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BIODEGRADABLE RADIOACTIVE PARTICLES

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ABSTRACT OF THE DISCLOSURE

Particles, preferably substantially spherical particles having a smooth outer surface and essentially void-free interior are produced, consisting essentially of solid, cold-water insoluble vehicle comprising a physiologically acceptable, parenterally metabolizable radioactive protein, said particles being substantially non-leachable upon short term exposure to cold water. The particles can be administered parenterally for diagnostic, prophylactic or therapeutic purposes. On administration in this way, they are broken down or solubilized by the body fluids over a predeterminable period ranging from minutes to several days, whereupon the radioisotopic material is excreted from the body thus limiting exposure to the radiation.

BACKGROUND OF THE INVENTION

(1) Field of the invention

It has heretofore been known to encapsulate natural products for food or pharmaceutical use in proteinacious materials, such as gelatin and albumin, and even small spherical particles of such encapsulated materials have been made, e.g. by processes such as those disclosed in U.S. Pats. 3,137,631; 3,016,308; 3,202,731; 2,800,457 and the like. These prior art processes, however, either produce capsular materials wherein a central core is surrounded by a thin shell, e.g. albumin or gelatin; or (for purposes of obtaining materials that can be handled and/or stored under adverse conditions) result in severe denaturization of the protein so that its solubility and other properties are impaired. Such materials are not suitable for parenteral administration in the animal organism. Similarly, while the use of radioisotope-labeled particulates parenterally in the animal body is known for diagnostic and treatment purposes, the materials heretofore used for such purposes have been relatively insoluble, very finely divided irregular or spherical particles which, when used, lodge in the body and remain there during substantially the entire life of the radioisotope. Such particles, for example, are shown in U.S. Pats. 3,334,050 and 3,147,225. While these are very useful for certain purposes where long-continued radioisotopic treatment, for example, is desirable and advantageous, there are other areas in which their use is less desirable and in some instances may be contra-indicated. Irregular macroaggregates of human serum albumin, labelled with radionuclides, have been used for diagnostic purposes. These materials cannot be prepared in narrow ranges of particle size and are prepared in particulate form directly in the solution in which they are to be used; they cannot be dried and sized or otherwise treated, and then resuspended.

SUMMARY OF THE INVENTION

The present invention provides means to prepare certain physiologically acceptable, parenterally metabolizable radioactive materials in the spherical form, in highly pure, undenatured condition which can be administered parenterally as a solid without injury to the organism. The desirable radioactive emissions of these particles are useful for diagnostic, prophylatic and therapeutic purposes. The

invention also contemplates the provision of a process for making such particles and their concomitant or subsequent treatment to modify their solubility characteristics without bringing about denaturization which would prevent their absorption in the body.

The particulate compositions of the invention comprise a physiologically acceptable, solid substantially water-insoluble (at body temperature) radioactive material which can be metabolized, or degraded in a manner which does not form toxic residues, apparently by the enzymes or other metabolic mechanisms in the parenteral body fluids, such as blood, serum, plasma, lymph and the like. When so metabolized or degraded, these substances are solubilized.

Suitable materials for the particulate compositions of the invention are physiologically acceptable proteinaceous substances such as albumin, gelatin, hemoglobin and the like. These materials are made radioactive by reacting them with appropriate radioactive materials, such as radio-iodine, radio-iron, radio-technetium or radio-chromium. The reaction is normally done by contacting the protein with a solution of a salt of the radioactive species (e.g. sodium iodide^{131} or iron^{59} chloride) for a period of about half an hour to several hours, usually at ambient or mildly elevated temperature (e.g. below about 50° C.) with moderate agitation. A convenient technique is to agitate the solution at 37° C. (body temperature) using a metabolic shaker.

For use in diagnostic procedures or treatment requiring radioisotopes to be directed to a particular locale within the body, the material is prepared in finely divided state, the sizes of the particles being closely controlled by sorting techniques so as to be in a narrow size range adapted to the specific use. Particles thus segregated into narrow ranges can be from about ½ to 1000 microns in average diameter and preferably the size ranges chosen do not vary more than about plus or minus 20% from the mean.

Preferably, spheroidal or essentially spherular particles are employed as being more uniform and more easily controlled with respect to radioisotope content and time of elimination from the body. Spherules from ½ to 60 microns in diameter are most useful for diagnostic purposes. Larger spherules, even up to 1 millimeter in diameter, can be used for certain therapeutic purposes. Being uniform in their dimensions, spheroidal or spherular particles are more easily controlled with respect to radioisotope content and time of elimination from the body. Particularly, they are preferred because, by matching the diameter of the spherules to the size of the body passages, e.g. arteries, capillaries, etc., one can predict their route through a healthy body and determine where they should lodge with high accuracy.

To make the particles of the invention, a convenient method consists in forming a sol by dispersing the suitable radioactive protein as heretofore described in warm water, then causing the vehicle to gel as by cooling or removing water, followed by drying. The dried material can be comminuted by grinding or the like to form particles of the size desired, grading by sieves or the like being entirely feasible.

