sizes and shapes.

Still another object of this invention is to provide a radioactive composition which can be implanted within the body whereby the carrier is absorbed by the physiological system.

In the accomplishment of the foregoing objects and other objects which will be apparent, reference will now be made to the following description and examples which set out the invention in detail. It is now provided that substantially water-insoluble radioactive salts are adsorbed on an absorbable gelatin sponge. It is further provided that alcohol solutions of the reactants employed to prepare the water-insoluble salt are deposited on segments of the absorbable gelatin sponge in order to form the substantially water-insoluble salt thereon. The volatile alcohol solvent is removed by evaporation and the salt itself is left on the absorbable gelatin sponge. The immediately foregoing process steps comprise a portion of the inventive contribution because conventional preparation of the salt in an aqueous medium is not possible with the absorbable gelatin sponge. The problems incident to preparing the water-insoluble radioactive salts on such a sponge will be referred to again in greater detail.

The absorbable gelatin sponge which comprises a portion of the herein disclosed composition is now widely known and used in the art. U.S. 2,465,357 describes in detail the preparation of such absorbable sponges. Essentially, they are prepared by preparing an aqueous solution of a skin gelatin or a bone gelatin. The solution is gently warmed and formalin solution is added thereto in order to harden the gelatin. The formalin added mixture is incubated at slightly above room temperature and the mixture is then beaten vigorously to produce a firm foam of from four to eight times the volume of the original solution. This foam is then placed in an oven until dry. The dry foam is then heated to a temperature of approximately 140° C. for about three hours. The resulting dry and firm gelatin sponge can then be cut with a knife into desired sizes and shapes. The amount of formalin added in the foregoing process will control the hardness of the sponge and its rate of absorption into the body. Also, the temperature employed in the final processing steps will influence the physical properties of the sponge and its rate of physiologic absorption. It has been found that a useful gelatin sponge material can be prepared from a wide variety of temperature curing steps and formalin concentrations. Among other operable procedures used to prepare such a sponge is included the following: to 100 gms. of water is added 5 gms. of skin gelatin and the gelatin-water mixture is warmed to a temperature of about 80° C. in order to induce the occurrence of the solution form. The solution is allowed to cool to about 35–40° C. and .1 cc. of formalin solution (40% aqueous solution of formaldehyde) is added thereto. The resulting solution is incubated at about 30–37° C. for approximately two hours, and the material is then beaten vigorously for about ten minutes. The foam is placed on a wire screen in a drying oven and large quantities of air of about 10% humidity are circulated therethrough at temperatures of about 30° C. This step is continued until the foam is dry, after which, the foam is heated to a temperature of approximately 140° C. for about three hours.

Segments of the absorbable gelatin sponge prepared as set out immediately hereinabove will not retain their dimensional integrity in the presence of water. If segments of such sponge are placed in water, they rapidly collapse and assume an amorphous form. The presence of this very serious problem precludes attempts to prepare the water-insoluble salts on such sponges in the conventional water-solvent systems. In the absence of the foregoing disadvantage, the composition could be readily made by combining an aqueous solution of, for example, zirconyl chloride with an aqueous solution of sodium radioactive phosphate to precipitate the substantially insoluble zirconyl radioactive phosphate salt in the aqueous mixture. The precipitation of the insoluble salt would occur on a segment of the absorbable gelatin sponge in contact with the aqueous mixture. Unfortunately, the deteriorating effect of the aqueous medium on the absorbable gelatin sponge prevents the adoption of the foregoing method.

It is, therefore, necessary that a method must be provided whereby the insoluble radioactive salt can be precipitated on segments of the absorbable gelatin sponge without violating the dimensional integrity of the gelatin segments. In order to attain such a desired composition, it is hereby provided that volatile alcohol solvents are used to dissolve the individual reactants providing an anion

and a cation and that such respective volatile alcohol solutions are combined on the absorbable gelatin segments whereupon the substantially water-insoluble salt consisting of said anion and cation is formed in adsorbing relationship to said absorbable gelatin sponge segments. It is of course provided that at least one of said ions is radioactive. The gelating sponge segments remain intact during and after contact with alcohol solvent systems.

Various approaches can be taken in forming the essentially water-insoluble salts on such gelatin sponge segments. A method that is preferred comprises depositing small volumes of the respective alcohol solution reactants, which provide said cation and anion, on a segment of the gelatin sponge. After the respective alcohol solutions of the reactants are contacted on the gelatin segment, the alcohol solvent is removed by evaporation and a segment of gelatin sponge with the substantially water-insoluble radioactive salt consisting of the foregoing cation and anion in dry form is obtained as a novel composition suitably adapted for implantation within the body.

