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(54) **Title:** RARE EARTH METAL COMPOUNDS, METHODS OF MAKING, AND METHODS OF USING THE SAME

(57) **Abstract:** Rare earth metal compounds, particularly lanthanum, cerium, and yttrium, are formed as porous particles and are effective in binding metals, metal ions, and phosphate. A method of making the particles and a method of using the particles is disclosed. The particles may be used in the gastrointestinal tract or the bloodstream to remove phosphate or to treat hyperphosphatemia in mammals. The particles may also be used to remove metals from fluids such as water.

RARE EARTH METAL COMPOUNDS, METHODS OF MAKING, AND METHODS OF USING THE SAME

[0001] The present application claims priority to USSN 60/396,989 filed May 24, 2002, to USSN 60/403,868 filed August 14, 2002, to USSN 60/430,284 filed December 2, 2002, to USSN 60/461,175 filed April 8, 2003, and to USSN 10/444,774 filed May 23, 2003, the entire contents of each is hereby incorporated by reference.

[0002] The present invention relates to rare earth metal compounds, particularly rare earth metal compounds having a porous structure. The present invention also includes methods of making the porous rare earth metal compounds and methods of using the compounds of the present invention. The compounds of the present invention can be used to bind or absorb metals such as arsenic, selenium, antimony and metal ions such as arsenic III^+ and V^+. The compounds of the present invention may therefore find use in water filters or other devices or methods to remove metals and metal ions from fluids, especially water.

[0003] The compounds of the present invention are also useful for binding or absorbing anions such as phosphate in the gastrointestinal tract of mammals. Accordingly, one use of the compounds of the present invention is to treat high serum phosphate levels in patients with end-stage renal disease undergoing kidney dialysis. In this aspect, the compounds may be provided in a filter that is fluidically connected with a kidney dialysis machine such that the phosphate content in the blood is reduced after passing through the filter.

[0004] In another aspect, the compounds can be used to deliver a lanthanum or other rare-earth metal compound that will bind phosphate present in the gut and prevent its transfer into the bloodstream. Compounds of the present invention can also be used to deliver drugs or to act as a filter or absorber in the gastrointestinal tract or in the blood stream. For example, the materials can be used to deliver inorganic chemicals in the gastrointestinal tract or elsewhere.

[0005] It has been found that the porous particle structure and the high surface area are beneficial to high absorption rates of anions. Advantageously, these properties permit the compounds of the present invention to be used to bind phosphate directly in a filtering device fluidically connected with kidney dialysis equipment.

[0006] The use of rare earth hydrated oxides, particularly hydrated oxides of La, Ce, and Y to bind phosphate is disclosed in Japanese published patent application 61-004529 (1986). Similarly, US Pat. No. 5,968,976 discloses a lanthanum carbonate hydrate to remove phosphate in the gastrointestinal tract and to treat hyperphosphatemia in patients with renal failure. It also shows that hydrated lanthanum carbonates with about 3 to 6 molecules of crystal water provide the highest removal rates. US Pat. No. 6,322,895 discloses a form of silicon with micron-sized or nano-sized pores that can be used to release drugs slowly in the body. US Pat. No. 5,782,792 discloses a method for the treatment of rheumatic arthritis where a "protein A immunoadsorbent" is placed on silica or another inert binder in a cartridge to physically remove antibodies from the bloodstream.

[0007] It has now unexpectedly been found that the specific surface area of compounds according to the present invention as measured by the BET method, varies depending on the method of preparation, and has a significant effect on the properties of the product. As a result, the specific properties of the resulting compound can be adjusted by varying one or more parameters in the method of making the compound. In this regard, the compounds of the present invention have a BET specific surface area of at least about 10 m^2/g and may have a BET specific surface area of at least about 20 m^2/g and alternatively may have a BET specific surface area of at least about 35 m^2/g. In one embodiment, the compounds have a BET specific surface area within the range of about 10 m^2/g and about 40 m^2/g.

[0008] It has also been found that modifications in the preparation method of the rare earth compounds will create different entities, e.g. different kinds of hydrated or amorphous oxycarbonates rather than carbonates, and that these compounds have distinct and improved properties. It has also been found that modifications of the preparation method create different porous physical structures with improved properties.

[0009] The compounds of the present invention and in particular, the lanthanum compounds and more particularly the lanthanum oxycarbonates of the present invention exhibit phosphate binding or removal of at least 40% of the initial concentration of phosphate after ten minutes. Desirably, the lanthanum compounds exhibit phosphate binding or removal of at least 60% of the initial concentration of phosphate after ten minutes. In other words, the lanthanum compounds and in particular, the lanthanum compounds and more particularly the lanthanum oxycarbonates of the present invention exhibit a phosphate binding capacity of at least 45 mg of phosphate per gram of lanthanum compound. Suitably, the lanthanum compounds exhibit a phosphate binding capacity of at least 50 mg PO_4/g of lanthanum compound, more suitably, a phosphate binding capacity of at least 75 mg PO_4/g of lanthanum compound. Desirably, the lanthanum compounds exhibit a phosphate binding capacity of at least 100 mg PO_4/g of lanthanum compound, more desirably, a phosphate binding capacity of at least 110 mg PO_4/g of lanthanum compound.

[0010] In accordance with the present invention, rare earth metal compounds, and in particular, rare earth metal oxychlorides and oxycarbonates are provided. The oxycarbonates may be hydrated or anhydrous. These compounds may be produced according to the present invention as particles having a porous structure. The rare earth metal compound particles of the present invention may conveniently be produced within a controllable range of surface areas with resultant variable and controllable adsorption rates of ions.

[0011] The porous particles or porous structures of the present invention are made of nano-sized to micron-sized crystals with controllable surface areas. The rare earth oxychloride is desirably lanthanum oxychloride (LaOCl). The rare earth oxycarbonate hydrate is desirably lanthanum oxycarbonate hydrate ($La_2O(CO_3)_2{\bullet}xH_2O$ where x is from and including 2 to and including 4). This compound will further be referred to in this text as $La_2O(CO_3)_2{\bullet}xH_2O$. The anhydrous rare earth oxycarbonate is desirably lanthanum oxycarbonate $La_2O_2CO_3$ or La_2CO_5 of which several crystalline forms exist. The lower temperature form will be identified as $La_2O_2CO_3$ and the form obtained at higher temperature or after a longer calcination time will be identified as La_2CO_5.

[0012] One skilled in the art, however, will understand that lanthanum oxycarbonate may be present as a mixture of the hydrate and the anhydrous form. In addition, the anhydrous lanthanum oxycarbonate may be present as a mixture of $La_2O_2CO_3$ and La_2CO_5 and may be present in more than a single crystalline form.

[0013] One method of making the rare earth metal compound particles includes making a solution of rare earth metal chloride, subjecting the solution to a substantially total evaporation process using a spray dryer or other suitable equipment to form an intermediate product, and calcining the obtained intermediate product at a temperature between about 500° and about 1200°C. The product of the calcination step may be washed, filtered, and dried to make a suitable finished product. Optionally, the intermediate product may be milled in a horizontal or vertical pressure media mill to a desired surface area and then further spray dried or dried by other means to produce a powder that may be further washed and filtered.

[0014] An alternative method of making the rare earth metal compounds, particularly rare earth metal anhydrous oxycarbonate particles includes making a solution of rare earth metal acetate, subjecting the solution to a substantially total evaporation process using a spray dryer or other suitable equipment to make an intermediate product, and calcining the obtained intermediate product at a temperature between about 400°C and about 700°C. The product of the calcination step may be washed, filtered, and dried to make a suitable finished product. Optionally, the intermediate product may be milled in a horizontal or vertical pressure media mill to a desired surface area, spray dried or dried by other means to produce a powder that may be washed, filtered, and dried.

[0015] Yet another method of making the rare earth metal compounds includes making rare earth metal oxycarbonate hydrate particles. The rare earth metal oxycarbonate hydrate particles can be made by successively making a solution of rare earth chloride, subjecting the solution to a slow, steady feed of a sodium carbonate solution at a temperature between about 30° and about 90°C while mixing, then filtering and washing the precipitate to form a filter cake, then drying the filter cake at a temperature of about 100° to 120°C to produce the desired rare earth oxycarbonate hydrate species. Optionally, the filter cake may be sequentially dried, slurried, and milled in a horizontal or vertical pressure media mill to a desired surface area, spray dried or dried by other means to produce a powder that may be washed, filtered, and dried.

[0016] Alternatively, the process for making rare earth metal oxycarbonate hydrate particles may be modified to produce anhydrous particles. This modification includes subjecting the dried filter cake to a thermal treatment at a specified temperature between about 400°C to about 700°C and for a specified time between 1h and 48h. Optionally, the product of the thermal treatment may be slurried and milled in a horizontal or vertical pressure media mill to a desired surface area, spray dried or dried by other means to produce a powder that may be washed, filtered, and dried.

[0017] In accordance with the present invention, compounds of the present invention may be used to treat patients with hyperphosphatemia. The compounds may be made into a form that may be delivered to a mammal and that may be used to remove phosphate from the gut or decrease phosphate absorption into the blood stream. For example, the compounds may be formulated to provide an orally ingestible form such as a liquid solution or suspension, a tablet, capsule, gelcap, or other suitable and known oral form. Accordingly, the present invention contemplates a method for treating hyperphosphatemia that comprises providing an effective amount of a compound of the present invention. Compounds made under different conditions will correspond to different oxycarbonates or oxychlorides, will have different surface areas, and will show differences in reaction rates with phosphate and different solubilization of lanthanum or another rare-earth metal into the gut. The present invention allows one to modify these properties according to the requirements of the treatment.

[0018] In another aspect of the present invention, compounds made according to this invention as a porous structure of sufficient mechanical strength may be placed in a device fluidically connected to a dialysis machine through which the blood flows, to directly remove phosphate by reaction of the rare-earth compound with phosphate in the bloodstream. The present invention therefore contemplates a device having an inlet and an outlet with one or more compounds of the present invention disposed between the inlet and the outlet. The present invention also contemplates a method of reducing the amount of phosphate in blood that comprises contacting the blood with one or more compounds of the present invention for a time sufficient to reduce the amount of phosphate in the blood.

[0019] In yet another aspect of the present invention, the compounds of the present invention may be used as a substrate for a filter having an inlet and outlet such that the compounds of the present invention are disposed between the inlet and the outlet. A fluid containing a metal, metal ion, phosphate or other ion may be passed from the inlet to contact the compounds of the present invention and through the outlet. Accordingly, in one aspect of the present invention a method of reducing the content of a metal in a fluid, for example water, comprises flowing the fluid through a filter that contains one or more compounds of the present invention to reduce the amount of metal present in the water.

BRIEF DESCRIPTION OF THE DRAWINGS

[0020] FIG. 1 is a general flow sheet of a process according to the present invention that produces LaOCl (lanthanum oxychloride).

[0021] FIG. 2 is a flow sheet of a process according to the present invention that produces a coated titanium dioxide structure.

[0022] FIG. 3 is a flow sheet of a process according to the present invention that produces lanthanum oxycarbonate

[0023] FIG. 4 is a graph showing the percentage of phosphate removed from a solution as a function of time by $LaO(CO_3)_2 \cdot x\ H_2O$, (where x is from and including 2 to and including 4), made according to the process of the present invention, as compared to the percentage of phosphate removed by commercial grade La carbonate $La_2(CO_3)_3 \cdot 4H_2O$ in the same conditions.

[0024] FIG. 5 is a graph showing the amount of phosphate removed from a solution as a function of time per g of a lanthanum compound used as a drug to treat hyperphosphatemia. The drug in one case is $La_2O(CO_3)_2 \cdot x\ H_2O$ (where x is from and including 2 to and including 4), made according to the process of the present invention. In the comparative case the drug is commercial grade La carbonate $La_2(CO_3)_3 \cdot 4H_2O$.

[0025] FIG. 6 is a graph showing the amount of phosphate removed from a solution as a function of time per g of a lanthanum compound used as a drug to treat hyperphosphatemia. The drug in one case is $La_2O_2CO_3$ made according to the process of the present invention. In the comparative case the drug is commercial grade La carbonate $La_2(CO_3)_3 \cdot 4H_2O$.

[0026] FIG. 7 is a graph showing the percentage of phosphate removed as a function of time by $La_2O_2CO_3$ made according to the process of the present invention, as compared to the percentage of phosphate removed by commercial grade La carbonate $La_2(CO_3)_3{\bullet}4H_2O$.

[0027] FIG. 8 is a graph showing a relationship between the specific surface area of the oxycarbonates made following the process of the present invention and the amount of phosphate bound or removed from solution 10 min after the addition of the oxycarbonate.

[0028] FIG. 9 is a graph showing a linear relationship between the specific surface area of the oxycarbonates of this invention and the first order rate constant calculated from the initial rate of reaction of phosphate.

