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CAPSULES AND METHOD OF PRODUCING

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The present invention relates to a new therapeutic form of radioactive compounds and more particularly to an improved encapsuled form of therapeutically useful radioactive compounds.

In the past radioactive compounds, such as sodium radioactive iodide (I-131), have been dispensed by measuring out, usually by remote control, of suitable volumes of an aqueous solution of a radioactive compound. For diagnostic uses in particular, most of the radioactive material is given orally and for such use it has been customary to measure or pipette the aqueous solution of the radioactive compound into a cup or glass immediately prior to administering orally to the patient. The foregoing method of administering radioactive materials results in serious contamination of glassware and other equipment, particularly where the radioactive material is used in the small clinic or by the private practitioner.

Recently the foregoing disadvantages have been in part overcome by adding an aqueous solution of a radioactive compound to a gelatin capsule which is filled with sodium phosphate, the latter serving to remove part or all of the water to form a hydrate with the result that the radioactive material is disposed on a fine, fluffy powder confined within the interior of the said capsule. Experience has shown that the latter capsules are not well suited for this purpose because the action of the water on the gelatin capsules during filling causes the development of irregular areas in the capsules. Moreover, when the capsules are damaged or broken, the remaining capsules and adjacent container becomes seriously radioactively contaminated. The latter contamination is even more serious if the breakage of the capsules occurs during the handling of the capsules while being given to the patient.

It is, therefore, an object of the present invention to provide an improved therapeutic form of radioactive compounds.

It is also an object of the invention to provide an improved therapeutic form of radioactive compounds permitting more conveniently administering accurately measured amounts of the radioactive therapeutic compounds.

It is a further object of the invention to provide an improved encapsuled form of therapeutic radioactive compounds.

It is a still further object of the invention to provide an improved encapsuled form for therapeutic radioactive compounds which reduces the danger of radioactive contamination to a minimum.

Other objects of the invention will be apparent to those skilled in the art from the following detailed description and the claims to follow.

It has been discovered that the foregoing and other objects of the present invention can be achieved by providing a gelatin capsule or capsule of other thermoplastic, water soluble, non-toxic material which has disposed interiorly as an integral part thereof or adsorbed on the interior wall a therapeutic or diagnostic dose of an organic or inorganic radioactive compound, such as sodium

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um radioactive iodide (N-131). More particularly, it has been found possible to provide a capsule composed of a non-toxic therapeutic water soluble material having interiorly disposed as an integral part thereof a therapeutic or diagnostic dose of a radioactive compound by forming a solution of the said radioactive compound in a relatively volatile essentially non-aqueous organic solvent, depositing a carefully measured volume of the said solution in an empty capsule or half thereof, and completely removing the solvent to leave the radioactive compound adsorbed on the inner walls of the capsule as a firmly attached integral part thereof.

The following specific examples are for the purpose of illustrating the present invention but should not be construed so as to limit the invention to the precise materials and proportions employed.

Example I

A solution of sodium radio-iodide (I-131) is prepared by reducing the mixture of iodide and iodate obtained as a product of nuclear fission. The sodium radio-iodide solution is evaporated to dryness and the iodide salt dissolved in a suitable volume of solvent consisting of approximately 95% ethanol to provide a solution of the said salt in a solvent having a limited amount of water and having an activity of about 0.5 mc./cc. The solution is then assayed by either beta or gamma counting, and an appropriate volume, as required to provide a capsule having an approximate activity of 30 μ c. suitable for diagnostic use, is pipetted either by hand or automatically, into each of a set of empty gelatin capsules. The alcohol solvent is then allowed to evaporate, which procedure may be accelerated by a stream of air, or very mild heat. When the solvent is removed, the cap of the capsule is applied, preferably after slight wetting with a trace of water or other suitable hygroscopic solution or solvent. After approximately one hour, the seal is complete, and the capsules are assayed again by the usual radio chemical means.

