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(54) Title: LAYERED MIXED METAL HYDROXIDES FOR THE STABILIZATION OF RADIOACTIVE COLLOIDS

(57) Abstract

A stabilized radionuclide-colloid composition useful in therapeutic radiation ablation therapies is disclosed. The composition contains a viscosity modifier layered mixed metal hydroxide and optionally an ion exchange medium to stabilize the radioactive colloid.

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LAYERED MIXED METAL HYDROXIDES FOR THE STABILIZATION OF RADIOACTIVE COLLOIDS

This invention relates to a composition, a method of making the composition, and a method of using the composition in treating arthritis and other diseases where a radioactive colloid is used in therapeutic and diagnostic procedures. In particular, the composition of this invention comprises a radioactive colloid having admixed therewith a stabilizing effective amount of a layered mixed metal hydroxide. The composition exhibits increased retention of radioactivity at a site of injection, for example, in a synovium, as compared with the retention of formulations without such a stabilizer.

Rheumatoid arthritis is a prevalent disease characterized by chronic inflammation of the synovial membrane lining the afflicted joint. Current treatment methods for severe cases of rheumatoid arthritis include the removal of the synovial membrane, e.g., synovectomy. Surgical synovectomy has many limitations, including the risk of the surgical procedure itself, and the fact that a surgeon often cannot remove all of the diseased membrane. The diseased tissue remaining eventually regenerates, causing the same symptoms which the surgery was meant to alleviate.

Radiation synovectomy is radiation-induced ablation of diseased synovial membrane tissue accomplished by injecting a radioactive compound into the diseased synovium. Early attempts to perform radiation synovectomy were hampered by migration of the radioactive compounds utilized and by leakage of such compounds from the synovium and into surrounding healthy tissues. The instability of labile radionuclide--complexes or the presence of small labeled particles resulted in radionuclide leakage out of the synovium and deposition in healthy tissues. Significant leakage of the radioactive compound from the injection site exposed normal tissues to dangerous levels of radiation. Because of these limitations, new radiolabeled compounds were sought which would have minimal leakage.

U.S. Patent No. 4,752,464 describes a composition comprising a radioactive colloid in which a radionuclide is entrapped within an iron hydroxide matrix. Radioactive colloids are useful in radiation ablation procedures, for example ablation of a synovium in rheumatoid arthritis, however their use may still result in significant leakage of radioactivity from a site of injection, e.g., a synovium, and into the surrounding normal tissues, exposing normal tissues to an undesirable amount of radiation. To compensate for the leakage, a radioactive metal having a short half-life, such as Dysprosium (Dy-165) has been proposed for use as the labeling radionuclide. Because of its short half-life (2.3 hours), the majority of Dy-165 radioactivity decays before significant leakage can occur, thereby minimizing the dose of radiation seen by normal tissues.

The use of radioactive metals having a short half-life severely limits the utility of the therapeutic radiation procedure in two ways. First, radioactive compositions prepared with short half-life isotopes lose a significant amount of radioactivity because of decay during shipment to distant locations. Second, to achieve a therapeutic dose of a composition comprising a radioactive metal having a short half-life, large amounts of radioactive materials must be used. As a result, clinical personnel must handle large amounts of radioactive materials.

There remains a need for a therapeutic radioactive composition which upon injection, for example into a synovium, would remain at the site of injection, e.g., within a synovium, for a prolonged period of time. Prolonged retention at the site of injection would allow use of radionuclides having a longer half-life in therapeutic procedures, including radiation synovectomy, without fear of significant leakage from the site of injection and radiation exposure to normal tissues.

It has now been found that the addition of a layered mixed metal hydroxide (LMMH) to a radiolabeled colloid composition results in a stabilized radiolabeled colloid composition. Use of the stabilized colloid-LMMH compositions in therapeutic procedures results in significantly reduced leakage of radioactivity from a site of injection, for example, a synovium. The stabilized colloidal compositions contain a radionuclide, a colloid, and a LMMH. The colloid may be a metal hydroxide colloid such as iron (II or III) hydroxide or a colloidal clay such as bentonite. The stabilized colloidal compositions may be prepared using

radionuclides having longer half-lives than previously used, greatly minimizing significant leakage from the site of injection and radiation exposure to normal tissues.