[0029] FIG. 10 is a flow sheet of a process according to the present invention that produces lanthanum oxycarbonate hydrate $La_2(CO_3)_2{\bullet}xH_2O$

[0030] FIG. 11 is a flow sheet of a process according to the present invention that produces anhydrous lanthanum oxycarbonate $La_2O_2CO_3$ or La_2CO_5.

[0031] FIG. 12 is a scanning electron micrograph of lanthanum oxychloride, made following the process of the present invention.

[0032] FIG. 13 is an X-Ray diffraction scan of lanthanum oxychloride LaOCl made according to the process of the present invention and compared with a standard library card of lanthanum oxychloride.

[0033] FIG. 14 is a graph showing the percentage of phosphate removed from a solution as a function of time by LaOCl made according to the process of the present invention, as compared to the amount of phosphate removed by commercial grades of La carbonate $La_2(CO_3)_3{\bullet}H_2O$ and $La_2(CO_3)_3{\bullet}\ 4H_2O$ in the same conditions.

[0034] FIG. 15 shows a scanning electron micrograph of $La_2O(CO_3)_2{\bullet}x\ H_2O$, where x is from and including 2 to and including 4.

[0035] FIG. 16 is an X-Ray diffraction scan of $La_2O(CO_3)_2{\bullet}x\ H_2O$ produced according to the present invention and includes a comparison with a "library standard" of $La_2O(CO_3)_2{\bullet}xH_2O$ where x is from and including 2 to and including 4.

[0036] FIG. 17 is a graph showing the rate of removal of phosphorous from a solution by $La_2O(CO_3)2\bullet xH_2O$ compared to the rate obtained with commercially available $La_2(CO_3)_3\bullet H_2O$ and $La_2(CO_3)_3\bullet 4H_2O$ in the same conditions.

[0037] FIG. 18 is a scanning electron micrograph of anhydrous lanthanum oxycarbonate $La_2O_2CO_3$.

[0038] FIG. 19 is an X-Ray diffraction scan of anhydrous $La_2O_2CO_3$ produced according to the present invention and includes a comparison with a “library standard” of $La_2O_2CO_3$.

[0039] FIG. 20 is a graph showing the rate of phosphorous removal obtained with $La_2O_2CO_3$ made following the process of the present invention and compared to the rate obtained for commercially available $La_2(CO_3)_3\bullet H_2O$ and $La_2(CO_3)_3\bullet 4H_2O$.

[0040] FIG. 21 is a scanning electron micrograph of La_2CO_5 made according to the process of the present invention.

[0041] FIG. 22 is an X-Ray diffraction scan of anhydrous La_2CO_5 produced according to the present invention and includes a comparison with a “library standard” of La_2CO_5.

[0042] FIG. 23 is a graph showing the rate of phosphorous removal obtained with La_2CO_5 made following the process of the present invention and compared to the rate obtained for commercially available $La_2(CO_3)_3\bullet H_2O$ and $La_2(CO_3)_3\bullet 4H_2O$.

[0043] FIG. 24 is a scanning electron micrograph of TiO_2 support material made according to the process of the present invention.

[0044] FIG. 25 is a scanning electron micrograph of a TiO_2 structure coated with LaOCl, made according to the process of the present invention, calcined at 800 °C.

[0045] FIG. 26 is a scanning electron micrograph of a TiO_2 structure coated with LaOCl, made according to the process of the present invention, calcined at 600 °C.

[0046] FIG. 27 is a scanning electron micrograph of a TiO_2 structure coated with LaOCl, made according to the process of the present invention, calcined at 900°C.

[0047] FIG. 28. shows X-Ray scans for TiO_2 coated with LaOCl and calcined at different temperatures following the process of the present invention, and compared to the X-Ray scan for pure LaOCl.

[0048] FIG. 29 shows the concentration of lanthanum in blood plasma as a function of time, for dogs treated with lanthanum oxycarbonates made according to the process of the present invention.

[0049] FIG. 30 shows the concentration of phosphorous in urine as a function of time in rats treated with lanthanum oxycarbonates made according to the process of the present invention, and compared to phosphorus concentration measured in untreated rats.

[0050] FIG. 31 shows a device having an inlet, an outlet, and one or more compounds of the present invention disposed between the inlet and the outlet.

DESCRIPTION OF THE INVENTION

[0051] Referring now to the drawings, the process of the present invention will be described. While the description will generally refer to lanthanum compounds, the use of lanthanum is merely for ease of description and is not intended to limit the invention and claims solely to lanthanum compounds. In fact, it is contemplated that the process and the compounds described in the present specification is equally applicable to rare earth metals other than lanthanum such as Ce and Y.

[0052] Turning now to FIG. 1, a process for making a rare earth oxychloride compound, and, in particular a lanthanum oxychloride compound according to one embodiment of the present invention is shown. First, a solution of lanthanum chloride is provided. The source of lanthanum chloride may be any suitable source and is not limited to any particular source. One source of lanthanum chloride solution is to dissolve commercial lanthanum chloride crystals in water or in an HCl solution. Another source is to dissolve lanthanum oxide in a hydrochloric acid solution.

[0053] The lanthanum chloride solution is evaporated to form an intermediate product. The evaporation 20 is conducted under conditions to achieve substantially total evaporation. Desirably, the evaporation is conducted at a temperature higher than the boiling point of the feed solution (lanthanum chloride) but lower than the temperature where significant crystal growth occurs. The resulting intermediate product may be an amorphous solid formed as a thin film or may have a spherical shape or a shape as part of a sphere.

[0054] The terms “substantially total evaporation” or “substantially complete evaporation” as used in the specification and claims refer to evaporation such that the resulting solid intermediate contains less than 15% free water, desirably less than 10% free water, and more desirably less than 1% free water. The term “free water” is understood and means water that is not chemically bound and can be removed by heating at a temperature below 150°C. After substantially total evaporation or substantially complete evaporation, the intermediate product will have no visible moisture present.

[0055] The evaporation step may be conducted in a spray dryer. In this case, the intermediate product will consist of a structure of spheres or parts of spheres. The spray dryer generally operates at a discharge temperature between about 120°C and about 500°C.

[0056] The intermediate product may then be calcined in any suitable calcination apparatus 30 by raising the temperature to a temperature between about 500°C to about 1200°C for a period of time from about 2 to about 24 h and then cooling to room temperature. The cooled product may be washed 40 by immersing it in water or dilute acid, to remove any water-soluble phase that may still be present after the calcination step 30.

[0057] The temperature and the length of time of the calcination process may be varied to adjust the particle size and the reactivity of the product. The particles resulting from calcination generally have a size between 1 and 1000 μm. The calcined particles consist of individual crystals, bound together in a structure with good physical strength and a porous structure. The individual crystals forming the particles generally have a size between 20 nm and 10 μm.

[0058] In accordance with another embodiment of the present invention as shown in FIG. 2, a feed solution of titanium chloride or titanium oxychloride is provided by any suitable source. One source is to dissolve anhydrous titanium chloride in water or in a hydrochloric acid solution. Chemical control agents or additives 104 may be introduced to this feed solution to influence the crystal form and the particle size of the final product. One chemical additive is sodium phosphate Na_3PO_4. The feed solution of titanium chloride or titanium oxychloride is mixed with the optional chemical control agent 104 in a suitable mixing step 110. The mixing may be conducted using any suitable known mixer.

[0059] The feed solution is evaporated to form an intermediate product, which in this instance is titanium dioxide (TiO_2). The evaporation 120 is conducted at a temperature higher than the boiling point of the feed solution but lower than the temperature where significant crystal growth occurs and to achieve substantially total evaporation. The resulting intermediate product may desirably be an amorphous solid formed as a thin film and may have a spherical shape or a shape as part of a sphere.

[0060] The intermediate product may then be calcined in any suitable calcination apparatus 130 by raising the temperature to a temperature between about 400°C to about 1200°C for a period of time from about 2 to about 24 h and then cooling to room temperature (25°C). The cooled product is then washed 140 by immersing it in water or dilute acid, to remove traces of any water-soluble phase that may still be present after the calcination step.

[0061] The method of manufacture of the intermediate product according to the present invention can be adjusted and chosen to make a structure with the required particle size and porosity. For example, the evaporation step 120 and the calcination step 130 can be adjusted for this purpose. The particle size and porosity can be adjusted to make the structure of the intermediate product suitable to be used as an inert filter in the bloodstream.

[0062] The washed TiO_2 product is then suspended or slurried in a solution of an inorganic compound. A desirable inorganic compound is a rare-earth or lanthanum compound, and in particular lanthanum chloride. This suspension of TiO_2 in the inorganic compound solution is again subjected to total evaporation 160 under conditions in the same range as defined in step 120 and to achieve substantially total evaporation. In this regard, the evaporation steps 120 and 160 may be conducted in a spray drier. The inorganic compound will precipitate as a salt, an oxide, or an oxy-salt. If the inorganic compound is lanthanum chloride, the precipitated product will be lanthanum oxychloride. If the original compound is lanthanum acetate, the precipitated product will be lanthanum oxide.

[0063] The product of step 160 is further calcined 170 at a temperature between 500° and 1100 °C for a period of 2 to 24 h. The temperature and the time of the calcination process influence the properties and the particle size of the product. After the second calcination step 170, the product may be washed 180.

[0064] The resulting product can be described as crystals of lanthanum oxychloride or lanthanum oxide formed on a TiO_2 substrate. The resulting product may be in the form of hollow thin-film spheres or parts of spheres. The spheres will have a size of about 1 μm to 1000 μm and will consist of a structure of individual bound particles. The individual particles have a size between 20 nm and 10 μm.

[0065] When the final product consists of crystals of lanthanum oxychloride on a TiO_2 substrate, these crystals may be hydrated. It has been found that this product will effectively react with phosphate and bind it as an insoluble compound. It is believed that, if this final product is released in the human stomach and gastrointestinal tract, the product will bind the phosphate that is present and decrease the transfer of phosphate from the stomach and gastrointestinal tract to the blood stream. Therefore, the product of this invention may be used to limit the phosphorous content in the bloodstream of patients on kidney dialysis.

[0066] According to another embodiment of the present invention, a process for making anhydrous lanthanum oxycarbonate is shown in FIG. 3. In this process, a solution of lanthanum acetate is made by any method. One method to make the lanthanum acetate solution is to dissolve commercial lanthanum acetate crystals in water or in an HCl solution.

[0067] The lanthanum acetate solution is evaporated to form an intermediate product. The evaporation 220 is conducted at a temperature higher than the boiling point of the lanthanum acetate solution but lower than the temperature where significant crystal growth occurs and under conditions to achieve substantially total evaporation. The resulting intermediate product may desirably be an amorphous solid formed as a thin film and may have a spherical shape or a shape as part of a sphere.

[0068] The intermediate product may then be calcined in any suitable calcination apparatus 230 by raising the temperature to a temperature between about 400°C to about 800°C for a period of time from about 2 to about 24 h and then cooled to room temperature. The cooled product may be washed 240 by immersing it in water or dilute acid, to remove any water-soluble phase that may still be present after the calcination step. The temperature and the length of time of the calcination process may be varied to adjust the particle size and the reactivity of the product.

[0069] The particles resulting from the calcination generally have a size between 1 and 1000 μm. The calcined particles consist of individual crystals, bound together in a structure with good physical strength and a porous structure. The individual crystals generally have a size between 20 nm and 10 μm.

[0070] The products made by methods shown in FIGs. 1, 2, and 3 comprise ceramic particles with a porous structure. Individual particles are in the micron size range. The particles are composed of crystallites in the nano-size range, fused together to create a structure with good strength and porosity.

[0071] The particles made according to the process of the present invention, have the following common properties:

a. They have low solubility in aqueous solutions, especially serum and gastro-intestinal fluid, compared to non-ceramic compounds.

b. Their hollow shape gives them a low bulk density compared to solid particles. Lower density particles are less likely to cause retention in the gastro-intestinal tract.

c. They have good phosphate binding kinetics. The observed kinetics are generally better than the commercial carbonate hydrates $La_2(CO_3)_3{\bullet}H_2O$ and $La_2(CO_3)_3{\bullet}4H_2O$. In the case of lanthanum oxychloride, the relationship between the amount of phosphate bound or absorbed and time tends to be closer to linear than for commercial hydrated lanthanum carbonates. The initial reaction rate is lower but does not significantly decrease with time over an extended period. This behavior is defined as linear or substantially linear binding kinetics. This is probably an indication of more selective phosphate binding in the presence of other anions.

d. Properties a, b, and c, above are expected to lead to less gastro-intestinal tract complications than existing products.

e. Because of their particular structure and low solubility, the products of the present invention have the potential to be used in a filtration device placed directly in the bloodstream.

