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RADIOACTIVE PREPARATION ABSORBABLE IN ORGANISM AND METHOD OF OBTAINING SAME

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ABSTRACT OF THE DISCLOSURE

Absorbable radioactive articles for tissue implantation are obtained by mixing methyl hydroxypropyl cellulose with water to form a viscous mixture. The mixture is centrifuged and the centrifugate is then mixed with a solution of a radioisotope of gold or yttrium. A shaped article is formed which is dried at a temperature below 150° C.

The present invention relates to the art of medicine and has particular reference to a radioactive preparation absorbable in organism and to a method of obtaining said preparation.

The herein-disclosed radioactive preparation absorbable in organisms is applicable in treating carcinoma of salivary glands, mammary gland, thyroid gland, as well as malignant tumors arising from muscular tissue, fasciae, intramuscular connective tissue, tendon sheaths, synovial bursae, cartilages, and the like (sarcoma, myosarcoma, angiosarcoma, chondrosarcoma, synovioma, and others), and also in treating cerebral tumors and in oncological practice in ophthalmology.

Known in the present state of the art of medicine are radioactive preparations absorbable in organisms such as a preparation in the form of films based on gelatin in conjunction with radioactive chromium phosphate (P^{32}), or a filiform preparation of germanium dioxide in combination with radioactive isotopes of Au^{198} and P^{32}.

The method of obtaining said filiform preparation containing the isotopes of Au^{198} consists in that powder-like germanium dioxide of a highest purity is wetted with an inactive solution of aurous chloride. The resulted mixture is melted at 1200° C. After a molten mass has been obtained, one proceeds to touch its surface with a silver or golden stick to draw threads therefrom which are then activated in a flux of thermal neutrons. Threads containing radioactive isotope of P^{32} are obtainable in a similar way using germanium dioxide and radioactive titanium phosphate as initial components. Threads 1.7 mm. in diameter are thus obtained which dissolve in the organism's fluids within 7 to 14 days.

There is known a method of obtaining radioactive preparations absorbable in organisms in the form of filaments made of a mixture of methyl cellulose, propylene glycol and yttrium oxide (Y^{90}), said method consisting in that 150 mg. of Y^{90} with acid-dissolved carrier are placed in a platinum crucible, then 100 mg. of disintegrated powder of inactive yttrium oxide are added thereto and the pH of the medium is brought up to 8.0, whereupon are added 1–2 drops of solution of NH_4OH and the contents of the crucible are dried and calcined until a dark-red precipitate appears which is mixed with 500 mg. of methyl cellulose in 1 ml. of propylene glycol.

This done, a filament is formed from the dough-like mass obtained and is then dried at 110° C. within 10–12 hours. The obtained thread is 1.1 mm. in diameter, possessing a linear activity of 1.0 to 1.8 mc./cm. and the preparation is absorbed in the organism within 7 days.

Another method of obtaining a filiform radioactive preparation absorbable in organism comprises mixing a methyl cellulose solution, starch, glycerol and radioactive isotope of Y^{90} in the form of yttrium oxide, with subsequent filament shaping and drying at 130–140° C. within 12 hours. A method of radioactive preparations in the form of films comprise mixing high-viscosity polyvinyl alcohol with gelatin, glycerol, a radioactive isotope and antibiotics to a uniform mass with the subsequent polymerization at 20–25° C. within 12 hours (cf. Am. J. Roentgenol. Rad. Therapy and Nuclear Med., 1956, 75, pp. 1084–1092; Collection of Abstracts on Nuclear Medicine, Moscow, 1962, v. 5, pp. 189–190; Proceedings of International Conference on Peaceful Use of Atomic Energy (held at Geneva, 1955), Moscow, 1958, v. 10, pp. 143–145).