Absorbable gelatin sponges prepared according to the process steps presented herein are absorbed in the body fluids, referred to generally as the physiological system, in about three to about ten days after they are placed therein. In that period of time, the essentially water-insoluble radioactive salt has expended its useful half-life and the radioactive energy therein has been beneficially exhausted. The gelatin sponge carrier is absorbed, and the radioactive salt is eventually absorbed.

It is understood that the method disclosed herein is applicable to the preparation of any radioactive salt so long as the salt so formed is essentially water-insoluble and so long as the individual reactants which provide the cation and anion used to form the salt are both soluble in volatile alcohol solvents. Representative radioactive salts which meet the foregoing conditions are radioactive chromium phosphate, $Cr^{51}PO_4$; ferric radioactive phosphate, $FeP^{32}O_4$; radioactive ferric phosphate, $Fe^{59}PO_4$; radioactive yttrium phosphate, $Y^{90}PO_4$; yttrium radioactive phosphate, $YP^{32}O_4$; zirconyl radioactive phosphate, $(ZrO)_3(P^{32}O_4)_2$; and the like.

The particular alcohol solvent employed does not depend on any particular critical property except its inherent volatile nature. Any alcohol which will dissolve the reactant used and will evaporate is operable. Since volatile alcohols which would otherwise have toxic disadvantages are removed by evaporation, there is no objection to using volatile alcohols such as methanol. Without intending any restrictions as to the identity and number, the following useful alcohol solvents may be mentioned: methanol, ethanol, propanol, isopropanol, butanol, pentanol, hexanol and the like. It is, of course, essential that the alcohol chosen be employed in its absolute state, that is an anhydrous alcohol system. Insignificant amounts of water mixed with such alcohols will not detract from the successful operation of the invention, but it is the preferred and well-advised practice to employ essentially anhydrous alcohol systems. It will be apparent in view of the present teaching that substantial amounts of water would deleteriously affect the dimensional integrity of the absorbable gelatin sponge and frustrate the declared objects of this invention.

The following examples are presented to illustrate the practice of this invention, but it is intended that such examples be not construed as exclusive illustrations.

EXAMPLE I

Chromic Radioactive Phosphate on Absorbable Gelatin

An aqueous solution of sodium radioactive phosphate is converted to radioactive phosphoric acid by passing said solution through a strong cation exchange resin, hydrogen form (Dowex C–3). The aqueous effluent is evaporated just to dryness in a gentle stream of nitrogen and the obtained residue is dissolved in absolute ethyl alcohol. The phosphoric acid has an activity of about 13–17 mc./mg. of phosphate ion. The alcohol solution is evaporated just to dryness and additional amounts of absolute ethyl alcohol are added to obtain an activity concentration of about 80–100 mc./ml. or about 5–6 mg. of phosphate ion/ml. An aliquot of the solution is assayed to exactly determine the activity in millicuries per milliliter. The reciprocal of this assay determination represents the number of milliliters per millicurie of activity.

Absorbable gelatin sponge prepared according to the procedure set out herein is cut into segments approximately 7 mm. square. The absorbable gelatin segments are impaled on a long needle held upright by insertion in a wooden base. To each absorbable gelatin segment is dispensed about 5 mc. of the alcohol solution of radioactive phosphoric acid or about 0.05 cc. of the foregoing solutions. The actual volume is determined by the previously ascertained number of milliliters per millicurie of activity. The segments with the radioactive phosphoric acid are immediately placed in an evacuated desiccator until all the alcohol is evaporated. About 0.1 cc. of a solution containing 10 mg. of chromic chloride per ml. of absolute ethyl alcohol is added to each gelatin sponge segment. This amount of chromic chloride is slightly more than the stoichiometric amount required to neutralize the radioactive phosphoric acid absorbed on the gelatin segment. The segments are placed again in an evacuated desiccator until the excess alcohol is evaporated. Following the preparation of such segments, a control assay is performed by dissolving a prepared gelatin segment composition in dilute sodium hydroxide solution to dissolve said gelatin sponge therein. A test tube containing this solution is placed in a beta well scintillator, and the assay for the gelatin segment composition is found to be in the range of 4.7–5.0 mc. per pellet of radioactive phosphorus activity. Once the assay has been determined, the remaining gelatin segments prepared in the same procedure are dispensed into vials and sterilized by autoclaving. The vials are dated and at the time of use the activity therein is determined by use of a suitable radioactive decay chart.