[0072] Different lanthanum oxycarbonates have been prepared by different methods. It has been found that, depending on the method of preparation, lanthanum oxycarbonate compounds with widely different reaction rates are obtained.

[0073] A desirable lanthanum oxycarbonate is $La_2O(CO_3)_2{\bullet}xH_2O$, where $2 \leq x \leq 4$. This lanthanum oxycarbonate is preferred because it exhibits a relatively high rate of removal of phosphate. To determine the reactivity of the lanthanum oxycarbonate compound with respect to phosphate, the following procedure was used. A stock solution containing 13.75 g/l of anhydrous Na_2HPO_4 and 8.5 g/l of HCl is prepared. The stock solution is adjusted to pH 3 by the addition of concentrated HCl. 100 ml of the stock solution is placed in a beaker with a stirring bar. A sample of lanthanum oxycarbonate powder is added to the solution. The amount of lanthanum oxycarbonate powder is such that the amount of La in suspension is 3 times the stoichiometric amount needed to react completely with the phosphate. Samples of the suspension are taken at intervals, through a filter that separated all solids from the liquid. The liquid sample is analyzed for phosphorous. FIG. 4 shows that after 10 min, $La_2O(CO_3)_2{\bullet}xH_2O$ has removed 86% of the phosphate in solution, whereas a commercial hydrated La carbonate $La_2(CO_3)_3{\bullet}4H_2O$ removes only 38% of the phosphate in the same experimental conditions after the same time.

[0074] FIG. 5 shows that the $La_2O(CO_3)_2{\bullet}xH_2O$ depicted in Fig. 4 has a capacity of phosphate removal of 110 mg PO_4 removed/g of La compound after 10 min in the conditions described above, compared to 45 mg PO_4/g for the commercial La carbonate taken as reference.

[0075] Another preferred lanthanum carbonate is the anhydrous La oxycarbonate $La_2O_2CO_3$. This compound is preferred because of its particularly high binding capacity for phosphate, expressed as mg PO_4 removed/ g of compound. FIG. 6

shows that $La_2O_2CO_3$ binds 120 mg PO_4/g of La compound after 10 min, whereas $La_2(CO_3)_3{\cdot}4H_2O$ used as reference only binds 45 mg PO_4/g La compound.

[0076] Fig. 7 shows the rate of reaction with phosphate of the oxycarbonate $La_2O_2CO_3$. After 10 min of reaction, 73% of the phosphate had been removed, compared to 38% for commercial lanthanum carbonate used as reference.

[0077] Samples of different oxycarbonates have been made by different methods as shown in Table 1 below.

Table 1

Sample	Compound	Example number corresponding to manufacturing method	BET surface area m^2/g	Fraction of PO_4 remaining after 10 min	Initial 1st order rate constant k_1 (min^{-1})
1	$La_2O(CO_3)_2{\cdot}xH_2O$	11	41.3	0.130	0.949
2	$La_2O(CO_3)_2{\cdot}xH2O$	11	35.9	0.153	0.929
3	$La_2O(CO_3)_2{\cdot}xH_2O$	11	38.8	0.171	0.837
4	La_2CO_5 (4 h milling)	7	25.6	0.275	0.545
5	$La_2O_2CO_3$	5	18	0.278	0.483
6	La_2CO_5 (2 h milling)	7	18.8	0.308	0.391
7	$La_2O_2CO_3$	7	16.5	0.327	0.36
8	La_2CO_5 (no milling)	5	11.9	0.483	0.434
9	$La_2(CO_3)_3{\cdot}4H_2O$	commercial sample	4.3	0.623	0.196
10	$La_2(CO_3)_3{\cdot}1H_2O$	commercial	2.9	0.790	0.094

[0078] For each sample, the surface area measured by the BET method and the fraction of phosphate remaining after 10 min of reaction have been tabulated. The table also shows the rate constant k_1 corresponding to the initial rate of reaction of phosphate, assuming the reaction is first order in phosphate concentration. The rate constant k_1 is defined by the following equation:

$$d[PO_4]/dt = - k_1 [PO_4]$$

where $[PO_4]$ is the phosphate concentration in solution (mol/liter), t is time (min) and k_1 is the first order rate constant (min^{-1}). The table gives the rate constant for the initial reaction rate, i.e. the rate constant calculated from the experimental points for the first minute of the reaction.

[0079] FIG. 8 shows that there is a good correlation between the specific surface area and the amount of phosphate reacted after 10 min. It appears that in this series of tests, the most important factor influencing the rate of reaction is the surface area, independently of the composition of the oxycarbonate or the method of manufacture. A high surface area can be achieved by adjusting the manufacturing method or by milling a manufactured product.

[0080] FIG. 9 shows that a good correlation is obtained for the same compounds by plotting the first order rate constant as given in Table I and the BET specific surface area. The correlation can be represented by a straight line going through the origin. In other words, within experimental error, the initial rate of reaction appears to be proportional to the phosphate concentration and also to the available surface area.

[0081] Without being bound by any theory, it is proposed that the observed dependence on surface area and phosphate concentration may be explained by a nucleophilic attack of the phosphate ion on the La atom in the oxycarbonate, with resultant formation of lanthanum phosphate $LaPO_4$. For example, if the oxycarbonate is $La_2O_2CO_3$, the reaction will be:

$$\tfrac{1}{2} La_2O_2CO_3 + PO_4^{3-} + 2H_2O \rightarrow LaPO_4 + \tfrac{1}{2} H_2CO_3 + 3OH^-$$

If the rate is limited by the diffusion of the PO_4^{3-} ion to the surface of the oxycarbonate and the available area of oxycarbonate, the observed relationship expressed in FIG. 9 can be explained. This mechanism does not require La to be present as a dissolved species. The present reasoning also provides an explanation for the decrease of the reaction rate after the first minutes: the formation of lanthanum phosphate on the surface of the oxycarbonate decreases the area available for reaction.

[0082] In general, data obtained at increasing pH show a decrease of the reaction rate. This may be explained by the decrease in concentration of the hydronium ion (H_3O^+), which may catalyze the reaction by facilitating the formation of the carbonic acid molecule from the oxycarbonate.

[0083] Turning now to FIG. 10, another process for making lanthanum oxycarbonate and in particular, lanthanum oxycarbonate tetra hydrate, is shown. First, an aqueous solution of lanthanum chloride is made by any method. One method to make the solution is to dissolve commercial lanthanum chloride crystals in water or in an HCl solution. Another method to make the lanthanum chloride solution is to dissolve lanthanum oxide in a hydrochloric acid solution.

[0084] The $LaCl_3$ solution is placed in a well-stirred tank reactor. The $LaCl_3$ solution is then heated to 80°C. A previously prepared analytical grade sodium carbonate is steadily added over a period of 2 hours with vigorous mixing. The mass of sodium carbonate required is calculated at 6 moles of sodium carbonate per 2 moles of $LaCl_3$. When the required mass of sodium carbonate solution is added, the resultant slurry or suspension is allowed to cure for 2 hours at 80°C. The suspension is then filtered and washed with demineralized water to produce a clear filtrate. The filter cake is placed in a convection oven at 105° C for 2 hours or until a stable weight is observed. The initial pH of the $LaCl_3$ solution is 2, while the final pH of the suspension after cure is 5.5. A white powder is produced. The resultant powder is a lanthanum oxycarbonate four hydrate ($La_2O(CO_3)_2{\bullet}xH_2O$). The number of water molecules in this compound is approximate and may vary between 2 and 4 (and including 2 and 4).

[0085] Turning now to FIG. 11 another process for making anhydrous lanthanum oxycarbonate is shown. First, an aqueous solution of lanthanum chloride is made by any method. One method to make the solution is to dissolve commercial lanthanum chloride crystals in water or in an HCl solution. Another method to make the lanthanum chloride solution is to dissolve lanthanum oxide in a hydrochloric acid solution.

[0086] The $LaCl_3$ solution is placed in a well-stirred tank reactor. The $LaCl_3$ solution is then heated to 80°C. A previously prepared analytical grade sodium carbonate is steadily added over 2 hours with vigorous mixing. The mass of sodium carbonate required is calculated at 6 moles of sodium carbonate per 2 moles of $LaCl_3$. When the required mass of sodium carbonate solution is added the resultant slurry or suspension is allowed to cure for 2 hours at 80°C. The suspension is then washed and filtered removing NaCl (a byproduct of the reaction) to produce a clear filtrate. The filter cake is placed in a convection oven at 105°C for 2 hours or until a stable weight is observed. The initial pH of the $LaCl_3$ solution is 2.2, while the final pH of the suspension after cure is 5.5. A white lanthanum oxycarbonate hydrate powder is produced. Next the lanthanum oxycarbonate hydrate is placed in an alumina tray, which is placed in a high temperature muffle furnace. The white powder is heated to 500°C and held at that temperature for 3 hours. Anhydrous $La_2C_2O_3$ is formed.

[0087] Alternatively, the anhydrous lanthanum oxycarbonate formed as indicated in the previous paragraph may be heated at 500 °C for 15 to 24 h instead of 3h or at 600 °C instead of 500 °C. The resulting product has the same chemical formula, but shows a different pattern in an X-Ray diffraction scan and exhibits a higher physical strength and a lower surface area. The product corresponding to a higher temperature or a longer calcination time is defined here as La_2CO_5.

[0088] Turning now to FIG. 31, a device 500 having an inlet 502 and an outlet 504 is shown. The device 500 may be in the form of a filter or other suitable container. Disposed between the inlet 502 and the outlet 504 is a substrate 506 in the form of a plurality of one or more compounds of the present invention. The device may be fluidically connected to a dialysis machine through which the blood flows, to directly remove phosphate by reaction of the rare-earth compound with phosphate in the bloodstream. In this connection, the present invention also contemplates a method of reducing the amount of phosphate in blood that comprises contacting the blood with one or more compounds of the present invention for a time sufficient to reduce the amount of phosphate in the blood.

[0089] In yet another aspect of the present invention, the device 500 may be provided in a fluid stream so that a fluid containing a metal, metal ion, phosphate or other ion may be passed from the inlet 502 through the substrate 506 to contact the compounds of the present invention and out the outlet 504. Accordingly, in one aspect of the present invention a method of reducing the content of a metal in a fluid, for example water, comprises flowing the fluid through a device 500 that contains one or more compounds of the present invention to reduce the amount of metal present in the water.

[0090] The following examples are meant to illustrate but not limit the present invention.

EXAMPLE 1

[0091] An aqueous solution containing 100 g/l of La as lanthanum chloride is injected in a spray dryer with an outlet temperature of 250 °C. The intermediate product corresponding to the spray-drying step is recovered in a bag filter. This intermediate product is calcined at 900°C for 4 hours. FIG. 12 shows a scanning electron micrograph of the product, enlarged 25,000 times. The micrograph shows a porous structure formed of needle-like particles. The X-Ray diffraction pattern of the product (FIG. 13) shows that it consists of lanthanum oxychloride LaOCl.

[0092] To determine the reactivity of the lanthanum compound with respect to phosphate, the following test was conducted. A stock solution containing 13.75 g/l of anhydrous Na_2HPO_4 and 8.5 g/l of HCl was prepared. The stock solution was adjusted to pH 3 by the addition of concentrated HCl. An amount of 100 ml of the stock solution was placed in a beaker with a stirring bar. The lanthanum oxychloride from above was added to the solution to form a suspension. The amount of lanthanum oxychloride was such that the amount of La in suspension was 3 times the stoichiometric amount needed to react completely with the phosphate. Samples of the suspension were taken at time intervals, through a filter that separated all solids from the liquid. The liquid sample was analyzed for phosphorous. FIG. 14 shows the rate of phosphate removed from solution.

EXAMPLE 2 (Comparative example)

[0093] To determine the reactivity of a commercial lanthanum with respect to phosphate, the relevant portion of Example 1 was repeated under the same conditions, except that commercial lanthanum carbonate $La_2(CO_3)_3{\cdot}H_2O$ and $La_2(CO_3)_3{\bullet}4H_2O$ was used instead of the lanthanum oxychloride of the present invention. Additional curves on FIG. 14 show the rate of removal of phosphate corresponding to commercial lanthanum carbonate $La_2(CO_3)_3{\cdot}H2O$ and $La_2(CO_3){\bullet}4H_2O$. FIG. 14 shows that the rate of removal of phosphate with the commercial lanthanum carbonate is faster at the beginning but slower after about 3 minutes.