Example II

A solution of sodium radio-iodide (I-131) is prepared by reducing the mixture of iodide and iodate obtained as a product of nuclear fission. This solution is evaporated to dryness and dissolved in a suitable volume of solvent consisting of a 50:50 mixture of methanol and ether to provide an activity of about 20 mc./cc. The solution is then assayed by either beta or gamma counting, and an appropriate volume, as required to give the desired uptake dose is pipetted either by hand or automatically, into each of a set of empty gelatin capsules. The solvent is allowed to evaporate, which procedure may be accelerated by a stream of air, or very mild heat. Thereafter, the cap of the capsule is applied, preferably after slight wetting with a trace of water or other suitable hygroscopic solution or solvent. After approximately one hour, the seal is complete, and the capsules are assayed again by the usual radio chemical means.

Example III

A solution of sodium radio-iodide (I-131) is prepared by reducing the mixture of iodide and iodate obtained as a product of nuclear fission. This solution is evaporated to dryness and dissolved in a suitable volume of solvent consisting of acetone to provide an activity of about 0.5 mc./cc. The solution is then assayed by either beta or gamma counting, and an appropriate volume, as required to give the desired uptake dose is pipetted either by hand or automatically, into each of a set of empty gelatin capsules. The solvent is allowed to evaporate, which procedure may be accelerated by a stream of air, or very mild heat. After complete removal of the acetone, the cap of

the capsule is applied, preferably after slight wetting with a trace of water or other suitable hygroscopic solution or solvent. After approximately one hour, the seal is complete, and the capsules are assayed again by the usual radio chemical means.

Example IV

A solution of sodium radio-iodide (I-131) is prepared by reducing the mixture of iodide and iodate obtained as a product of nuclear fission. This is evaporated to dryness and dissolved in a suitable volume of solvent consisting of dioxane to provide an activity of about 20 mc./cc. The solution is then assayed by either beta or gamma counting, and an appropriate volume, as required to give the desired uptake dose is pipetted either by hand or automatically, into each of a set of empty gelatin capsules. The dioxane is allowed to evaporate, which procedure may be accelerated by a stream of air, or very mild heat. At the end of this procedure, the cap of the capsule is applied, preferably after slight wetting with a trace of water or other suitable hygroscopic solution or solvent. After approximately one hour, the seal is complete, and the capsules are assayed again by the usual radio chemical means.

Example V

A solution is prepared by adding a small amount of potassium dihydrogen phosphate to a solution of radioactive phosphoric acid, commonly referred to as P-32. The solution is evaporated to dryness and dissolved in a suitable volume of aqueous ethanol consisting of at least about 85% ethanol to produce the desired concentration of radioactive phosphorous for diagnostic use. The solution is then assayed by beta counting, and an appropriate volume as required to give the desired uptake dose is pipetted either by hand or automatically, into each of a set of empty gelatin capsules. The solvent is allowed to evaporate, which procedure may be accelerated by a stream of air or very mild heat. At the end of this procedure, the cap of the capsule is applied, preferably after slight wetting with a trace of water or other suitable hygroscopic solution or solvent. After approximately one hour, the seal is complete, and the capsules are assayed again by the usual radio chemical means.

Example VI

Sodium iodide, the sodium atoms of which are comprised of sodium-22 or sodium-24, is dissolved in a suitable volume of 95% ethanol to provide the desired concentration of radioactive sodium. The solution is then assayed by either beta or gamma counting, and an appropriate volume as required to give the desired uptake dose for therapeutic purposes is pipetted either by hand or automatically, into each of a set of empty gelatin capsules. The alcohol is allowed to evaporate, which procedure may be accelerated by a stream of air or very mild heat. Thereafter, the cap of the capsule is applied, preferably after slight wetting with a trace of water or other suitable hygroscopic solution or solvent. After approximately one hour, the seal is complete, and the capsules are assayed again by the usual radio chemical means.

Example VII

Ferric chloride, the ferric iron atoms thereof being comprised of radioactive iron (Fe-55 or Fe-59), is dissolved in a suitable volume of methanol to provide the desired concentration of radioactive sodium. The solution is then assayed by beta or gamma counting, and an appropriate volume, as required to give the desired uptake dose for diagnostic purposes is pipetted either by hand or automatically, into each of a set of empty gelatin capsules. The alcohol is allowed to evaporate, which procedure may be accelerated by a stream of air or very mild heat, and thereafter the cap of the capsule is applied, preferably after slight wetting with a trace of water or other suitable hygroscopic solution or solvent. After

approximately one hour, the seal is complete, and the capsules are assayed again by the usual radio chemical means.

