

[54] BIODEGRADABLE RADIOACTIVE
POLYSACCHARIDE PARTICLES

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[56] References Cited

UNITED STATES PATENTS

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[57] ABSTRACT

Particles, preferably substantially spherical particles having a smooth outer surface, consisting essentially of solid, cold-water insoluble vehicle comprising a physiologically acceptable, parenterally metabolizable radioactive polysaccharide, 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.

13 Claims, No Drawings

BIODEGRADABLE RADIOACTIVE POLYSACCHARIDE PARTICLES

BACKGROUND OF THE INVENTION

1. Field of the Invention

It has heretofore been known to encapsulate natural products for food or pharmaceutical use in 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. Pat. Nos. 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 dematurization 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. Pat. Nos. 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, labeled 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, prophylactic and therapeutic purposes. The invention also contemplates the provision of a process for making particles and their concomitant or subsequent treatment to make them radioactive and to modify their solubility characteristics without bringing about denaturation 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 polysaccharide 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 polysaccharide substances such as starch, glycogen, inulin and

the like. These materials are made radioactive by reacting them with appropriate radioactive materials, such as radio-cerium, radio-ytterbium or radio-strontium. The reaction is normally done by contacting the polysaccharide with a solution of a salt of the radioactive specie (e.g. cerium¹⁴⁴ 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 shaking device.

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 1/2 to 1000 microns in average diameter and preferably the size ranges chosen do not vary more than about plus or minus 20 percent 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 1/2 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 polysaccharide 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 polysaccharide 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 free-flowing, unagglomerated form.

After drying, the particles can be heat-treated if desired to modify their solubility, and then washed to remove surface contamination by radioisotopes. They can be screened or otherwise graded to desired size ranges.

Depending upon the particular polysaccharides employed, gelled particles which are more or less soluble in water are obtained. For the purposes of the invention it is preferred that the particles have limited solubility, so that they will not dissolve in water or physiological saline solution at 37° C. during a period of at least 15 minutes. If the gelled particles are more soluble and so do not pass this test, they are subjected to heat treatment in the dry state, e.g. by heating to 200° C., as described in more detail hereinafter, until they meet the required solubility specification.

The radioactive particles of the invention can be soaked in water at 37° C. for at least 15 minutes without dissolving or 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-glycogen, such as glycogen labeled with cerium¹⁴⁴, e.g. by stirring into a warm, inert fluid which is immiscible with the solution of glycogen and in which the glycogen itself is not soluble, small spherules of the glycogen 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 glycogen solution through the medium of the warmed, inert liquid, so that dry, practically perfectly round, free-flowing tiny spherules of radio-glycogen 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.

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 polysaccharide 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 polysaccharide include such materials as isotopes of cerium, iodine, yttrium, indium, ytterbium, technetium, and any other radionuclide which is capable of reacting with the polysaccharide. 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.

A particularly useful polysaccharide for use in the invention is the natural product glycogen. Glycogen may be made radioactive by contacting it with a solution of the salt of a radioactive metal whose radiation is desired in the final product. For example, a solution of glycogen can be contacted with a solution of cerium¹⁴⁴ chloride at a pH of about 7. Inulin is also a suitable polysaccharide to use. Another useful polysaccharide is starch. For example, starch in the form of starch phosphate may be made radioactive by contacting it with radio-cerium.

A particularly valuable feature of the invention is that the polysaccharides can be made radioactive either before or after they are made into microspherules. For example, in addition to preparing glycogen-cerium microspherules as described above, one can also pre-

pare them by making non-radioactive plain glycogen spherules first. The non-radioactive spherules are then reacted with the radio-salt to give the radioactive microspherules. This procedure has a marked advantage if one wants to prepare the spherules ahead of time, using them later with fresh radioactivity which has not been subject to decay. It also allows one to handle, sieve, grade, dispense, etc. non-radioactive microspherules. Thus, the manipulation of radioactive materials, often behind lead or concrete shielding, with its concurrent health physics problems, is minimized.

For use in diagnostic procedures, a suspension of the particles of the invention, such as microspherules of glycogen 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 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 species 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 I

Prelabeled Glycogen/Cerium-144

One gram of glycogen is dissolved in 30 cc. of water by mixing and warming with stirring. Five millicuries of cerium¹⁴⁴ chloride are added, and the mixture is incubated for 15 minutes at 30°-40° C.

The solution is then injected 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 materials obtained. Using a container which is greater in height than in diameter, with a 25 gauge hypodermic needle and stirring at about 500 rpm with a 2-1/2 inch propeller-type stirrer, microspherular particles of about 10 to 20 microns in diameter are obtained. Stirring is continued while heating to 110° C. until all of 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 radioactive glycogen/Ce¹⁴⁴ are obtained. The microspheres are about 10 to 20 microns in diameter and are unagglomerated, free-flowing, light straw colored powder.