The afore-discussed radioactive preparations absorbable in organisms suffer from a number of disadvantages. The preparations made as films based upon gelatin are liable to quickly dissolve in the organism (in 3–4 days), resulting in that the liberated isotope is resorbed from the site of injection, thereby inflicting a radiation load upon the sound organs and tissues, such films possess inadequate mechanical strength making manipulation difficult when placing and fixing the films in the operative field. The application of gelatin as a base constituent demands special storage precautions for the preparations, since gelatin is a good nutrient medium for the growth of microorganisms. Preparations based upon gelatin cannot be subjected to heat treatment. Filiform preparations based upon germanium dioxide or methyl cellulose possess but insufficiently elasticity and mechanical strength, are too large in diameter (1.1–1.7 mm.) which impedes the use of conventional surgical needles for suturing tissues with such filaments or threads and requires that special devices to be employed. The preparations based on polyvinyl alcohol suffer from the disadvantage that their manufacture is complicated and takes too much time (up to 72 hrs.) which is quite undesirable inasmuch as short-lived isotopes are preferably employed as a source of ionizing radiation.

It is an essential object of the present invention to obtain radioactive preparations capable of being absorbed in organisms within a definite and predetermined period.

It is another object of the present invention to obtain said preparation featuring high elasticity and mechanical strength.

It is still another object of the present invention to obtain said preparation featuring an adequate distribution of isotopes over the emitting surface.

The essential and other objects of the invention have been accomplished due to the fact that a radioactive preparation absorbable in organism, according to the invention, contains methyl oxypropyl cellulose in combination with radioactive isotopes. Methyl oxypropyl cellulose is also known as methyl hydroxypropyl cellulose.

It is preferable to employ radioactive preparations absorbable in organisms and containing methyl oxypropyl cellulose in combination with radioactive isotope of Au^{198}, or such preparations containing methyl oxypropyl

cellulose in combination with radioactive isotope of Y^{90} in the form of yttrium silicate.

The herein-disclosed radioactive preparations absorbable in organisms can be made as films, filaments or threads, granules, and the like.

The most frequently used forms of the proposed preparation are films and threads. Films are in effect thin (0.08 to 0.1 mm.), transparent or light-red coloured preparations featuring high mechanical strength and good elasticity, and their specific activity being 0.1–1.0 mc./cm.^{2}.

The present preparation when filiform, is in fact fine, elastic threads 20–50 cm. long and 0.3–0.5 mm. in diameter, and their linear activity being 0.025–0.3 mc./cm.

The film-shaped preparation is applicable in treating carcinoma of salivary glands, mammary gland and malignant tumors arising from muscular tissue, fasciae, intramuscular connective tissue, tendon sheaths, synovial bursae, cartilages, and the like. In the above stated cases, after excision of a tumor, radioactive films absorbable in the organism are laid throughout the length of the operative field and fixed by suturing.

The application of films is indicated in treating cerebral tumors intimately interconnected with major intracranial vessels, or tumors found in close proximity to vitally important centres, as well as for oncological practice in ophthalmology, in cases where tumors are rather small in size. In all such cases, the use of radioactive films of this invention will not produce radiation effect on the sound tissues surrounding the preparation and located 6–7 mm. away, whereas the absorbed dose at the focus of lesion is high enough for an effective curative effect upon the tumor.

The filiform radioactive preparation of this invention is used for stitching small-sized tumors such as those of the eye, tumors occurring in the central nervous system, especially in those cases where intratissue beam therapy is the only means to affect the growth of a neoplasm. They are also useful for stitching up the pathways of possible metastatic spreading of the tumor (i.e., along lymphatic vessels and at lymphatic nodes).

Intratissue beam therapy combined with the use of radio-active films and threads absorbable in the organism may be particularly effective when applied in conjunction with external irradiation. As it is commonly known, in some localizations of malignant neoplasms the implantation therapy proves to yield especially good results in the form of an additional effect on the residual tumor after external irradiation.

At the same time external irradiation serves as an additional factor to the intratissue beam therapy aiming at the affecting of the ways of possible metastatic spreading.

The effectiveness of the therapeutic effect of the proposed preparations used in the form of threads and films, containing isotope of Y^{90} has been tested on the tumors of sarcoma-45 and NMP–1 (a conventional name of the strain of a tumor isolated in the Institute of Medical Radiology of the USSR) As it has been found for a complete curing of the tumor of sarcoma-45 having an average diameter of tumors equal to 0.9 ± 0.1 cm. at the beginning of treatment procedure, it is sufficient to apply threads of the preparation having a linear activity of 0.025–0.05 mc./cm. which when referred to an averaged absorbed dose in the tissues surrounding the preparation over a distance of the mean path of beta-particles at complete decay of the isotope, amounts to 2230–4460 rad.