In the method of the present invention a radioactive colloid is stabilized by the addition of a layered mixed metal hydroxide (LMMH). Such stabilized radioactive colloids are useful in the therapeutic radiation treatment of arthritis to ablate diseased tissues.

Stabilization of radioactive colloids includes the prevention of leakage of radioactive nuclides from a site of injection into surrounding normal tissues. The stabilized compositions of the present invention contain therapeutic radionuclides, radionuclide-absorbing colloids, and stabilizing LMMHs.

While not wishing to be bound by theory, the addition of LMMH to the radioactive colloid composition may achieve stabilization by increasing the viscosity of the composition.

PREPARATION OF COMPONENTS OF THE STABILIZED PRODUCT

COLLOIDS

Colloidal materials useful in the present invention include any which are capable of being labeled with a therapeutically useful radionuclide. The term colloid is meant to include both the material in the dispersed phase and the dispersion medium comprising the colloidal system. The dispersion medium may be liquid or gaseous, and preferably is liquid. Useful colloids are anionic colloidal materials, including, but not

limited to, metal hydroxide colloids such as iron hydroxide colloid, colloidal clays such as bentonite, macroaggregated protein such as macroaggregated albumin, ion exchange gels or resins, and polyamines. The preferred metal hydroxides are iron hydroxide, including iron (II) hydroxide and iron (III) hydroxide, and aluminum hydroxide.

Bentonite, a colloidal clay primarily composed of montmorillonite ($Al_2O_3 \cdot 4SiO_2 \cdot H_2O$), may bind radioactive metals by entrapment in the highly viscous colloidal matrix, or by ion exchange.

RADIONUCLIDES

Radionuclides useful in the present invention include those having therapeutic efficacy, for example in radiation ablation therapies such as radiation synovectomy. Radionuclides are preferably those of the rare earth class and other metals having nuclear properties of therapeutic value. Examples of such metals include Holmium (Ho-166), Samarium (Sm-153), Lutetium (Lu-177), Lanthanum (La-140), Gadolinium (Gd-159), Ytterbium (Yb-175), Indium (In-115m), Yttrium (Y-90), Scandium (Sc-47), and Rhenium (Re-186), (Re-188).

The respective radionuclides can be produced in several ways. In a nuclear reactor, a nuclide is bombarded with neutrons to obtain a nuclide with additional neutrons in its nucleus. For example:

$$\text{Ho-165} + \text{neutron} \rightarrow \text{Ho-166} + \text{gamma}$$

Typically, the desired radionuclide can be prepared by irradiating an appropriate target, such as

the metal oxide. Another method of obtaining radionuclides is by bombarding nuclides with particles in a linear accelerator or cyclotron. Yet another way of obtaining radionuclides is to isolate them from fission product mixtures. Radionuclides may be obtained by methods known in the art.

PREPARATION OF RADIOACTIVE COLLOID

Labeling of the colloid may be accomplished by ion exchange, sorption, entrapment, or other known methods for bonding a radionuclide to an anionic colloid.

Radiolabeled metal hydroxide colloids useful in the method of the present invention include those produced by a coprecipitation method as described in U.S. Patent No. 4,752,464. Using the coprecipitation method, the radionuclide is dissolved in concentrated hydrochloric acid to produce a chloride form of the radionuclide. To this solution is then added a solution of iron or aluminum chloride. Sodium hydroxide is then added to this solution in an amount sufficient to adjust the pH of the solution to a valve from 4 to 9. The product is an aggregated precipitate of iron or aluminum hydroxide within which is entrapped the radionuclide utilized. Preferably, the product of coprecipitation process includes particles in the size range of 3-20 μm.

Useful radiolabeled metal hydroxide colloids may also be produced by sorption of a radionuclide onto a previously prepared metal hydroxide colloid. In this procedure, a metal hydroxide colloid may first be prepared, for example, by reacting a metal salt with sodium hydroxide. The resultant metal hydroxide colloid

is then reacted with nuclide to produce the radioactive colloid.