EXAMPLE 3

[0094] An aqueous HCl solution having a volume of 334.75 ml and containing $LaCl_3$ (lanthanum chloride) at a concentration of 29.2 wt % as La_2O_3 was added to a four liter beaker and heated to 80°C with stirring. The initial pH of the $LaCl_3$ solution was 2.2. Two hundred and sixty five ml of an aqueous solution containing 63.59 g of sodium carbonate (Na_2CO_3) was metered into the heated beaker using a small pump at a steady flow rate for 2 hours. Using a Buchner filtering apparatus fitted with filter paper, the filtrate was separated from the white powder product. The filter cake was mixed four times with 2 liters of distilled water and filtered to wash away the NaCl formed during the reaction. The washed filter cake was placed into a convection oven set at 105° C for 2 hours, or until a stable weight was observed. FIG. 15 shows a scanning electron micrograph of the product, enlarged 120,000 times. The micrograph shows the needle-like structure of the compound. The X-Ray diffraction pattern of the product (FIG. 16) shows that it consists of hydrated lanthanum oxycarbonate hydrate ($La_2O(CO_3)_2 \cdot xH_2O$), with $2 \leq x \leq 4$.

[0095] To determine the reactivity of the lanthanum compound with respect to phosphate, the following test was conducted. A stock solution containing 13.75 g/l of anhydrous Na_2HPO_4 and 8.5 g/l of HCl was prepared. The stock solution was adjusted to pH 3 by the addition of concentrated HCl. An amount of 100 ml of the stock solution was placed in a beaker with a stirring bar. Lanthanum oxycarbonate hydrate powder made as described above was added to the solution. The amount of lanthanum oxycarbonate hydrate powder was such that the amount of La in suspension was 3 times the stoichiometric amount needed to react completely with the phosphate. Samples of the suspension were taken at time intervals through a filter that separated all solids from the liquid. The liquid sample was analyzed for phosphorous. FIG. 17 shows the rate of phosphate removed from solution.

EXAMPLE 4 (Comparative example)

[0096] To determine the reactivity of a commercial lanthanum with respect to phosphate, the second part of Example 3 was repeated under the same conditions, except that commercial lanthanum carbonate $La_2(CO_3)_3 \cdot H_2O$ and $La_2(CO_3)_3 \cdot 4H_2O$ was used instead of the lanthanum oxychloride of the present invention. FIG. 17 shows the rate of phosphate removed using the commercial lanthanum carbonate $La_2(CO_3)3{\bullet}H_2O$ and $La_2(CO_3)_3{\bullet}4H_2O$. FIG. 17 shows that the rate of removal of phosphate with the lanthanum oxycarbonate is faster than with the commercial lanthanum carbonate hydrate ($La_2(CO_3)_3{\bullet}H_2O$ and $La_2(CO_3)_3{\bullet}4H_2O$).

EXAMPLE 5

[0097] An aqueous HCl solution having a volume of 334.75 ml and containing $LaCl_3$ (lanthanum chloride) at a concentration of 29.2 wt % as La_2O_3 was added to a 4 liter beaker and heated to 80°C with stirring. The initial pH of the $LaCl_3$ solution was 2.2. Two hundred and sixty five ml of an aqueous solution containing 63.59 g of sodium carbonate (Na_2CO_3) was metered into the heated beaker using a small pump at a steady flow rate for 2 hours. Using a Buchner filtering apparatus fitted with filter paper the filtrate was separated from the white powder product. The filter cake was mixed four times with 2 liters of distilled water and filtered to wash away the NaCl formed during the reaction. The washed filter cake was placed into a convection oven set at 105°C for 2 hours until a stable weight was observed. Finally, the lanthanum oxycarbonate was placed in an alumina tray in a muffle furnace. The furnace temperature was ramped to 500°C and held at that temperature for 3 hours. The resultant product was determined to be anhydrous lanthanum oxycarbonate $La_2O_2CO_3$.

[0098] The process was repeated three times. In one case, the surface area of the white powder was determined to be 26.95 m^2/gm. In the other two instances, the surface area and reaction rate is shown in Table 1. FIG. 18 is a scanning electron micrograph of the structure, enlarged 60,000 times. The micrograph shows that the structure in this compound is made of equidimensional or approximately round particles of about 100 nm in size. FIG. 19 is an X-ray diffraction pattern showing that the product made here is an anhydrous lanthanum oxycarbonate written as $La_2O_2CO_3$.

[0099] To determine the reactivity of this lanthanum compound with respect to phosphate, the following test was conducted. A stock solution containing 13.75 g/l of anhydrous Na_2HPO_4 and 8.5 g/l of HCl was prepared. The stock solution was adjusted to pH 3 by the addition of concentrated HCl. An amount of 100 ml of the stock solution was placed in a beaker with a stirring bar. Anhydrous lanthanum oxycarbonate made as described above, was added to the solution. The amount of anhydrous lanthanum oxycarbonate was such that the amount of La in suspension was 3 times the stoichiometric amount needed to react completely with the phosphate. Samples of the suspension were taken at intervals, through a filter that separated all solids from the liquid. The liquid sample was analyzed for phosphorous. FIG. 20 shows the rate of phosphate removed.

EXAMPLE 6 (Comparative example)

[00100] To determine the reactivity of a commercial lanthanum with respect to phosphate, the second part of Example 5 was repeated under the same conditions, except that commercial lanthanum carbonate $La_2(CO_3)_3{\bullet}H_2O$ and $La_2(CO_3)_3{\bullet}4H_2O$ was used instead of the $La_2O_2CO_3$ of the present invention. FIG. 20 shows the rate of removal of phosphate using the commercial lanthanum carbonate $La_2(CO_3)_3{\bullet}H_2O$ and $La_2(CO_3)_3{\bullet}4H_2O$. FIG. 20 shows that the rate of removal of phosphate with the anhydrous lanthanum oxycarbonate produced according to the process of the present invention is faster than the rate observed with commercial lanthanum carbonate hydrate $La_2(CO_3)_3{\bullet}H_2O$ and $La_2(CO_3)_3{\bullet}4H_2O$.

EXAMPLE 7

[00101] A solution containing 100 g/l of La as lanthanum acetate is injected in a spray-drier with an outlet temperature of 250°C. The intermediate product corresponding to the spray-drying step is recovered in a bag filter. This intermediate product is calcined at 600°C for 4 hours. FIG. 21 shows a scanning electron micrograph of the product, enlarged 80,000 times. FIG. 22 shows the X-Ray diffraction pattern of the product and it shows that it consists of anhydrous lanthanum oxycarbonate. The X-Ray pattern is different from the pattern corresponding to Example 5, even though the chemical composition of the compound is the same. The formula for this compound is written as (La_2CO_5). Comparing FIGS. 21 and 18 shows that the compound of the present example shows a structure of leaves and needles as opposed to the round particles formed in Example 5. The particles may be used in a device to directly remove phosphate from an aqueous or non-aqueous medium, e.g., the gut or the bloodstream.

[00102] To determine the reactivity of the lanthanum compound with respect to phosphate, the following test was conducted. A stock solution containing 13.75 g/l of anhydrous Na_2HPO_4 and 8.5 g/l of HCl was prepared. The stock solution was adjusted to pH 3 by the addition of concentrated HCl. An amount of 100 ml of the stock solution was placed in a beaker with a stirring bar. La_2CO_5 powder, made as described above, was added to the solution. The amount of lanthanum oxycarbonate was such that the amount of La in suspension was 3 times the stoichiometric amount needed to react completely with the phosphate. Samples of the suspension were taken at intervals through a filter that separated all solids from the liquid. The liquid sample was analyzed for phosphorous. FIG. 23 shows the rate of phosphate removed from solution.

EXAMPLE 8 (Comparative example)

[00103] To determine the reactivity of a commercial lanthanum with respect to phosphate commercial lanthanum carbonate $La_2(CO_3)_3 \bullet H_2O$ and $La_2(CO_3)_3 \bullet 4H_2O$ was used instead of the lanthanum oxycarbonate made according to the present invention as described above. FIG. 23 shows the rate of phosphate removal for the commercial lanthanum carbonate $La_2(CO_3)_3 \bullet H_2O$ and $La_2(CO_3)_3 \bullet 4H_2O$. FIG. 23 also shows that the rate of phosphate removal with the lanthanum oxycarbonate is faster than the rate of phosphate removal with commercial lanthanum carbonate hydrate $La_2(CO_3)_3 \bullet H_2O$ and $La_2(CO_3)_3 \bullet 4H_2O$.

EXAMPLE 9

[00104] To a solution of titanium chloride or oxychloride containing 120 g/l Ti and 450 g/l Cl is added the equivalent of 2.2 g/l of sodium phosphate Na_3PO_4. The solution is injected in a spray dryer with an outlet temperature of 250 °C. The spray dryer product is calcined at 1050 °C for 4 h. The product is subjected to two washing steps in 2 molar HCl and to two washing steps in water. FIG. 24 is a scanning electron micrograph of the TiO_2 material obtained. It shows a porous structure with individual particles of about 250 nm connected in a structure. This structure shows good mechanical strength. This material can be used as an inert filtering material in a fluid stream such as blood.

EXAMPLE 10

[00105] The product of Example 9 is re-slurried into a solution of lanthanum chloride containing 100 g/l La. The slurry contains approximately 30% TiO_2 by weight. The slurry is spray dried in a spray dryer with an outlet temperature of 250° C. The product of the spray drier is further calcined at 800° C for 5 h. It consists of a porous TiO_2 structure with a coating of nano-sized lanthanum oxychloride. FIG. 25 is a scanning electron micrograph of this coated product. The electron micrograph shows that the TiO_2 particles are several microns in size. The LaOCl is present as a crystallized deposit with elongated crystals, often about 1 μm long and 0.1 μm across, firmly attached to the TiO_2 catalyst support surface as a film of nano-size thickness. The LaOCl growth is controlled by the TiO_2 catalyst support structure. Orientation of rutile crystals works as a template for LaOCl crystal growth. The particle size of the deposit can be varied from the nanometer to the micron range by varying the temperature of the second calcination step.

[00106] FIG. 26 is a scanning electron micrograph corresponding to calcination at 600° C instead of 800° C. It shows LaOCl particles that are smaller and less well attached to the TiO_2 substrate. FIG. 27 is a scanning electron micrograph corresponding to calcination at 900°C instead of 800 °C. The product is similar to the product made at 800° C, but the LaOCl deposit is present as somewhat larger crystals and more compact layer coating the TiO2 support crystals. FIG. 28 shows the X-Ray diffraction patterns corresponding to calcinations at 600°, 800° and 900° C. The figure also shows the pattern corresponding to pure LaOCl. The peaks that do not appear in the pure LaOCl pattern correspond to rutile TiO_2. As the temperature increases, the peaks tend to become higher and narrower, showing that the crystal size of the LaOCl as well as TiO_2 increases with the temperature.

EXAMPLE 11

[00107] An aqueous HCl solution having a volume of 334.75 ml and containing $LaCl_3$ (lanthanum chloride) at a concentration of 29.2 wt % as La_2O_3 was added to a 4 liter beaker and heated to 80°C with stirring. The initial pH of the $LaCl_3$ solution was 2.2. Two hundred and sixty five ml of an aqueous solution containing 63.59 g of sodium carbonate (Na_2CO_3) was metered into the heated beaker using a small pump at a steady flow rate for 2 hours. Using a Buchner filtering apparatus fitted with filter paper the filtrate was separated from the white powder product. The filter cake was mixed four times, each with 2 liters of distilled water and filtered to wash away the NaCl formed during the reaction. The washed filter cake was placed into a convection oven set at 105 °C for 2 hours or until a stable weight was observed. The X-Ray diffraction pattern of the product shows that it consists of hydrated lanthanum oxycarbonate $La_2O(CO_3)_2 \cdot xH_2O$, where $2 \leq x \leq 4$. The surface area of the product was determined by the BET method. The test was repeated 3 times and slightly different surface areas and different reaction rates were obtained as shown in Table 1.

EXAMPLE 12

[00108] Six adult beagle dogs were dosed orally with capsules of lanthanum oxycarbonate $La_2O(CO_3)_2 \bullet xH_2O$ (compound A) or $La_2O_2CO_3$ (compound B) in a cross-over design using a dose of 2250 mg elemental lanthanum twice daily (6 hours apart). The doses were administered 30 minutes after provision of food to the animals. At least 14 days washout was allowed between the crossover arms. Plasma was obtained pre-dose and 1.5, 3, 6, 7.5, 9, 12, 24, 36, 48, 60, and 72 hours after dosing and analyzed for lanthanum using ICP-MS. Urine was collected by catheterization before and approximately 24 hours after dosing and creatinine and phosphorus concentrations measured.

[00109] The tests led to reduction of urine phosphate excretion, a marker of phosphorous binding. Values of phosphate excretion in urine are shown in Table 2 below.

Table 2

La Oxycarbonate compound	Median phosphorus/creatinine ratio (% reduction compared to pre-dose value)	10^{th} and 90^{th} percentiles
A	48.4%	22.6-84.4%
B	37.0%	-4.1-63.1%

Plasma lanthanum exposure: Overall plasma lanthanum exposure in the dogs is summarized in Table 3 below. The plasma concentration curves are shown in FIG. 29.