Example VIII

To provide a therapeutic dose of sodium radioactive iodide, carrier free, a 95% ethanol solution of sodium radioactive iodide, carrier free, equivalent to 10-50 mcs. of I-131 activity is formed. The solution is then assayed by either beta or gamma counting and an appropriate volume of the solution is pipetted into an empty gelatin capsule to provide therein a therapeutic dose. The alcohol is allowed to evaporate, which procedure may be accelerated by a stream of air or very mild heat. At the end of this procedure, the cap of the capsule is applied, preferably after slight wetting with a trace of water or other suitable hygroscopic solution or solvent. After approximately one hour, the seal is complete, and the capsules are assayed again by the usual radio chemical means.

Example IX

A solution of sodium radio-iodide is prepared by reducing the mixture of iodide and iodate obtained as a product of nuclear fission. This is evaporated to dryness and dissolved in a suitable volume of solvent consisting of 95% ethanol. The solution is then assayed by either beta or gamma counting, and an appropriate volume as required to give the desired uptake dose is pipetted either by hand or automatically into each of a set of empty methyl cellulose capsules. The alcohol is allowed to evaporate, which procedure may be accelerated by a stream of air or very mild heat. At the end of this procedure, the cap of the capsule is applied, preferably after slight wetting with a trace of water or other suitable hygroscopic solution or solvent. After approximately one hour, the seal is complete, and the capsules are assayed again by the usual radio chemical means.

Example X

A solution of radioactive sucrose comprised of atoms of carbon₁₄ is prepared by dissolving the required amount of radioactive sucrose in 85% ethyl alcohol to provide the desired concentration of radioactive sucrose in solution. The solution is then assayed by beta counting, and an appropriate volume, as required to give the desired dose is pipetted either by hand or automatically into each of a set of empty methyl cellulose capsules. The alcohol is allowed to evaporate, which procedure may be accelerated by a stream of air or very mild heat. At the end of this procedure, the cap of the capsule is applied, preferably after slight wetting with a trace of water or other suitable hygroscopic solution or solvent. After approximately one hour, the seal is complete, and the capsules are assayed again by the usual radio chemical means.

Another organic compound having high specific activity which is useful therapeutically (2-50 mc. activity) or for diagnostic purposes (5-100 μ c. activity) in the form of radioactive capsules is tritioestreptomycin which contains hydrogen₃ atoms. Gelatin capsules having tritioestreptomycin adsorbed on the inner surface as an integral part thereof can be readily prepared in accordance with the foregoing example by forming the desired concentration of tritioestreptomycin chloride in methyl alcohol as the solvent, and thereafter removing the solvent as in the preceding examples. Penicillin containing radioactive carbon₁₄ or sulfur₃₅ can also be utilized in the preparation of radioactive capsules as described herein. The foregoing are merely illustrative of the many pharmaceutically useful radioactive organic compounds having high specific activity which are within the scope of the present invention.

Included among the radioactive elements which are of diagnostic or therapeutic value which can be adsorbed from the gastrointestinal tract or useful in treating said tract and can be conveniently administered in the form of

radioactive capsules prepared as disclosed herein are the alkali metals potassium and rubidium and calcium, zinc, and copper. In each instance a form of the desired element is selected which is soluble in a suitable concentration in alcohol or other relatively volatile organic solvent which contains only a limited amount of water and the radioactive salt is deposited within the interior of a thermoplastic, water soluble capsule as described herein wherein it diffuses into the wall surfaces to provide the capsule with an integral interior coating of the radioactive compound.

While the present invention has employed, for the purposes of illustrating the invention, primarily gelatin and methyl cellulose capsules, it should be readily understood that other thermoplastic, water soluble, non-toxic materials which are therapeutically acceptable can be used without departing from the scope of the present invention. For example, capsules can also be made of polyvinyl alcohol.

Capsules of radioactive therapeutic compounds prepared in the foregoing manner are found to have an extremely firmly adhering diffused film or adsorbed layer of the radioactive material on the inner surface of the thermoplastic, water soluble capsule which is not detached during preparation, handling, transportation, or use of the capsules, and which can be opened and shaken thoroughly without loss of a significant amount of the radioactive therapeutic compound. The radioactive capsules of the present invention are, nevertheless, very rapidly disintegrated when administering orally and produce a measurable amount of radioactivity in the blood stream very soon after being orally administered to the patient.