LAYERED MIXED METAL HYDROXIDES (LMMH)

LMMH may be represented by the following formula:

$$Li_mD_dT(OH)_{(m+2d+3+na)}A_a^n$$

where:

m represents the number of Li ions present;

D represents divalent metal ions;

d is the number of ions of D in the formula;

T represents trivalent metal ions;

A represents monovalent or polyvalent anions other than OH ions;

a is the number of ions of A in the formula;

n is the valence of A; and

(m+2d+3+na) is equal to or greater than 3.

Layered mixed metal hydroxides are preferably prepared by an instantaneous ("flash") coprecipitation wherein soluble metal compounds, e.g., salts of the metals, are intimately mixed (using non-shearing agitation or mixing) with an appropriate alkaline material which supplies hydroxyl groups to form the mixed metal hydroxide crystals. A distinguishing feature of the composition is that the crystals are essentially a monolayer, that is, one layer of the mixed metal hydroxide per unit cell of the crystal. These are termed "monodispersed" crystals when they are in a

liquid carrier and are individual crystals of monolayer mixed metal hydroxides. (See EPO No. 0,207,811, U.S. Patent Nos. 4,664,843 and 4,790,954.)

In the above Formula I, m may be from 0 to about 1, and most preferably m is 0.5 to about 0.75 when not 0. The D metal may be Mg, Ca, Ba, Sr, Mn, Fe, Co, Ni, Cu, Zn, and most preferably D is Mg, Ca, or mixtures of these. The value of d may be from 0 to about 4, provided that both m and d are not 0, and preferably the value of d is from about 1 to about 3 and most preferably about 1. The T metal is preferably trivalent, and may be Al, Ga, Cr, or Fe; preferably T is Al or Fe, and most preferably T is Al. The A anions may be monovalent or polyvalent, including divalent and trivalent, and they may be inorganic ions such as halide, sulfate, nitrate, phosphate, carbonate. Preferably the A anions are halide, sulfate, phosphate or carbonate or they may be hydrophilic organic ions such as glycolate, lignosulfonate, polycarboxylate or polyacrylate. These anions often are the same as the anions which form part of the metal compound precursors from which these crystals are formed. Since "n" is a negative number, "na" is also a negative number.

Methods for preparing a LMMH useful in the present invention, are disclosed in U.S. Patent No. 4,790,945 to Burba et al. To produce LMMH, according to the Burba et al. method, a mixture of the selected soluble metal compounds, especially the acid salts (e.g., chloride, nitrate, sulfate, phosphate, etc.), are dissolved in an aqueous carrier. The ratios of the metal ions in the solution are predetermined to give the ratios desired in the final product. The concentration limit of the metal compounds in the solution is governed

in part by the saturation concentration of the least soluble of the metal compounds in the solution. Any non-dissolved portion of the metal compounds may remain in the final product as a separate phase. This is usually not a serious problem if the concentration of such separate phase is a relatively low amount in comparison to the soluble portions, and preferably is not more than about 20 percent of the amount of the soluble portions. The solution is then mixed rapidly and intimately with an alkaline source of OH^- ions while substantially avoiding shearing agitation thereby forming monodispersed crystals of LMMH. One convenient way of achieving such mixing is by flowing the diverse feed streams into a mixing tee from which the mixture flows, carrying the reaction product, including the monodispersed LMMHs of the above Formula I. The mixture may then be filtered, washed with fresh water to remove extraneous soluble ions (such as Na^+, NH^{+4} ions, and other soluble ions) which are not part of the desired product.

A preferred method of preparing the Formula I LMMH composition, is to react a solution of metal salts, preferably magnesium and aluminum salts (approximately 0.25 molar), with an appropriate base such as ammonium or sodium hydroxide in quantities sufficient to precipitate the LMMH. For ammonium hydroxide, the preferable range is between 1 and 1.5 equivalents of OH^- per equivalent of anion.