Preferably, however, the aqueous vehicle containing the radioactive protein is formed directly into tiny spheroids or spherules by causing gelation to take place in that form. While these gelled particles are prevented from coalescing, the water is removed and the particles are dried to a freeflowing, unagglomerated form. Spherules formed from sol-forming proteins do not shrink greatly during drying.

When thus prepared, the essentially cold water-insoluble particles can be washed to remove surface contamination by radioisotopes. They can be subjected to heat treat-

ment to modify their solubility, and screened or otherwise graded to desired size range. They can be soaked in water at 37° C. for at least 15 minutes without leaching out any radioactivity. In many cases they can be thus treated for periods of hours or even days without disintegration or loss of radioactivity. In physiological fluids such as blood serum, however, they soon begin to be broken down and eventually are completely solubilized.

Thus, for example, it has been found that by dispersing a solution of radio-albumin, such as albumin iodinated with iodine^{131}, e.g. by stirring into a warm, inert fluid which is immiscible with the solution of albumin and in which the albumin itself is not soluble, small spherules of the albumin are formed. The speed of stirring, use of baffles and the like controls the size of the particles obtained; empirical methods are used to establish parameters of dispersion to yield spheroidal particles of any particular size. Alternatively, and preferably for continuous production, tiny droplets of the aqueous liquid are injected through a small orifice into a moving stream of the warm, inert fluid. The water is removed from the albumin solution through the medium of the warmed, inert liquid, so that dry, practically perfectly round, free-flowing tiny spherules of radio-albumin are obtained. These spherules are from 1 to 500 microns or even up to a millimeter in diameter and can be obtained through the process in very narrow, predetermined size distribution ranges. They are substantially undenatured, and can be administered parenterally in the animal organism. When so administered, it is surprisingly found that they are readily broken down, probably by the enzymes in the body fluids, and converted to soluble form.

When albumin is used in this invention, a very convenient starting material is the radio-iodinated albumin which is an article of commerce. It is available as iodinated albumin made radioactive with either the isotope iodine^{125} or iodine^{131}. The latter isotope is particularly well known in nuclear medicine. After making the radioactive particles it is found that the radioisotopes cannot be leached from the resulting radioactive spherules upon immersion in water for periods of time of from about 15 minutes up to several days.

Other albumins may be used for this purpose including those already known in the art, such as albumin made radioactive with the isotope technetium^{99m}. Analogous reaction products of albumin with other metallic derivatives may also be used.

The albumin referred to herein is broadly any of the several natural proteins which are so described. Such albumins include those of egg, blood serum, milk and the like, as obtained from various animal species. For the purpose of this invention, the preferred albumins are animal albumins from serum, human serum albumin, and in general, for eventual use in a given animal organism, albumin obtained from the serum of that organism.

Suitable inert liquids for the process of making the spherules of the invention include vegetable oils, for example, cottonseed oil, corn oil, olive oil and the like; low melting animal fats; mineral oils, particularly those having boiling points above about 150° C.; inert hydrocarbons, halogenated hydrocarbons, and the like. The function of the inert liquid is to remove water from the protein and to cause gelling, and it will be apparent that various solvents can be used to accomplish this end.

The radioisotopes which can be incorporated into the spherical particles of albumin include such materials as isotopes of cerium, iodine, yttrium, indium, ytterbium, technetium, and any other radionuclide which is capable of reacting with the protein. These are of course selected with respect to the type and intensity of emitted radiation, to be adapted to the use for which the particles are intended.

For use in diagnostic procedures, the particles of the invention, such as microspherules of albumin containing a radionuclide, are suspended in a pharmaceutical extending medium suitable for parenteral administration. This may be, e.g., physiological saline, or dextran or gelatin solutions. A quantity of such a composition containing the desired amount of radioactivity, e.g. one millicurie, is injected, e.g. intravenously into the animal body. The material thus injected circulates throughout the body in the blood stream and, because of the selected particle size, will lodge in a particular, predetermined organ, e.g. the lung. Radiation detectors, or autoradiography, may then be employed to visualize the organ. Because the microspherical particles remain substantially intact for a short time in the animal organism, a period of time ranging up to several days is available for such diagnostic procedure. Thereafter, the body enzymes begin to attack the material, causing it to become solubilized and absorbed. The radioisotope, or its decay product, is, however, swept away from the localized area in the blood stream and excreted, generally by the kidneys.

For therapeutic or prophylactic use, the products are administered as described above except that the activity is usually much higher (e.g. 50 millicuries), and the biodegradability of the particles is adjusted so as to retain the radionuclide until it has delivered the energy required for these purposes.

It will be apparent that the particular material chosen to prepare the particles of the invention which convey radioisotopes into predetermined, temporary location in the body is not critical.

It is only necessary that it possesses a sufficient number of radioactive atoms, or that it can combine with enough radioactive specie to emit radiation of the desired intensity and energy; that the product be physiologically acceptable; capable of being prepared in essentially insoluble form with respect to water at 37° C. and capable of being metabolized or degraded by body fluids to soluble form.