Table 3

La oxycarbonate compound tested	Mean (sd) Area Under the $Curve_{0\text{-}72h}$ (ng.h/mL); (standard deviation)	Maximum concentration C_{max} (ng/mL); (standard deviation)
A	54.6 (28.0)	2.77 (2.1)
B	42.7 (34.8)	2.45 (2.2)

EXAMPLE 13 – First *in vivo* study in rats

[00110] Groups of six adult Sprague-Dawley rats underwent 5/6th nephrectomy in two stages over a period of 2 weeks and were then allowed to recover for a further two weeks prior to being randomized for treatment. The groups received vehicle (0.5% w/v carboxymethyl cellulose), or lanthanum oxycarbonate A or B suspended in vehicle, once daily for 14 days by oral lavage (10ml/kg/day). The dose delivered 314 mg elemental lanthanum/kg/day. Dosing was carried out immediately before the dark (feeding) cycle on each day. Urine samples (24 hours) were collected prior to surgery, prior to the commencement of treatment, and twice weekly during the treatment period. Volume and phosphorus concentration were measured.

[00111] Feeding – During the acclimatization and surgery period, the animals were given Teklad phosphate sufficient diet (0.5% Ca, 0.3%P; Teklad No. TD85343), ad libitum. At the beginning of the treatment period, animals were pair fed based upon the average food consumption of the vehicle-treated animals the previous week.

[00112] 5/6 Nephrectomy – After one week of acclimatization, all animals were subjected to 5/6 nephrectomy surgery. The surgery was performed in two stages. First, the two lower branches of the left renal artery were ligated. One week later, a right nephrectomy was performed. Prior to each surgery, animals were anesthetized with an intra-peritoneal injection of ketamine/xylazine mixture (Ketaject a 100mg/ml and Xyla-ject at 20mg/ml) administered at 10 ml/kg. After each surgery, 0.25 mg/kg Buprenorphine was administered for relief of post-surgical pain. After surgery, animals were allowed to stabilize for 2 weeks to beginning treatment.

[00113] The results showing urine phosphorus excretion are given in FIG. 30. The results show a decrease in phosphorus excretion, a marker of dietary phosphorus binding, after administration of the lanthanum oxycarbonate (at time > 0), compared to untreated rats.

EXAMPLE 14: Second *in vivo* study in rats

[00114] Six young adult male Sprague-Dawley rats were randomly assigned to each group. Test items were lanthanum oxycarbonates $La_2O_2CO_3$ and La_2CO_5 (compound B and compound C), each tested at 0.3 and 0.6% of diet. There was an additional negative control group receiving Sigmacell cellulose in place of the test item.

[00115] The test items were mixed thoroughly into Teklad 7012CM diet. All groups received equivalent amounts of dietary nutrients.

[00116] Table 4 outlines the dietary composition of each group:

Table 4

Group ID	Treatment	Test Item	Sigmacell cellulose	Teklad Diet
I	Negative control	0.0%	1.2%	98.8%
II	Compound B – Mid level	0.3%	0.9%	98.8%
III	Compound B – High level	0.6%	0.6%	98.8%
IV	Compound C – Mid level	0.3%	0.9%	98.8%
V	Compound C – High level	0.6%	0.6%	98.8%

[00117] Rats were maintained in the animal facility for at least five days prior to use, housed individually in stainless steel hanging cages. On the first day of testing, they were placed individually in metabolic cages along with their test diet. Every 24 hours, their output of urine and feces was measured and collected and their general health visually assessed. The study continued for 4 days. Food consumption for each day of the study was recorded. Starting and ending animal weights were recorded.

[00118] Plasma samples were collected via retro-orbital bleeding from the control (I) and high-dose oxycarbonate groups, III and V. The rats were then euthanized with CO_2 in accordance with the IACUC study protocol.

[00119] Urine samples were assayed for phosphorus, calcium, and creatinine concentration in a Hitachi 912 analyzer using Roche reagents. Urinary excretion of phosphorus per day was calculated for each rat from daily urine volume and phosphorus concentration. No significant changes were seen in animal weight, urine volume or creatinine excretion between groups. Food consumption was good for all groups.

[00120] Even though lanthanum dosage was relatively low compared to the amount of phosphate in the diet, phosphate excretion for 0.3 or 0.6% La added to the diet decreased as shown in Table 5 below. Table 5 shows average levels of urinary phosphate over days 2, 3, and 4 of the test. Urine phosphorus excretion is a marker of dietary phosphorous binding.

Table 5

	Urinary phosphate excretion (mg/day)
Control	4.3
Compound B =$La_2O_2CO_3$	2.3
Compound C = La_2CO_5	1.9

EXAMPLE 15:

[00121] Tests were run to determine the binding efficiency of eight different compounds for twenty-four different elements. The compounds tested are given in Table 6.

Table 6

Test ID	Compound	Preparation Technique
1	La_2O_3	Calcined the commercial (Prochem) $La_2(CO_3)_3 \bullet H_2O$ at 850°C for 16hrs.
2	La_2CO_5	Prepared by spray drying lanthanum acetate solution and calcining at 600°C for 7hrs (method corresponding to FIG. 3)
3	LaOCl	Prepared by spray drying lanthanum chloride solution and calcining at 700°C for 10hrs (method corresponding to FIG. 1)
4	$La_2(CO_3)_3 \bullet 4H_2O$	Purchased from Prochem (comparative example)
5	Ti carbonate	Made by the method of FIG. 11, where the $LaCl_3$ solution is replaced by a $TiOCl_2$ solution.
6	TiO_2	Made by the method corresponding to FIG. 2, with addition of sodium chloride.
7	$La_2O(CO_3)_2 \bullet xH_2O$	Precipitation by adding sodium carbonate solution to lanthanum chloride solution at 80°C (Method corresponding to FIG. 10)
8	$La_2O_2CO_3$	Precipitation by adding sodium carbonate solution to lanthanum chloride solution at 80°C followed by calcination at 500°C for 3hrs. (Method of FIG. 11)

[00122] The main objective of the tests was to investigate the efficiency at which the compounds bind arsenic and selenium, in view of their use in removing those elements from drinking water. Twenty-one different anions were also included to explore further possibilities. The tests were performed as follows:

[00123] The compounds given in Table 6 were added to water and a spike and were vigorously shaken at room temperature for 18hrs. The samples were filtered and the filtrate analyzed for a suite of elements including Sb, As, Be, Cd, Ca, Cr, Co, Cu, Fe, Pb, Mg, Mn, Mo, Ni, Se, Tl, Ti, V, Zn, Al, Ba, B, Ag, and P.

[00124] The spike solution was made as follows:

1. In a 500ml volumetric cylinder add 400ml of de-ionized water.
2. Add standard solutions of the elements given above to make solutions containing approximately 1 mg/l of each element.
3. Dilute to 500mls with de-ionized water.

[00125] The tests were conducted as follows:

1. Weigh 0.50g of each compound into its own 50ml centrifuge tube.

2. Add 30.0ml of the spike solution to each.
3. Cap tightly and shake vigorously for 18hrs.
4. Filter solution from each centrifuge tube through 0.2μm syringe filter. Obtain ~6ml of filtrate.
5. Dilute filtrates 5:10 with 2% HNO_3. Final Matrix is 1% HNO_3.
6. Submit for analysis.

[00126] The results of the tests are given in Table 7.

Table 7

	% of the Analyte Removed																						
	Sb	As	Be	Cd	Ca	Cr	Co	Cu	Fe	Pb	Mg	Mn	Mo	Ni	Se	Tl	Ti	V	Zn	Al	Ba	B	Ag	P
La_2O_3	89	85	**97**	**95**	21	**100**	69	89	**92**	**92**	0	**94**	89	28	72	8	**90**	**95**	**95**	85	23	0	47	**96**
La_2CO_5	**96**	**93**	**100**	83	0	**100**	52	**97**	**100**	99	0	**99**	**98**	17	79	8	**100**	**99**	**100**	**93**	0	0	73	**99**
LaOCl	86	76	89	46	0	**100**	28	88	**100**	99	0	28	**94**	0	71	13	**100**	**99**	24	**92**	7	0	**96**	**96**
$La_2(CO_3)_3.4H_2O$	84	25	41	37	28	**94**	20	0	56	**90**	0	20	**98**	1	78	5	**100**	**99**	16	11	23	0	48	71
$Ti(CO_3)_2$	**96**	**93**	**100**	**100**	**99**	**99**	**99**	**98**	**100**	**98**	79	**100**	**91**	**98**	**97**	**96**	24	**100**	**100**	**92**	**100**	0	**99**	**98**
TiO_2	**96**	**93**	8	4	0	6	0	11	49	**97**	0	1	**97**	0	**97**	62	0	86	0	0	0	30	**99**	66
$La_2O(CO_3)_2.xH_2O$	87	29	53	37	28	**100**	20	10	58	**98**	0	25	**99**	0	79	8	**100**	**99**	16	60	26	0	44	74
$La_2O_2CO_3$	**97**	**92**	**100**	85	21	**100**	59	**98**	**100**	99	0	**99**	**99**	34	81	12	**100**	**99**	**100**	**92**	23	0	87	**99**

[00127] The most efficient compounds for removing both arsenic and selenium appear to be the titanium-based compounds 5 and 6. The lanthanum oxycarbonates made according to the process of the present invention remove at least 90% of the arsenic. Their efficiency at removing Se is in the range 70 to 80%. Commercial lanthanum carbonate (4 in Table 6) is less effective.

[00128] The tests show that the lanthanum and titanium compounds made following the process of the present invention are also effective at removing Sb, Cr, Pb, Mo from solution. They also confirm the efficient removal of phosphorus discussed in the previous examples.

[00129] While the invention has been described in conjunction with specific embodiments, it is to be understood that many alternatives, modifications, and variations will be apparent to those skilled in the art in light of the foregoing description. Accordingly, this invention is intended to embrace all such alternatives, modifications, and variations that fall within the spirit and scope of the appended claims.

What is claimed:

1. A rare earth compound selected from the group consisting of rare earth oxychloride, a rare earth anhydrous oxycarbonate, and a rare earth hydrated oxycarbonate wherein the compound has an absorption capacity of at least 45 mg. phosphate per gram of compound.

2. The compound of claim 1 wherein the rare earth is selected from the group consisting of lanthanum, cerium, and yttrium.

3. The compound of claim 1 wherein the rare earth is lanthanum.

4. The compound of claim 1 wherein the compound is a particle with a porous structure.

5. The compound of claim 4 wherein the porous structure is made by total evaporation of a rare earth salt solution followed by calcination.

6. The compound of claim 5 wherein the evaporation is conducted in a spray dryer.

7. The compound of claim 5 wherein the evaporation temperature is between about 120° and 500°C.

8. The compound of claim 5 wherein the calcination temperature is between about 400° and about 1200°C.

9. The compound of claim 1 having a size between about 1 and about 1000 μm.

10. The compound of claim 9 wherein the compound is formed from individual crystals having a size between about 20 nm and about 10 μm.

11. The compound of claim 6 wherein the product comprises of spheres or parts of spheres.

12. The compound of claim 5 wherein the rare earth salt solution comprises a solution selected from the group consisting of rare earth chloride and rare earth acetate.

13. The compound of claim 5 wherein the rare earth salt solution in neutralized with sodium carbonate, followed by washing, filtering, and drying.

14. The compound of 13 wherein the neutralization process takes place at a temperature of about 80°C.

15. The compound of claim 14 wherein the drying takes place at a temperature of about 105°C.

16. The compound of claim 15 wherein the drying takes place for a period of about 2 hours.

17. The compound of claim 1 wherein the compound exhibits a low solubility in fluids selected from the group consisting of gastrointestinal tract fluid and blood serum.

18. The compound of claim 1 wherein the compound has a low bulk density.

19. The compound of claim 1 wherein the compound is selective for binding phosphate ions.

20. The compound of claim 1 wherein the compound exhibits substantially linear phosphate binding kinetics.

21. A device having an inlet and an outlet comprising rare earth compound selected from the group consisting of rare earth oxychloride, a rare earth anhydrous

oxycarbonate, and a rare earth hydrated oxycarbonate wherein the compound has an absorption capacity of at least 45 mg. phosphate per gram of compound and wherein the compound is disposed between the inlet and the outlet.

22. A method of treating hyperphosphatemia in a mammal comprising providing an effective amount of rare earth compound selected from the group consisting of rare earth oxychloride, a rare earth anhydrous oxycarbonate, and a rare earth hydrated oxycarbonate wherein the compound has an absorption capacity of at least 45 mg. phosphate per gram of compound.