Curing of the same tumor with the use of films containing the isotope of Y^{90} has taken place when the specific activity of the films has been equal to 0.18 mc./cm.^{2} (the average diameter of the tumors before beginning of the treatment having been equal to 1.0 ± 0.1 mm.) which when referred to an averaged absorbed dose in the tissues surrounding the preparation over a distance of the mean path of beta-particles, amounts to 9300 rad. Curing of the tumor NMP–1 has occurred after treatment with radioactive films containing the isotope of Y^{90} and having a specific activity of 0.373 mc./cm.^{2} (an averaged absorbed dose being 20,000 rad).

Determination of the radiation load on the organs and tissues when using threads and films containing isotope of Au^{198} has shown that the absorbed doses in the organs and tissues under investigation resulting from accumulation of Au^{198} therein, have been not in excess of 0.841 ± 0.011 percent of the absorbed dose at the site of implantation of the preparation. In the case of the preparations containing isotope of Y^{90} it has been found that the latter does not practically resorb from the site of implantation and is not excreted along with urine and feces, therefore the entire energy from beta-emission of said isotope is absorbed by the tissues surrounding the preparation.

One more object of the present invention is to provide a method of obtaining the abovesaid radioactive preparation absorbable in organism.

The proposed method, according to the invention, consists in that methyl oxypropyl cellulose is mixed with distilled water, then centrifuged and the resultant centrifugate is mixed with a solution of radioactive isotope, whereupon the mixture is shaped and dried.

It is most preferable that colloidal solution of Au^{198} or of Y^{90} (in the form of yttrium silicate) be made use of as the solution of radioactive isotope.

For obtaining film-like radioactive preparations absorbable in organisms methyl oxypropyl cellulose at a dynamic viscosity of 10–50 cp. is mixed with distilled water in the amounts required for obtaining a viscous solution, at a temperature of 20–50° C., then the mixture is centrifuged and the resultant centrifugate is mixed with a colloidal solution of Au^{198} or a colloidal solution of yttrium silicate (Y^{90}) taken in amounts that the content of methyl oxypropyl cellulose in the mixture is from 2.7 to 4 weight percent and the specific activity of the mixture is equal to 0.2–2.0 mc./ml., whereupon the mixture obtained is applied to a plain horizontal surface at a rate of 0.4–0.5 ml. of the solution per sq. cm. of the surface being coated, then dried at a temperature not above 50° C. until a dry film is formed.

For obtaining filiform radioactive preparations adsorbable in organisms, methyl oxypropyl cellulose at a dynamic viscosity of 10 to 50 cp. is mixed with distilled water in the amounts necessary for obtaining a paste which is then centrifuged and the centrifugate is mixed with a colloidal solution of Au^{198} or a colloidal solution of yttrium silicate (Y^{90}) in amounts that the content of methyl oxypropyl cellulose in the mixture is 10–25 weight percent and its specific activity is equal to 4–10 mc./g., whereupon threads or filaments, are shaped from the mixture obtained and dried at 100–150° C. until a dry filament is formed.

The above-described method is carried into effect as follows.

Methyl oxypropyl cellulose taken in an amount of 3–4 weight percent in the case of films and 12–25 weight percent in the case of paste, is mixed with distilled water. The concentration of the mixture should be selected so that when mixing it with a solution of radioactive isotope the weight percentage of methyl oxypropyl cellulose be equal to 2.7–4 for films and 10–25 for threads. When said percentage is below 2.7 the film will be too thin and inadequately strong, whereas if that percentage is in excess of 4, the film gets overthickened and less elastic. Similar conditions are encountered when threads or filaments are prepared, i.e., the lower limit of the weight percentage of methyl oxypropyl cellulose must be not less than 10, the threads or filaments lose their shape, whereas if said percentage is above 25, it hampers the shaping processes.