The radioactivity of the capsules prepared in the herein described manner is capable of being measured accurately from the outside of the capsule as there is no interference or shielding of the radiation by the solid filler or carrier which has heretofore been used within the gelatin or other thermoplastic capsules. It is thus possible to directly intercompare with a suitable electronic measuring device for gamma rays the amount of activity in the thyroid with that contained in an identical capsule from the same lot as the capsule administered to the patient.

It is also possible, in the absence of a soluble solid filler or carrier for the radioactive material, to seal together the sections of the thermoplastic, water soluble capsule by moistening the contiguous ends of the capsule by traces of water or other suitable adhesive material immediately prior to joining the sections of the capsule.

Others may readily adapt the invention for use under various conditions of service, by employing one or more of the novel features disclosed or equivalents thereof. As at present advised with respect to the apparent scope of our invention, we desire to claim the following subject matter.

We claim:

1. An article of manufacture comprising a pharmaceutical radioactive capsule formed essentially of a non-toxic, water soluble, thermoplastic material adapted to being ingested and rapidly disintegrating on contact with water in the gastro-intestinal tract, and having a firmly adhering pharmaceutically useful radioactive compound absorbable from the gastro-intestinal tract adsorbed on an inner surface of said capsule as an integral part thereof, whereby accidental contamination during handling and storage is substantially eliminated.

2. An article of manufacture as claimed in claim 1 wherein the said thermoplastic material is gelatin.

3. An article of manufacture as claimed in claim 1 wherein the said thermoplastic material is methyl cellulose.

4. An article of manufacture as claimed in claim 1 wherein the said thermoplastic material is polyvinyl alcohol.

5. An article of manufacture as claimed in claim 1 wherein the radioactive compound is an alkali metal iodide containing radioactive iodine atoms.

6. An article of manufacture as claimed in claim 1 wherein the radioactive compound is potassium dihydrogen phosphate containing radioactive phosphorous atoms.

7. An article of manufacture as claimed in claim 1 wherein the radioactive compound is an alkali metal iodide containing radioactive alkali metal atoms.

8. An article of manufacture as claimed in claim 1 wherein the radioactive compound is ferric chloride wherein the ferric ions are comprised of radioactive iron atoms.

9. An article of manufacture as claimed in claim 1 wherein the radioactive compound is comprised of an organic compound having high specific activity which is absorbable from the gastrointestinal tract.

10. An article of manufacture as claimed in claim 9 wherein the said organic compound is sucrose containing radioactive carbon atoms.

11. A method of making a pharmaceutical radioactive capsule having disposed on the interior surface thereof a firmly adherent integral film of a radioactive compound useful for therapeutic or diagnostic purposes which comprises forming a solution of a radioactive compound which is absorbable from the gastrointestinal tract in a relatively volatile organic solvent having a limited amount of water therein, introducing into a capsule composed of a non-toxic, water soluble, thermoplastic material an accurately measured volume of the said radioactive solution to provide an accurately determined amount of radioactivity within the capsule, removing the said volatile solvent from the solution within the capsule to provide on the interior surface of the capsule a thin, firmly adherent adsorbed film of radioactive compound without alternating the normal configuration of the said capsule.

12. A method of making a pharmaceutical capsule as claimed in claim 11 wherein the said solvent contains a maximum of 20% water.

13. A method of making a pharmaceutical capsule as claimed in claim 11 wherein the said solvent contains between about 5 and 15% water.

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CERTIFICATE OF CORRECTION

Patent No. 2,911,338

November 3, 1959

Donalee L. Tabern et al.

It is hereby certified that error appears in the printed specification of the above numbered patent requiring correction and that the said Letters Patent should read as corrected below.

Column 2, line 1, for "N-131" read -- I-131 --; column 4, line 5, for "does" read -- dose --.

Signed and sealed this 10th day of May 1960.

(SEAL)

Attest:

KARL H. AXLINE
Attesting Officer

ROBERT C. WATSON
Commissioner of Patents

UNITED STATES PATENT OFFICE
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