23. A method of making a lanthanum compound comprising;

a. providing a lanthanum chloride solution;

b. mixing a sodium carbonate solution with the lanthanum chloride solution to form a precipitate selected from the group consisting of lanthanum oxychloride, lanthanum anhydrous oxycarbonate, lanthanum hydrated oxycarbonate, and mixtures thereof;

c. filtering precipitate; and,

d. drying the precipitate.

24. The method of claim 23 further comprising calcining the dried precipitate at a temperature of about 500 °C to about 600° for about 3 to 7 hours.

25. A lanthanum oxycarbonate with a BET specific surface area within the range of about 10 m^2/g to about 40 m^2/g.

26. The lanthanum oxycarbonate of claim 25 wherein the lanthanum oxycarbonate has an absorption capacity of at least 45 mg phosphate/ g lanthanum oxycarbonate.

27. A TiO_2 particle coated with a lanthanum compound.

28. The particle of claim 27 wherein the lanthanum compound is selected from the group consisting of lanthanum oxychloride, lanthanum oxycarbonate, hydrated lanthanum oxycarbonate, and mixtures thereof.

29. The particle of claim 28 wherein the lanthanum compound has an absorption capacity of at least 45 mg. phosphate per gram of compound.

30. A method of making a TiO_2 structure comprising:

a. forming a titanium chloride feed solution;

b. subjecting the feed solution to a controlled temperature evaporation process at a temperature higher than the boiling point of the solution but lower than the temperature where crystallization of the product becomes significant;

c. calcining the hydrolyzed product;

d. re-slurrying the calcined hydrolyzed product in a solution containing a lanthanum compound to form a suspension;

e. subjecting the suspension to total evaporation to form a final product; and

f. calcining the final product.

31. The method of claim 30 wherein the first calcination temperature is between about 400° C and about 1200°C and the calcination time is between about 2 and about 24 hours.

32. The method of claim 31 wherein the second calcination temperature is between about 650 and about 1100 °C and the calcination time is between about 2 and about 24 hours.

33. The method of claim 30 wherein the calcined hydrolyzed product comprises hollow spheres or parts of spheres.

34. The method of claim 30 wherein the final product is selected from the group consisting of lanthanum oxide, lanthanum oxychloride, lanthanum oxycarbonate, and mixtures thereof.

35. The method of claim 34 wherein the final product comprises crystals having a size in the range from about 20 nm to about 20 microns.

36. A method for reducing the metal content in a fluid comprising contacting the fluid with a lanthanum compound selected from the group consisting of lanthanum oxycarbonate, La_2CO_5, $La_2O_2CO_3$, and mixtures thereof, wherein the lanthanum compound has an absorption capacity of at least 45 mg. phosphate per gram of compound.

FIG. 1

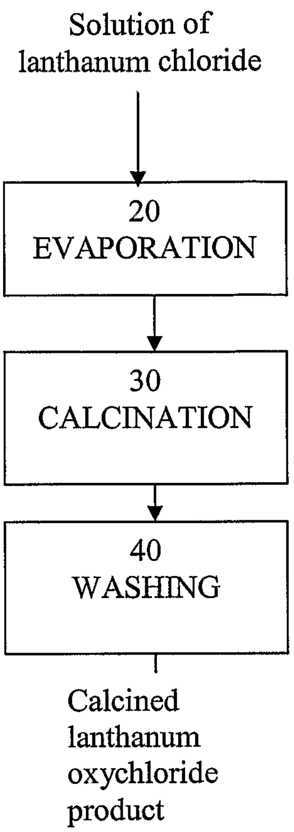

Solution of
lanthanum chloride
20
EVAPORATION
30
CALCINATION
40
WASHING
Calcined
lanthanum
oxychloride
product

FIG. 2

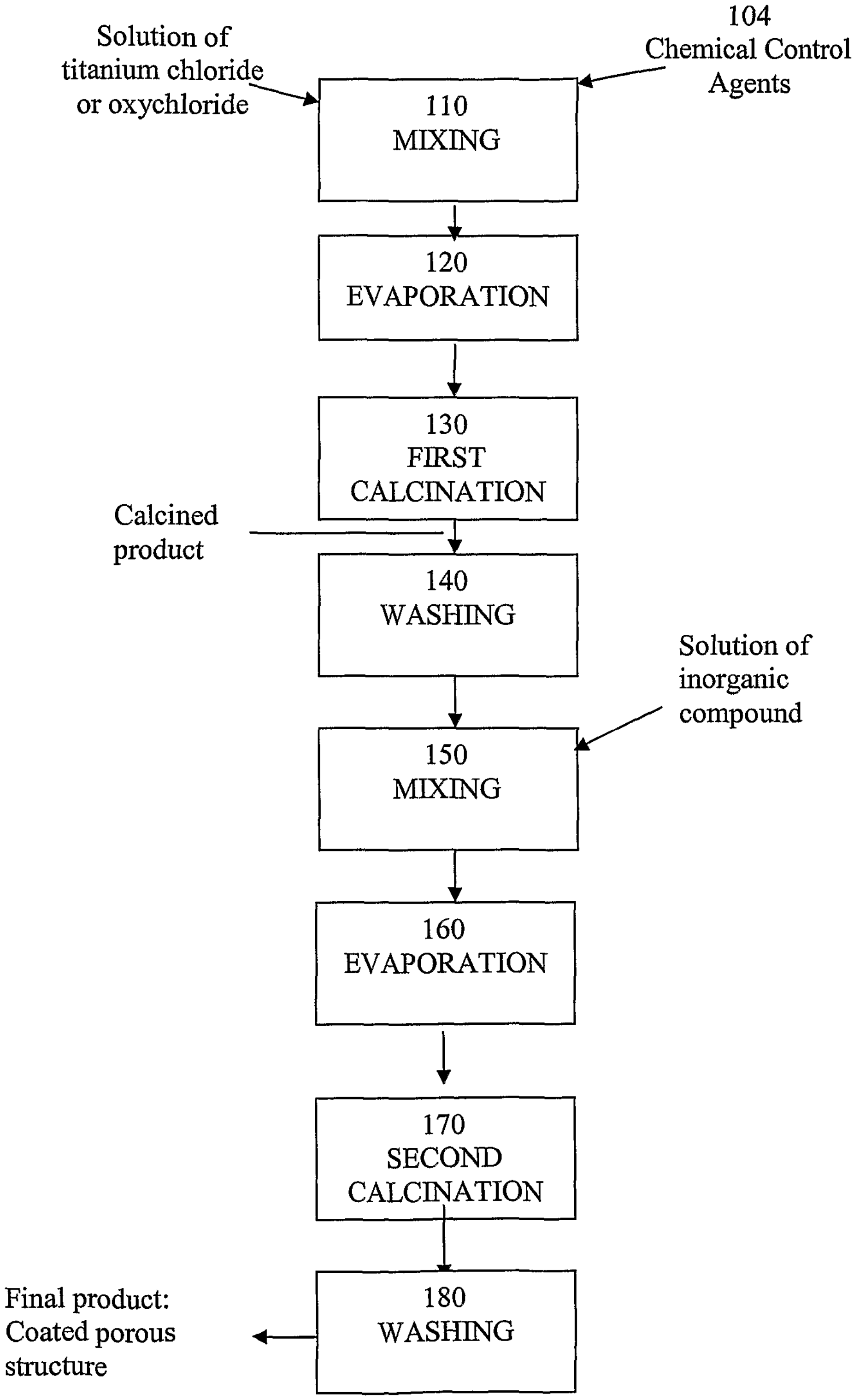

Solution of
titanium chloride
or oxychloride
104
Chemical Control
Agents
110
MIXING
120
EVAPORATION
130
FIRST
CALCINATION
Calcined
product
140
WASHING
Solution of
inorganic
compound
150
MIXING
160
EVAPORATION
170
SECOND
CALCINATION
Final product:
Coated porous
structure
180
WASHING

FIG. 3

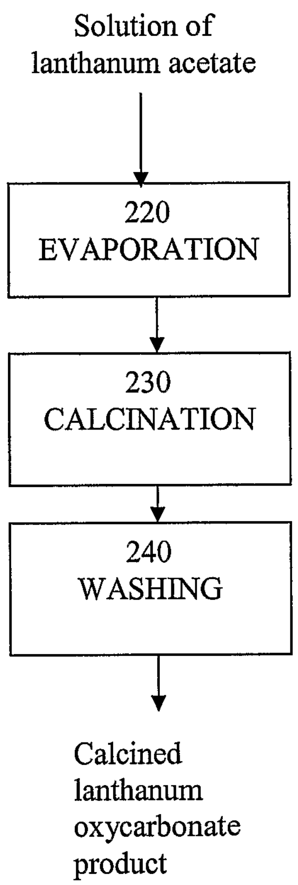

Solution of lanthanum acetate
220
EVAPORATION
230
CALCINATION
240
WASHING
Calcined lanthanum oxycarbonate product

FIG. 4

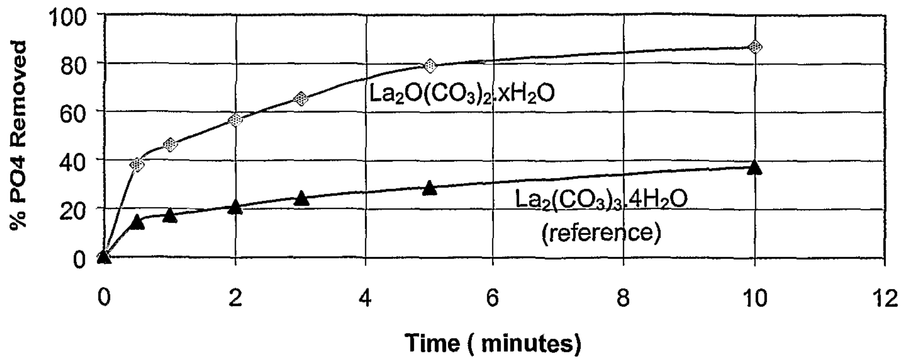

100
80
60
40
20
0
% PO4 Removed
La2O(CO3)2.xH2O
La2(CO3)3.4H2O
(reference)
0
2
4
6
8
10
12
Time (minutes)

FIG. 5

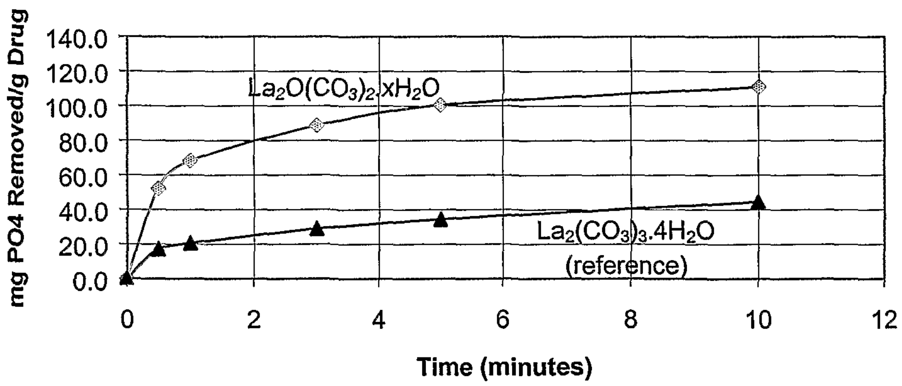

140.0
120.0
100.0
80.0
60.0
40.0
20.0
0.0
mg PO4 Removed/g Drug
La2O(CO3)2.xH2O
La2(CO3)3.4H2O
(reference)
0
2
4
6
8
10
12
Time (minutes)

FIG. 6

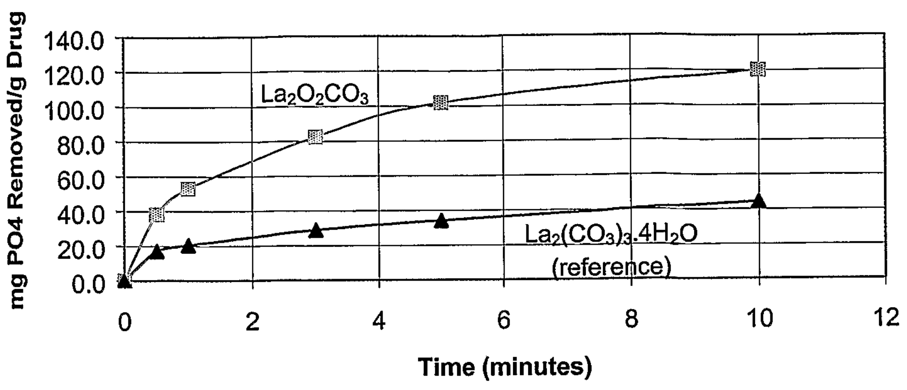

mg PO4 Removed/g Drug
140.0
120.0
100.0
80.0
60.0
40.0
20.0
0.0
0
2
4
6
8
10
12
Time (minutes)
La2O2CO3
La2(CO3)3.4H2O
(reference)