It is expedient that methyl oxypropyl cellulose be mixed with distilled water at 20–50° C. under continuous stirring to accelerate the process. As a result, a viscous solution is obtained in the case of films, or a paste in

the case of threads or filaments. The obtained mixture is centrifuged to eliminate air bubbles arising in the viscous solution during stirring and which impeding adequate spreading of isotopes over the emitting surface of the film, as well as to eliminate solid impurities present in the paste-like mass.

The viscous solution is centrifuged at 2000–3000 r.p.m. within 10–15 min., whereas the paste, at 5000 r.p.m. during 10 min. The centrifugate is mixed with a solution of radioactive isotope.

Use may be made either of beta- or gamma-emitting short-lived isotopes such as Y^{90}, Au^{198}, P^{32}, Pd^{103} and others.

Said radioactive isotopes are utilized as solutions. It is favourable to employ as the solutions of radioactive isotopes, colloidal solutions of Au^{198} or of yttrium silicate (Y^{90}), since when using colloidal solutions, isotopes are less liable to resorb from the site of implantation during the preparation absorption, at the same time maintaining a uniform distribution of isotopes over the emitting surface of films and threads. The absorption period of the preparations in the organism rises with an increase in the viscosity of methyl oxypropyl celloluse; it should therefore be borne in mind that if the most short-lived isotopes (Y^{90}, Au^{198}) are used as radiation sources, lower-viscosity methyl oxypropyl cellulose is to be employed. The absorption period must be not less than 3–5 half-life periods of the isotope selected, or the isotope, liberated after a complete absorption of the preparation and possessing still rather high radioactivity, will resorb from the site of implantation, thus imposing a surplus radiation load upon the sound organs and tissues. Centrifugate and colloidal solutions of radioactive isotopes are mixed in such amounts that the weight percentage of methyl oxypropyl cellulose in the mixture is 2.7 to 4 and the mixture specific activity equals 0.2–2.0 mc./ml. in the case of films, and 10–25 and 4–10 mc./g., respectively, for threads or filaments. Then for obtaining a film, the resultant mixture is applied onto a plain horizontal surface at a rate of 0.4–0.5 ml. of solution per sq. cm. of the surface and is dried at a temperature of not above 50° C. till a dry film is obtained. The specific activity of the finished film ranges within 0.1 to 1.0 mc./cm.^{2}, the isotopes being adequately spread over the emitting surface. The estimated value of the coefficient of variation (C) for the films containing Y^{90} is 3.11% and for the films containing Au^{198} is 0.98%.

The finished films are sterilized and stored in an absolute ethyl alcohol contained in sterile ampoules. It takes 2–5 hours for the films to sterilize in an absolute ethyl alcohol, the extraction of isotopes by the absolute ethyl alcohol being not in excess of 2.10^{-6} to 3.10^{-6} weight percent.

To obtain filiform preparations the mixture of methyl oxypropyl cellulose with the colloidal solution of isotope is shaped into filaments which are then dried at 100–150° C. till a dry filament is formed.

Filaments intended to prepare the granules therefrom are cut into lengths 3–4 mm. long.

The finished filaments possess a linear activity of 0.025–0.3 mc./cm., the coefficient of variation for those containing the isotope of Au^{198} being 0.86%, for those containing the isotope of Y^{90}, 2.64%. Threads or granules are sealed up into ampoules and sterilized at 130° C. for 2–3 hours.

Films and threads or filaments thus obtained possess good elasticity, high mechanical strength, feature an adequate distribution of isotopes throughout the emitting surface, small diameter in case of threads or filaments (0.3–0.5 mm.) or thickness in case of films (0.08–0.1 mm.). The use of methyl oxypropyl cellulose of different viscosity makes it possible to obtain preparations with different periods of absorption in organisms, said periods being alterable to suit the particular anatomic region where the preparation is to be injected and the half-life of the radioactive isotope selected. Moreover, methyl oxypropyl cellulose is not a nutrient medium for the growth of microorganisms and does not possess cancerogenic properties.

In order that the present invention may be better understood, given below are a few examples of the embodiment of the method of obtaining a radioactive preparation absorbable in organisms.