The precipitation should be done with little or no shear so that the resultant flock is not destroyed. One method of accomplishing this is to flow two streams, the salt stream and the base stream, against one another so that they impinge in a low shear converging zone such

as would be found in a mixing tee. The reaction product is then filtered and washed, producing a filter cake of about 10 percent solids. (See European Patent Application No. 02 07 811)

The LMMH crystals have a positive charge associated with the surface of the LMMH crystals, and are consequently less readily dispersed in non-polar than in polar fluids. It may be desirable to modify the LMMH to render it more readily dispersed in the fluid of choice. Such modification may be accomplished, for example, by treating the LMMH crystals, for example, with an aliphatic carboxylic or fatty acid, such as stearic acid.

ION EXCHANGE MEDIUM

In addition, the stabilized radioactive colloid composition may also include an anionic exchange medium to bind up excess nuclide in the radioactive composition. The ion exchange medium may also bind up radionuclides which become displaced from colloid at the site of injection, and help to prevent leakage of radioactivity from a site of injection. Ion exchange media useful in the present invention include negatively charged clays, for example, betonite, or other well known commercially available anionic exchange media.

PREPARATION OF THE STABILIZED PRODUCT

STABILIZED RADIOACTIVE COLLOIDS

The stabilized radiolabeled colloids of the present invention are generally prepared by mixing a colloid with a LMMH. The colloid may be radiolabeled prior to or simultaneously with the LMMH mixing step. In general, the colloidal material will be in suspension

or solution. The LMMH may be in solid form, or in suspension. The amount of LMMH in the final colloidal composition will vary with the intended use, and will be that amount which is effective in reducing leakage of radioactivity from a site of injection of the composition. Generally, the amount of LMMH in the final composition will be in the range of from 0.01 weight percent to 2.5 weight percent of the total composition.

The LMMH is mixed with a colloid which carries the radionuclide including, but not limited to, iron hydroxide or negatively charged clays such as bentonite. The amount of the colloid in the final composition will vary according to the type of colloid and with the specific intended use of the composition, but generally will be in the range of 0.5 weight percent to 2.5 weight percent of the total composition.

In addition, an ion exchange medium may be added to the stabilized radioactive colloid composition to bind up excess radionuclide. The ion exchange medium may be a negatively charged clay such a bentonite. Generally, the amount of ion exchange medium in the composition will be approximately less than 1.0 weight percent of the total composition.

The stabilized radiolabeled colloidal compositions of the present invention are useful in therapeutic and diagnostic procedures, and are particularly useful in the therapeutic radiation treatments for arthritis. These compositions are especially useful in therapeutic radiation ablation procedures, for example, radiation synovectomy. In such procedures, a therapeutically effective amount of the radioactive composition is administered to a patient in

need of such treatment, for example, by injection into the synovium of an arthritic knee. The radiolabeled colloidal compositions are injected with the aid of a pharmaceutically acceptable carrier. Pharmaceutically acceptable carriers are a liquid medium in which the radiolabeled colloidal composition can be dissolved or suspended and include, for example, water, buffers such as phosphonate or carbonate, glycols, saline, or phosphate buffered saline.

The therapeutically effective amount will vary with many factors including the half-life of the radionuclide utilized, the particular colloid used, the site of injection, and the desired amount of radioactivity to be delivered to the site of injection. Depending upon the therapeutic procedure, the desired amount of radioactivity delivered to the site of injection is that amount sufficient to kill or ablate the diseased tissue or cells. In general, this will be a sufficient amount of radioactive material to deliver from about 500 to about 150,000 rads to the diseased tissue. A more preferred dosage is that which delivers from 2,000 to 50,000 rads to the diseased tissue.

The invention will be further clarified by consideration of the following examples, which are intended to be purely exemplary of the method of the invention.

Example 1 Preparation of LMMH, $MgAl(OH)_{4.7}Cl_{0.3}$

LMMH was prepared according to the method of Burba, disclosed in U.S. Patent No. 4,790,954 which is hereby incorporated by reference. In general, a solution of $MgCl_2 \cdot AlCl_3$ (0.25 M) was pumped into one arm of a mixing tee. NH_4OH (0.25 M) was pumped into a second, opposite arm of the tee so that the two

solutions met in the tee. The coprecipitation product was poured out of the third arm and into a beaker, and consisted essentially of delicate flocs of monospheres, monolayer, and microcrystals of LMMH, having the approximate formula $MgAl(OH)_{4.7}Cl_{0.3}$ suspended in an aqueous solution of NH_4Cl. The product was filtered, washed and drain-dried.