FIG. 7

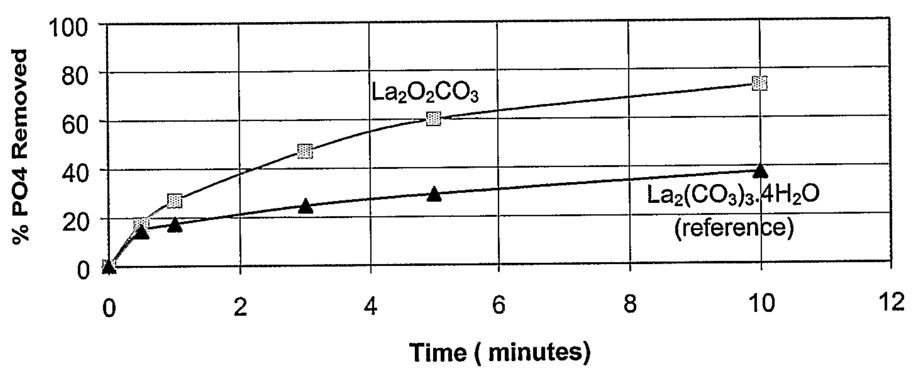

% PO4 Removed
100
80
60
40
20
0
0
2
4
6
8
10
12
Time (minutes)
La2O2CO3
La2(CO3)3.4H2O
(reference)

FIG. 8

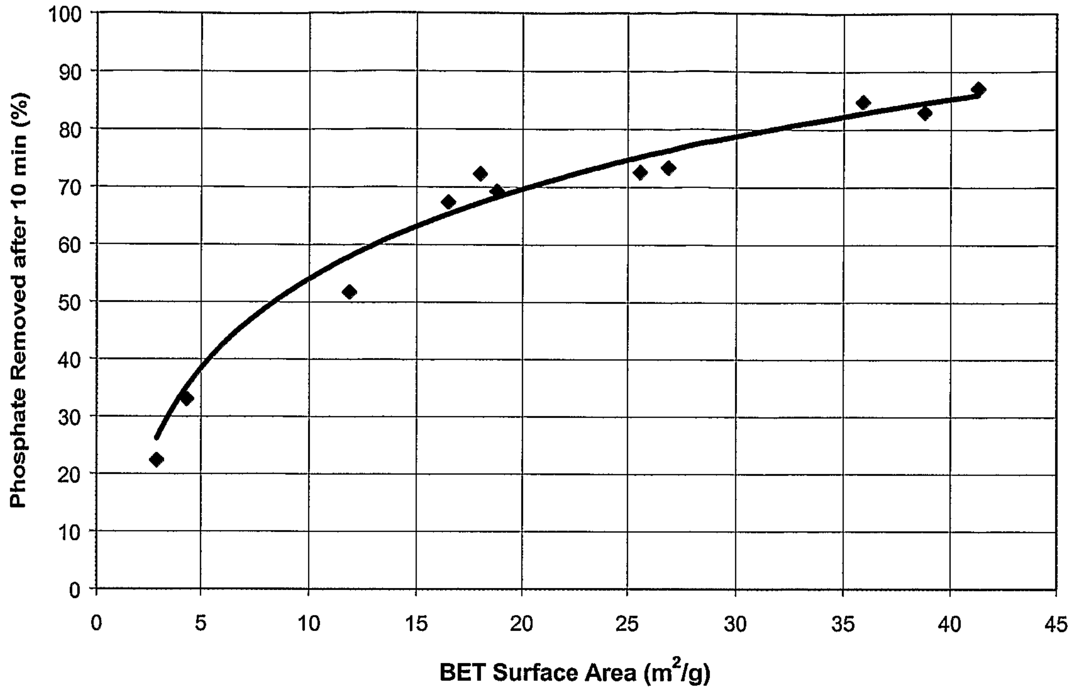

100
90
80
70
60
50
40
30
20
10
0
Phosphate Removed after 10 min (%)
0
5
10
15
20
25
30
35
40
45
BET Surface Area (m2/g)

FIG. 9

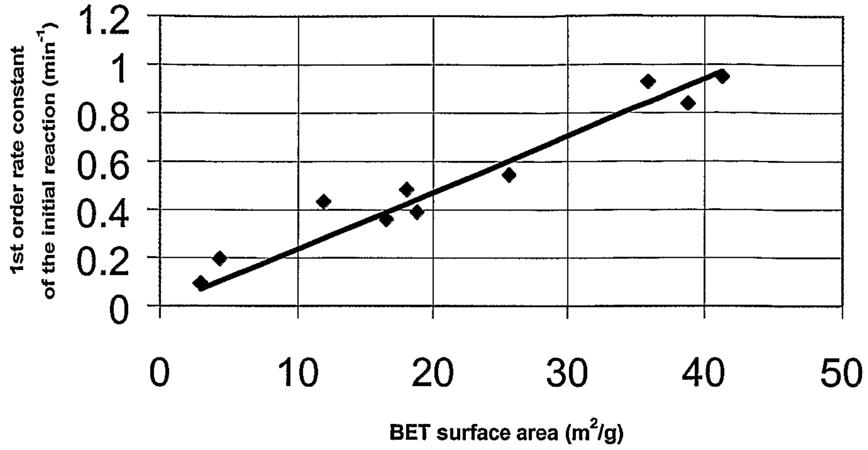
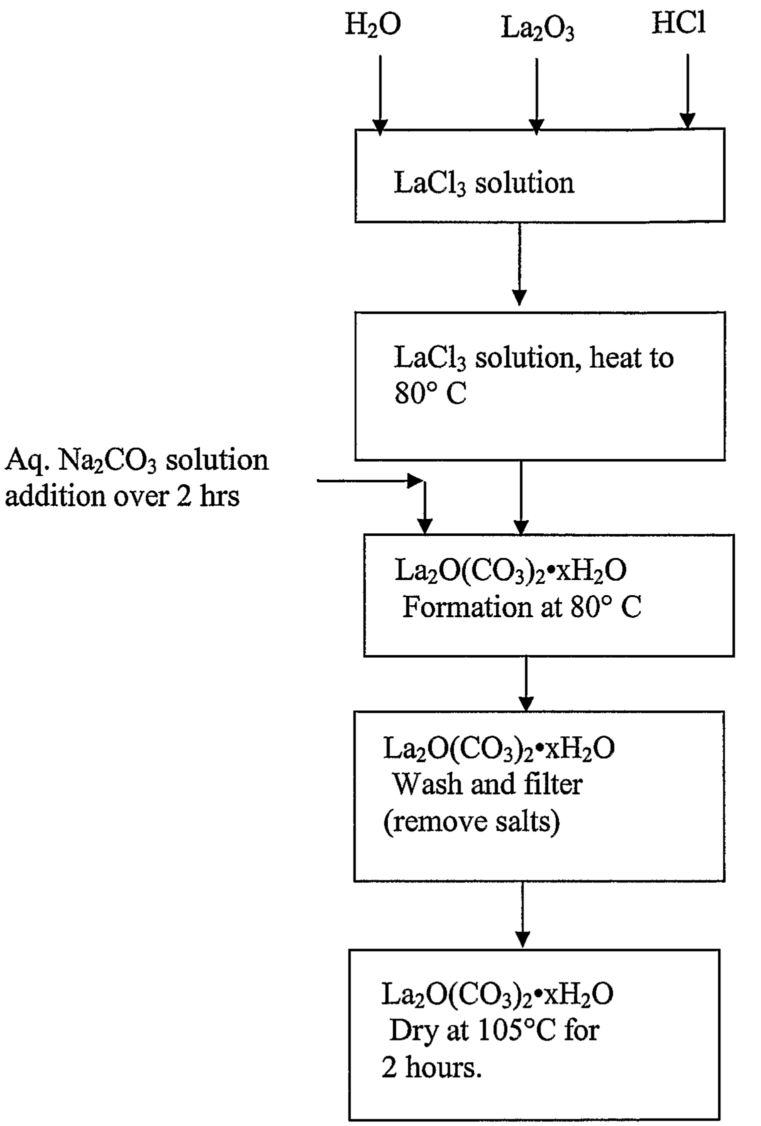

1st order rate constant
of the initial reaction (min-1)
1.2
1
0.8
0.6
0.4
0.2
0
0
10
20
30
40
50
BET surface area (m2/g)

FIG. 10



x, the number of water molecules in the compound, is larger or equal to 2 and smaller or equal to 4.

FIG. 11

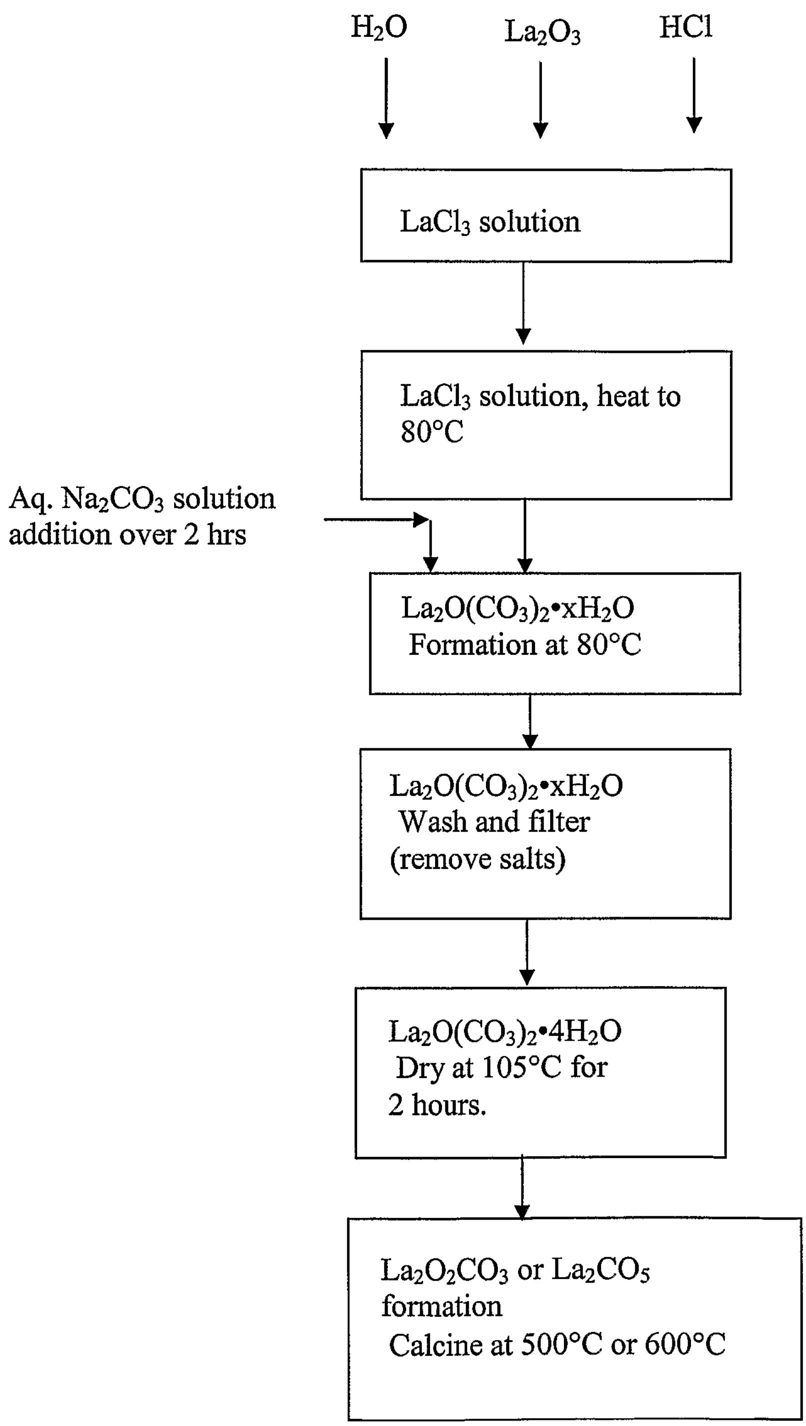

H_2O
La_2O_3
HCl
$LaCl_3$ solution
$LaCl_3$ solution, heat to 80°C
Aq. Na_2CO_3 solution addition over 2 hrs
$La_2O(CO_3)_2 \cdot xH_2O$ Formation at 80°C
$La_2O(CO_3)_2 \cdot xH_2O$ Wash and filter (remove salts)
$La_2O(CO_3)_2 \cdot 4H_2O$ Dry at 105°C for 2 hours.
$La_2O_2CO_3$ or La_2CO_5 formation Calcine at 500°C or 600°C