Lower temperatures can be used for drying by heating at sub-atmospheric pressures conveniently by using a water aspirator or with a vacuum pump, reducing the temperature in proportion to the reduction of pressure.

The resulting particles, which are free-flowing, unagglomerated, tiny spherules about 10 to 20 microns in diameter, dissolve rapidly in water. To treat these particles to make them less soluble, they are heated at 200° C. in the dry form for 30 minutes. Particles thus treated dissolve in physiological saline solution in approximately 20 minutes. If heating in this manner is continued for two hours, the particles dissolve in physiological saline in about 30 minutes. However, no radioactivity is leached from the particles if they are placed in water at 37° C. for 15 minutes. If heated at 200° C. for 13 hours, the particles do not dissolve in physiological saline solution. The particles are more rapidly solubilized in the body fluids than in physiological saline solutions.

EXAMPLE 2

Prelabeled Starch Phosphate/Cerium-144

10 milliliters of a 2 percent aqueous solution of starch phosphate are mixed with 1 millicurie of radio-cerium (as cerium chloride). The mixture is incubated for a few minutes at 30°-40° C. It is injected through a No. 27 needle into a stream of cottonseed oil warmed to about 50° C., moving at the rate of about 12 feet per minute. The starch solution breaks up into droplets, which as suspended in the 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. After washing with heptane and acetone, the microspherules are air dried and isolated as a dry, free-flowing powder.

EXAMPLE 3

Postlabeled Glycogen/Cerium-144

250 milligrams of glycogen microspherules are made by the processes described in Examples 1 or 2, respectively, but omitting the admixture of radioactive nuclide. They are suspended in 10 ml. of acetone containing 20 microcuries of cerium-144 chloride (added, for example, as 25 microliters of a standard radio-cerium

chloride solution). The suspension is agitated at 37° C. for 18 hours. At this time 97 percent of the radioactivity is found to have been absorbed by the microspherules. After filtration and washing with more acetone, followed by air drying, the spherules are recovered as a free-flowing light straw colored powder. They are heat-treated at 200° C. for 18 hours, by warming in an oven. When soaked in 5 cc. of physiological saline solution, less than about 5 percent of the radioactivity is removed from 65 milligrams of the spherules in 22 hours.

EXAMPLE 4

A convenient method for continuous production of spheroidal particles is the following: A 10 percent aqueous solution of radio-glycogen (radio-cerium) 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-glycogen 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 dry, free-flowing unagglomerated storable spherules suitable for radioactive labeling for diagnostic or therapeutic purposes, of a predetermined size with narrow distribution range not more than about 20 percent of the selected mean about one-half micron to 1 millimeter in diameter so as to lodge within vessels carrying body fluids at pre-selected location, consisting essentially of gelled, dehydrated physiologically acceptable parenterally metabolizable polysaccharide treated by heating to a temperature up to about 200° C. to control solubility thereof in water, to a predetermined degree so that said spherules will not dissolve in water or physiological saline solution at 37° C. during a period of at least 15 minutes and are metabolized in body fluids.
2. Particles according to claim 1 which are radioactive, said particles being resistant to leaching of said radioactivity when immersed in water at 37° C. for at least about 15 minutes.
3. Spherules according to claim 2 wherein the radioactive polysaccharide is glycogen.
4. Spherules according to claim 2 wherein the radioactive polysaccharide is starch.
5. Spherules according to claim 2 composed of glycogen labeled with radioactive cerium.
6. Spherules according to claim 2 composed of glycogen labeled with radioactive strontium.
7. Spherules according to claim 2 composed of starch labeled with radioactive cerium.
8. A parenterally injectable composition comprising spherules according to claim 1 suspended in a pharmaceutical extending medium.
9. A parenterally injectable composition comprising spherules according to claim 2 suspended in a pharmaceutical extending medium.
10. A process for preparing dry, free-flowing unagglomerated, storable, substantially spherular particles essentially composed of a physiologically acceptable

parenterally metabolizable polysaccharide which comprises
 mixing said polysaccharide in warm water to form a sol, injecting the sol in droplet form into a warm, water-immiscible inert liquid,
 stirring the mixture while bringing about gelation to spherular form,
 drying the spherules by removing water therefrom while maintaining them in the said inert liquid and preventing them from coalescing, and

removing the dried gelled particles from the inert liquid.

11. The process according to claim 10 in which the polysaccharide includes radioactive material.

12. The process according to claim 10 in which the polysaccharide is glycogen.

13. The process according to claim 10 in which the polysaccharide is radioactive glycogen.

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