The following specific examples will more clearly illustrate the specific embodiments of the invention. In these examples, all parts are by weight unless otherwise specified. As a practical matter, radioactive materials are dispensed in terms of their radiation level rather than by exact weight and wherever radiation level is mentioned, this is the exact amount of radionuclide used.

EXAMPLE 1

A solution of radioactive albumin is prepared from albumin and radio-iodine by the method of J. Lab. and Clin. Med. V. 42 pg. 598 (1953). Its concentration is 25% by weight in water and its specific activity is 50 millicuries per gram. Four milliliters of this solution are injected, conveniently through a hypodermic needle, into about 1 liter of vegetable oil (cottonseed oil) which is heated to about 30–50° C. The rate of stirring determines the ultimate size of the spherular material obtained. Using a container which is greater in height than in diameter, with a 25 gauge hypodermic needle and stirring at about 500 r.p.m. with a 2½" propeller-type stirrer, microspherular particles of about 10–20 microns in diameter are obtained. Stirring is continued while heating to 110° C. until all the water in the microspheres is removed, as may be determined by removal from the mixture of a small number of spheres to determine whether or not they are still tacky. After removal of the water, the particles are filtered away from the oil and washed with diethyl ether. Microspherular particles of radio-iodinated albumin are obtained. They are about 10–20 microns in diameter and are an unagglomerated, free-flowing tan powder.

EXAMPLE 2

A solution of radioactive albumin is prepared from albumin and radio-iodine by the chloramine-T method Biochem. J. V. 89 pg. 114 (1963). Its specific activity is 1 millicurie per milligram. Four milliliters of this solution are injected into stirred vegetable oil and are converted

into microspherular particles after the manner of Example 1. The microspherules are an unagglomerated, free-flowing tan powder.

EXAMPLE 3

Commercially-obtained pharmaceutical grade radioactive human serum albumin (radio-iodine) solution (6% concentration by weight, obtainable from E. R. Squibb and Sons, New York, N.Y.), is injected into stirred vegetable oil and is converted into microspherular form in the manner of Example 1. The microspherules of radio-iodinated human serum albumin obtained are in the form of an unagglomerated, free-flowing tan powder.

EXAMPLE 4

A solution of radioactive albumin is prepared from albumin and radio-technetium by the method of H. S. Stern et al. (J. Nucl. Med. V. 5 pg. 936 (1964)). Four milliliters of this solution are injected into stirred vegetable oil and converted into microspherules in the manner of Example 1. The microspherules of techneciated albumin are obtained as an unagglomerated, free-flowing tan powder.

EXAMPLE 5

Commercially-obtained pharmaceutical grade radioactive human serum albumin (radio-chromium, specific activity 1 millicurie per 50 milligrams, obtainable from E. R. Squibb and Sons, New York, N.Y.) is injected into stirred vegetable oil and converted into microspherular form in the manner of Example 1. Microspherules of radio-chromated albumin are obtained as an unagglomerated, free-flowing tan powder.

EXAMPLE 6

A solution of radioactive hemoglobin is prepared by shaking together a solution of hemoglobin (200 milligrams in 10 ml. water) and a radio-ferric chloride (0.1 millicurie, 0.0066 mgms Fe), at 37° C. for 16 hours.

A solution of radioactive hemoglobin (2%) is injected into stirred cottonseed oil at 30–50 C. and converted into microspherular form in the manner of Example 1. The microspherules of radio-iron hemoglobin are obtained as an unagglomerated, free-flowing, dark reddish-brown powder.

EXAMPLE 7

A convenient method for continuous production of spheroidal particles is the following: A 25% aqueous solution of radio-albumin (radio-iodine) at room temperature, is passed through a number 27 needle into a stream

of cottonseed oil warmed to about 50° C., moving at a rate of about 12 feet per minute. The radio-albumin solution breaks up into droplets, which are suspended in oil. The stream of droplets-in-oil is carried through a 50 ft. long tube, heated to ca. 115° C. This dries the droplets to microspherules of about 20–50 microns diameter. The oil and dried spherules are run into a tube and, after cooling, they are collected, the oil being removed by filtration. After warming again to about 50° C., the oil is recirculated.

What is claimed is:

1. Tiny, free-flowing, dry radioactive particles of the order of about one-half micron to 1 millimeter in largest dimension, consisting essentially of a gelled vehicle of physiologically acceptable parenterally metabolizable, radioisotope-containing, sol-forming protein of the class consisting of albumin, gelatin and hemoglobin, said particles being resistant to leaching of said radioisotope when immersed in water at 37° C. for at least about 15 minutes.

2. Particles according to claim 1 which are substantially spherular in form.

3. Spherules according to claim 2, wherein the radioactive protein is albumin.

4. Spherules according to claim 2 composed of albumin labelled with radioactive iodine.

5. Spherules according to claim 2 composed of albumin labelled with radioactive chromium.

6. Spherules according to clai m2 composed of albumin labelled with radioactive technetium.

7. Spherules according to claim 2 composed of hemoglobin labelled with radioactive iron.

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