Example 2 Stabilization of Ho-166-Iron Hydroxide Colloid with LMMH

A volume of 15 ml of 0.01 M $FeSO_4$ solution was placed in each of 4 vials and 15 ml of 0.1 N NaOH was added to each vial. This was mixed and allowed to stand for 10 minutes. The vials were centrifuged for 2-3 minutes and the liquid fraction was removed by decanting. The solids were washed with 15 ml of water and the suspension was again centrifuged and decanted. Fifteen ml of phosphate buffer (0.4 M, pH 7) was added and the solids were isolated by centrifugation followed by decanting. The solids were resuspended in 5 ml of phosphate buffer and combined into one 20 ml vial. After centrifuging the liquid was again removed by decanting. The solids were resuspended in 5 ml of Ho-166 solution (3×10^{-4} M Ho in 0.1 N HCl containing tracer amounts of Ho-166) and an additional 5 ml of water. The suspension was adjusted to a pH of approximately 7-8 using HCl.

To a vial containing the Ho-166-colloid was added 5.0 ml of $MgAl(OH)_{4.7}Cl_{0.3}$ (11.8 percent by weight in distilled water) as prepared in Example 1 and the suspension was mixed to suspend the colloids in the LMMH medium. After mixing, the composition was viscous.

A volume of 100 µl of this suspension was injected into the synovium in the stifle of an anesthetized rabbit. A 2 inch NaI detector connected to a multichannel analyzer was used to determine the amount of Ho-166 activity in the synovium as a function of time by counting the gamma photons using repeated one minute counts. No loss of activity from the synovium was detected for the time period studied, one hour. A control formulation lacking LMMH was tested in the rabbit's opposite stifle. A measurable loss of activity (approximately 2 percent) from the control synovium was detected for the one hour test period.

Example 3 Stabilization of Sm-153-Iron Hydroxide Colloid by LMMH

A mass of 0.203 g of $FeSO_4 \cdot 7H_2O$ was dissolved in 100 ml of deionized water. A volume of 4 ml of this 0.2 percent $FeSO_4$ solution was placed in a vial and 800 µl of 1.0 N NaOH was added. The dark green solid that was formed was allowed to settle to the bottom of the vial and the excess liquid was decanted. The solid was washed four times by resuspending in 4 ml of deionized water, centrifuging at 4500 RPM for 1 to 2 minutes, and decanting.

A volume of 50 µl of Sm-153 solution (3×10^{-4} molar Sm, in 0.1 N HCl containing tracer amounts of Sm-153) was added to the prepared colloid. LMMH, prepared as described for Example 1, was diluted in water to provide a LMMH dispersion of 11.8 weight percent. One ml of the LMMH dispersion was added to the Sm-153-colloid mixture, mixed and the pH adjusted to approximately 8-9 with HCl.

A volume of 100 µl of the resulting Sm-153-iron hydroxide-LMMH dispersion was injected into the synovium in the stifle of an anesthetized rabbit. The Sm-153 activity in the synovium was determined over time by placing a NaI scintillation detector over the knee area and counting the gamma photons using repeated one minute counts. The number of counts remaining in the synovium (corrected for decay) was then plotted as a function of time. The results showed no measurable loss of activity from the synovium over 120 minutes.

Example 4 Stabilization of a Sm-153 Iron Hydroxide Colloid with LMMH and Bentonite

Into a vial was placed 2 ml of 0.2 percent $FeSO_4$ (wt/vol). To this was added, dropwise, approximately 4 ml of 0.1 N NaOH. A dark green solid was allowed to settle in the bottom of the vial and the supernatant was removed. The solid was resuspended in 4 ml of distilled water. The dispersion was then centrifuged at 4500 RPM for 3 minutes and the resulting supernatant removed. This distilled water washing step was repeated two additional times. After the last decanting of the supernatant, 200 µl of Sm solution (3×10^{-4} molar Sm in 0.1 N HCl containing tracer amounts of Sm-153) was added, followed by the addition of 200 µl of isotonic saline.