EXAMPLE II

Zirconyl Radioactive Phosphate on Absorbable Sponge

A radioactive phosphoric acid is obtained by process steps similar to those described in Example I. Disk-shaped segments of absorbable gelatin sponge about 8 mm. in diameter are impaled on a long needle held upright on a wooden base. To each absorbable gelatin segment is dispensed about 5 mc. of radioactive phosphoric acid. The segments are immediately placed in an evacuated desiccator until all the absolute ethyl alcohol is evaporated therefrom. A solution of zirconyl chloride is prepared by dissolving about 100 mg. of zirconyl chloride per milliliter of absolute methanol. To each gelatin segment is then added slightly more than a stoichiometric amount of said zirconyl chloride solution which is necessary to neutralize the phosphoric acid. The absorbable gelatin segments are again placed in an evacuated desiccator until the excess n-propanol is evaporated.

A controlled absorbable gelatin segment with the radioactive salt thereon is selected and dissolved in dilute sodium hydroxide solution to assay the activity prior to dispensing the composition into vials. The beta emissions of the radioactive phosphorus in the zirconyl phosphate salt is assayed for an activity of about five to six millicuries per segment. The balance of the segment compositions is then sealed in vials, autoclaved and labeled so that the practitioner can, with the aid of an appropriate decay chart, know the activity per segment at the time of use.

EXAMPLE III

Radioactive Chromic Phosphate on Absorbable Gelatin Sponge

Absorbable gelatin sponges are cut into cubic shapes approximately 10 mm. square and impaled on long needles

which are inserted in a heavy wooden base. To each cubic segment is dispensed about 10 mc. of high specific activity radioactive chromic chloride dissolved in absolute isopropanol. The segments are immediately placed in an evacuated desiccator until all the alcohol is evaporated. To each segment is then added a solution of phosphoric acid dissolved in isopropanol in slightly more than a stoichiometric amount necessary to neutralize said chromic chloride. The pellets are then placed in the evacuated desiccator until excess alcohol is evaporated. One pellet is dissolved in a sodium hydroxide solution and assayed as in the previous examples. An activity of about 9–10 mc. per segment is determined in a well scintillation counter.

Others may practice the invention in any of the numerous ways which will be suggested by this disclosure to one skilled in the art. All such practice of the invention is considered to be a part hereof provided it falls within the scope of the appended claims.

I claim:

1. A method of making a radioactive composition consisting of a substantially water-insoluble radioactive salt on a gelatin sponge which is absorbable in the physiological system which comprises the steps of dispensing a volatile alcohol solvent containing a reactant providing a cation and a volatile alcohol solvent containing a reactant providing an anion on a gelatin sponge segment, removing the volatile alcohol solvent and thereby obtaining a substantially water-insoluble salt consisting of said cation and said anion, one of said ions being radioactive.

2. A method of making a radioactive composition consisting of a substantially water-insoluble radioactive salt on a gelatin sponge absorbable in the physiological system which comprises the steps of dispensing a volatile alcohol solvent having dissolved therein a reactant containing a cation for the substantially water-insoluble salt, dispensing on a said carrier a volatile alcohol solvent solution containing a reactant providing an anion for the substantially water-insoluble salt, removing the volatile alcohol solvent by evaporation and thereby obtaining a substantially water-insoluble salt composed of said cation and said anion, whereby one of said ions is radioactive.

3. A method of making a radioactive composition consisting of a substantially water-insoluble radioactive salt on a gelatin sponge segment absorbable in the physiological system which comprises the steps of dispensing a volatile alcohol solvent having dissolved therein an anion-providing reactant on the segment, removing the volatile alcohol solvent by evaporation, thereafter dispensing on said gelatin sponge segment a volatile alcohol solvent having dissolved therein a cation-providing reactant, removing the volatile alcohol solvent by evaporation and thereby obtaining a substantially water-insoluble salt consisting of said cation and said anion, whereby one of said ions are radioactive.

4. The method of making radioactive compositions according to claim 3 whereby the cation-containing reactant is chromic chloride and the anion-containing reactant is radioactive phosphoric acid.

5. The method for making radioactive compositions as defined in claim 3 whereby the cation-providing reactant is zirconyl chloride and the anion-providing reactant is radioactive phosphoric acid.

6. A process for making radioactive compositions by the process steps of claim 3 whereby the volatile alcohol solvent is substantially anhydrous ethanol.

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