EXAMPLE 1

A batch of 1.2 g. of methyl oxypropyl cellulose at a dynamic viscosity of 20 cp. is mixed with 29 g. of distilled water at 40° C. while continuously stirring till a transparent, slightly opalescent uniform solution is obtained. Then the solution obtained is subjected to centrifugation at 3000 r.p.m. for 10 min. The resulting centrifugate is transferred into a clean glass chemical vessel, and 6 ml. of colloidal solution of yttrium silicate (Y^{90}) with a specific activity of 8.3 mc./ml. are added thereto. Then the resultant radioactive mixture is carefully and cautiously agitated with a glass stick, the specific activity of the mixture becoming 1.66 mc./ml.; this done, the mixture is poured into a Petri dish preliminarily coated with glycerol and possessing a plain horizontal surface. Then the Petri dish coated with the radioactive mixture is placed in a drying cabinet at 40° C. and kept there till a thin readily separated film is obtained. The area of the film is 60 cm.^{2}, its specific activity being 0.83 mc./cm.^{2}.

The finished film is placed in glass sterile ampoules containing an absolute ethyl alcohol and the ampoules are sealed.

EXAMPLE 2

A batch of 1.2 g. of methyl oxypropyl cellulose at a dynamic viscosity of 50 cp. is mixed with distilled water at 40° C. while continuously stirring till obtaining a uniform paste. Then the resultant paste is centrifuged at 5000 r.p.m. for 15 min., whereupon 0.2 ml. of glycerol and 2.5 ml. of colloidal solution of Au^{198} with a specific activity of 20 mc./ml. are added and the mixture is thoroughly agitated. The paste obtained possesses a specific activity of 5 mc./g.

The obtained radioactive paste is shaped into threads or filaments by using a special device, the threads or filaments are placed onto a glass heated up to 80° C. which is then quickly transferred into a drying cabinet and kept there for 15 min. The threads or filaments obtained possess a linear activity of 0.125 mc./cm.; they are sealed up in sterile ampoules and sterilized at 130° C. for 2 hrs.

What is claimed is:

1. A method for preparing shaped absorbable radioactive articles for tissue implantation which comprises mixing methyl oxypropyl cellulose having a viscosity range of from 10 to 50 cp. (1%) with water in sufficient amounts to form viscous solutions to pastes of the mixture; centrifuging the resultant mixture; mixing the centrifugate with a colloid or solution of a radioisotope from the group of radiogold (Au^{198}) and radio-yttrium (Y^{90}); forming said shaped articles from said radioactive mixture; and then removing the water from said shaped article by heating at temperatures below about 150° C.

2. The method according to claim **1** wherein the radio-yttrium (Y^{90}) is in the form of yttrium silicate.

3. A method for preparing absorbable tissue implantable films according to claim **1** wherein the initial methyl oxypropyl cellulose solution comprises 3 to 5% by weight of methyl oxypropyl cellulose and the radioisotope is admixed with the centrifugate in an amount to provide a specific activity of 0.2 to 2.0 mc./ml. and then casting the radioactive mixture on a small surface in an amount of 0.4 to 0.5 ml./cm.^{2} of said surface and drying said casting at a temperature below about 50° C. until a dry film is formed.

4. A method for forming absorbable tissue implantable filaments according to claim **1** wherein the methyl oxy-

propyl cellulose is mixed with sufficient water to form a paste and wherein the radioisotope is added to the centrifugate in an amount to provide a specific activity of 4.0 to 10.0 mc./gm.; thereafter forming the radioactive mixture into filaments and then drying said filaments at temperatures not exceeding about 150° C.

5. A radioactive absorbable shaped article for tissue implantation comprising a mixture of methyl oxypropyl cellulose of dynamic viscosity 10–50 cp. (1%) and a radioactive isotope of Au^{198} or Y^{90}, said isotope being uniformly distributed through the methyl oxypropyl cellulose matrix from colloid or solution, and said shaped article having specific activities of 0.05 to 1.0 mc./cm.^{2} for films and 0.02 to 0.3 mc./cm. for filaments.

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