A volume of 300 µl of a LMMH dispersion containing 1.4 percent Bentonite (Gold Star®) and 0.21 percent LMMH (prepared as described in Example 1 and diluted in deionized water) was then added. After mixing, the dispersion was allowed to stand for 10 minutes, after which time 10 µl of 0.1 NaOH was added

followed by an additional 300 µl of the LMMH-Bentonite dispersion.

A laboratory rabbit was anesthetized and 300 µl of the prepared radiolabeled colloid-LMMH-Bentonite dispersion was injected into the synovium of the right knee. The Sm-153 activity in the synovium was determined over time by placing a NaI scintillation detector over the knee area and counting the gamma photons using repeated one minute counts. The number of counts remaining in the synovium (corrected for decay) was then plotted as a function of time. No leakage of radioactivity from the synovium was detected over the 2.5 hours duration of the experiment.

Control

The procedure was repeated using 300 µl of the radiolabeled colloid to which no LMMH-Bentonite had been added. The same rabbit was injected with this control dispersion in the left knee synovium. The amount of activity remaining in the synovium was determined in the same manner as described above. In the control, left knee, a decrease in the amount of activity remaining in the synovium was evident by a decrease in the counts in the synovium with time.

Example 5 Stabilization of Sm-153-Bentonite with LMMH

A volume of 500 µl of LMMH-Bentonite dispersion containing 1.4 percent Bentonite and 0.21 percent LMMH (prepared as described for Example 1 and diluted in deionized water) was placed in a vial. Ten (10) µl of Sm solution (3×10^{-4} molar Sm, in 0.1 NHCl containing tracer amounts of Sm-153) was added. A volume of 100 µl of the resulting Sm-153-LMMH-bentonite dispersion was

injected into the right knee synovium of an anesthetized rabbit. The amount of activity in the synovium as a function of time was determined and calculated as described in Example 1. Material prepared in the same manner was also injected into the left knee synovium of the rabbit. The number of counts in the synovium as a function of time remained constant for both samples.

Having described the invention above, various modifications of the techniques, procedures, material and equipment will be apparent to those in the art. It is intended that all such variations within the scope and spirit of the appended claims be embraced thereby.

1. A composition comprising:

a colloid capable of being labeled with a radionuclide;

a radionuclide; and

a layered mixed metal hydroxide having the formula:

$$Li_mD_dT(OH)_{(m+2d+3+na)}A^n_a$$

wherein:

m is 0 to 1;

D is a divalent metal ion of magnesium, calcium, barium, strontium, manganese, iron, cobalt, nickel, copper, or zinc or a mixture thereof;

d is 0 to 4;

provided that both m and d are not 0;

T is a trivalent metal ion of aluminum, gallium, chromium, or iron;

A is a monovalent or polyvalent ion of halide, sulfate, nitrate, phosphate, carbonate, glycolate, lignosulfate, polycarboxylate or polyacrylate;

n is the valence of the anion A;

a is the number of anions A in the formula; and the sum of

$$(m+2d+3+na)$$

is equal to or greater than 3.

2. The composition of Claim 1 wherein the colloid is an iron (II), iron (III), or aluminum hydroxide colloid, bentonite, macroaggregated albumin, ion exchange gel or ion exchange resin.

3. The composition of Claim 2 wherein the colloid is iron (II) hydroxide, iron (III) hydroxide or bentonite.

4. The composition of Claim 1 further comprising an ion exchange medium.

5. The composition of Claim 1 wherein m is 0.5 to 0.75; D is magnesium or calcium, or a mixture thereof; d is 1 to 3; and t is aluminum or iron.

6. The composition of Claim 1 wherein m is 0, D is magnesium, and T is aluminum.

7. The composition of Claim 5 wherein said layered mixed metal hydroxide has the formula:

$$Mg_xAl_y(OH)_zA^n_a$$

wherein:

x is 1 to 3;

y is 1;

z is 3 to 5;

A is a halide, sulfate, phosphate, or carbonate;

n is the valence of A; and

a is 0.1 to 1.0.

8. The composition of Claim 7 wherein x is 1, y is 1, z is 4.7, and a is 0.3.

9. The composition of any one of Claims 1 to 8 wherein the radionuclide is Sm-153, Ho-166, Lu-177, La-140, Gd-159, Yb-175, In-115m, Y-90, Sc-47, Re-186, or Re-188.

10. The composition of Claim 9 wherein the radionuclide is Sm-153 or Ho-166.

11. A process for preparing a stabilized radioactive colloid composition comprising the steps of:

(A) labeling a colloid with a radionuclide, wherein the colloid is an iron (II), iron (III) or aluminum hydroxide colloid, bentonite, macroaggregated albumin, ion exchange gel or ion exchange resin; and

(B) adding to the labeled colloid a layered mixed metal hydroxide; wherein the layered mixed metal hydroxide is represented by the formula

$$Li_mD_dT(OH)_{(m+2d+3+na)}A^n_a$$

wherein:

m is in the range of 0 to approximately 1;

D is a divalent metal ion of magnesium, calcium, barium, strontium, manganese, iron, cobalt, nickel, copper, or zinc or a mixture thereof;

d is 0 to 4;

provided both d and m are not 0;

T is a metal ion of aluminum, gallium, chromium, or iron;

A is a monovalent or polyvalent ion of halide, sulfate, nitrate, phosphate, carbonate, glycolate, lignosulfate, polycarboxylate or polyacrylate;

n is the valence of the anion A;

a is the number of anions A in the formula;

and the sum of (m+2d+3+na) is equal to or greater than 3.

12. The method of Claim 10 wherein:

m is in the range of 0.5 to 0.75;

D is magnesium or calcium, or a mixture thereof;

d is from 1 to 3; and

T is a metal halide, metal sulfate, or metal phosphate.

13. The process of Claim 12 wherein the layered mixed metal hydroxide has the formula:

$$Mg_xAl_y(OH)_zA_a^n$$

wherein:

x is 1 to 3;

y is 1;

z is 3 to 5;

A is a halide, sulfate, phosphate, or carbonate;

n is the valence of A; and

a is approximately 0.1 to 1.0;

wherein the radionuclide is Sm-153, Ho-166, Lu-177, La-140, Gd-159, Yb-175, In-115m, Y-90, Sc-47, Re-186, or Re-188.

14. The process of Claim 13 wherein the radionuclide is Sm-153 or Ho-166

15. A stabilized radioactive colloid composition as defined in any of Claims 1-10 for use as a therapeutic radiation ablation treatment method comprising:

administering to a patient in need of such treatment a therapeutically effective amount of a stabilized radioactive colloid composition wherein the radioactive colloid is defined as claimed in any one of Claims 1-10, with a pharmaceutically acceptable carrier.

16. The use of a stabilized radioactive colloid composition as defined in any of Claims 1-10 as a therapeutic radiation ablation treatment method comprising:

administering to a patient in need of such treatment a therapeutically effective amount of a stabilized radioactive colloid composition wherein the

radioactive colloid is defined as claimed in any one of Claims 1-10, with a pharmaceutically acceptable carrier.

17. The use of Claim 15 or 16 wherein the therapeutic radiation ablation treatment is for treating rheumatoid arthritis.

18. A therapeutic radiation ablation treatment method comprising:

administering to a patient in need of such treatment a therapeutically effective amount of a stabilized radioactive colloid composition wherein the radioactive colloid is defined as claimed in any one of Claims 1-10, with a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US92/01157

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC (5): A61K 49/02
U.S.Cl.: 424/1.1

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
U.S.	424/1.1 252/625

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	US, A, 4,790,954 (BURBA, III ET AL.) 13 December 1988 (See Abstract).	1-18
A	US, A, 4,752,464 (LIEBERMAN ET AL.) 21 June 1988 (See Abstract).	1-18
A	US, A, 4,915,932 (McLAREN ET AL.) 10 April 1990 (See Abstract).	1-18

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
21 April 1992	05 MAY 1992
International Searching Authority	**Signature of Authorized Officer**
ISA/US	Chhaya Sayala

Form PCT/ISA/210 (second sheet) (Rev.11-87)