FIG. 12

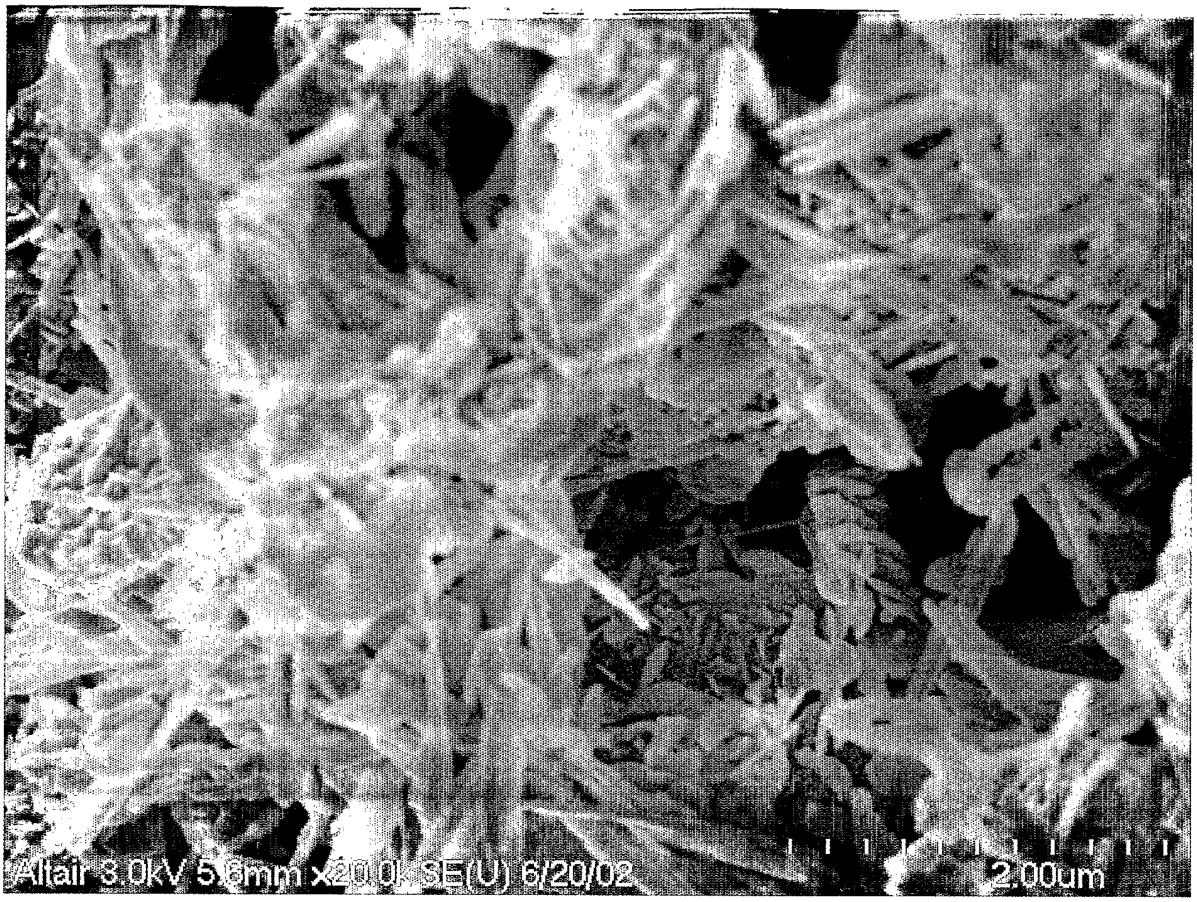


FIG. 13

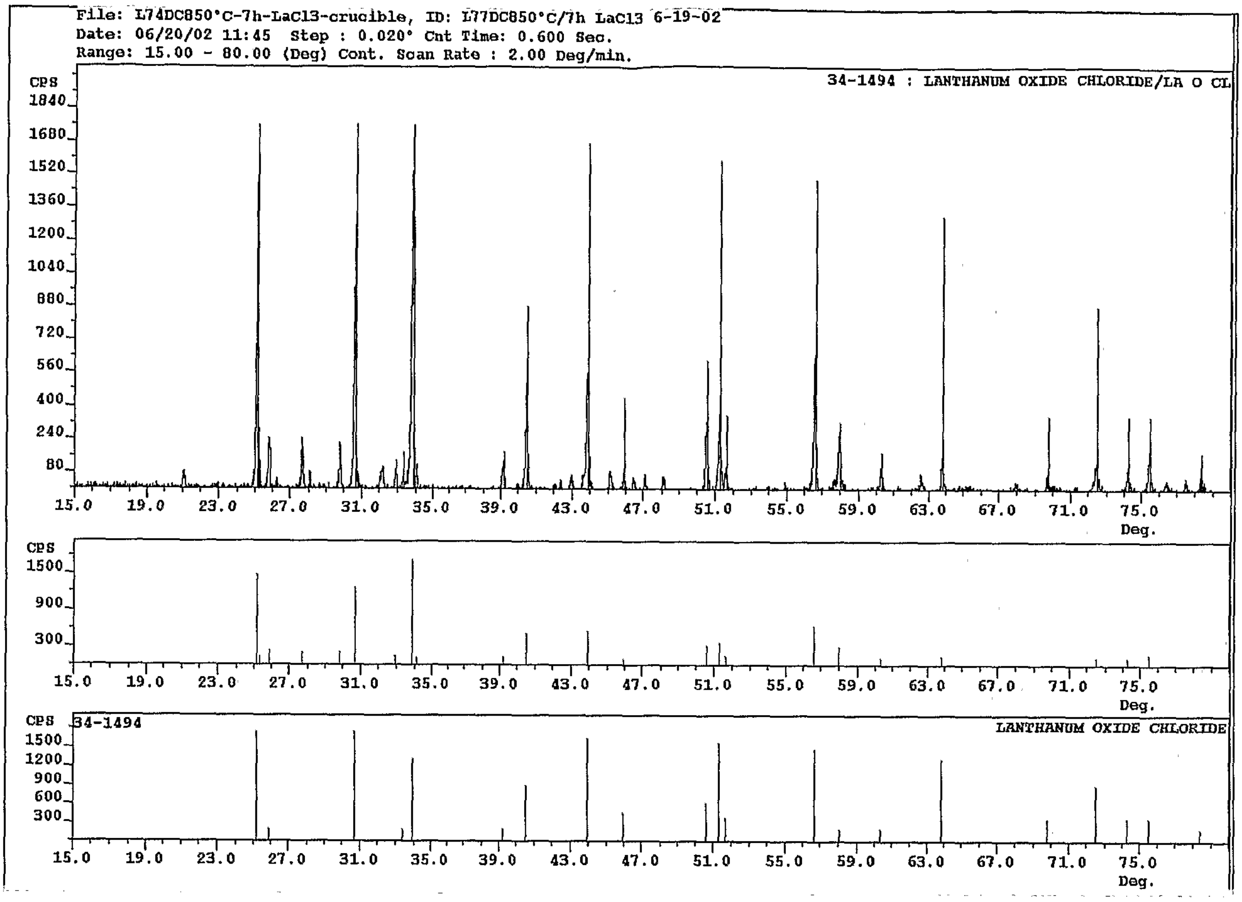

File: L74DC850°C-7h-LaCl3-crucible, ID: L77DC850°C/7h LaCl3 6-19-02
Date: 06/20/02 11:45 Step : 0.020° Cnt Time: 0.600 Sec.
Range: 15.00 - 80.00 (Deg) Cont. Scan Rate : 2.00 Deg/min.
34-1494 : LANTHANUM OXIDE CHLORIDE/LA O CL
CPS
Deg.
34-1494
LANTHANUM OXIDE CHLORIDE

FIG. 14

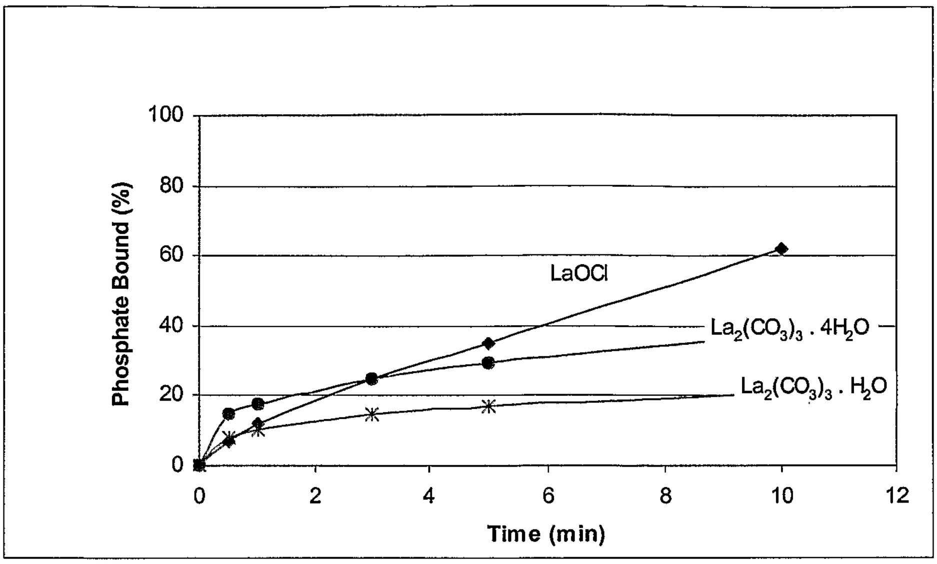

100
80
60
40
20
0
Phosphate Bound (%)
0
2
4
6
8
10
12
Time (min)
LaOCl
La2(CO3)3 . 4H2O
La2(CO3)3 . H2O

FIG. 15

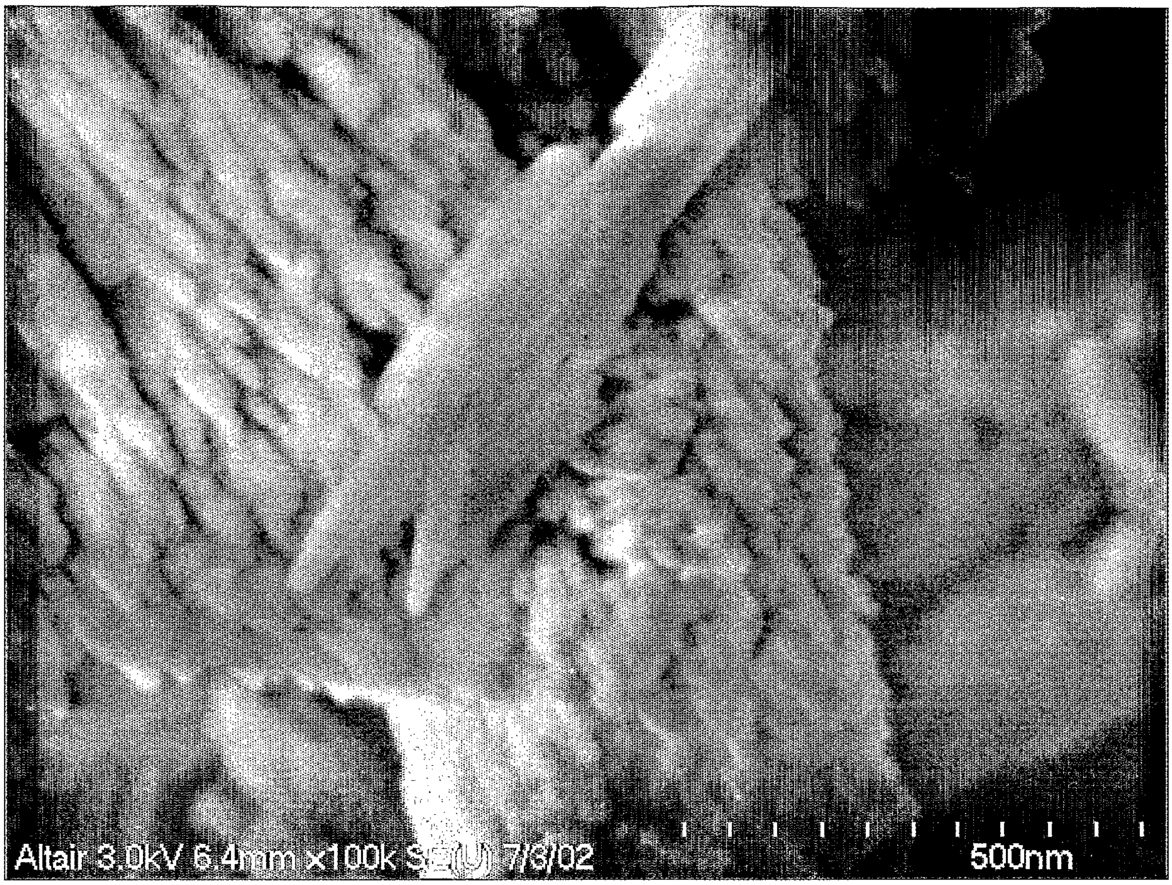


FIG. 16

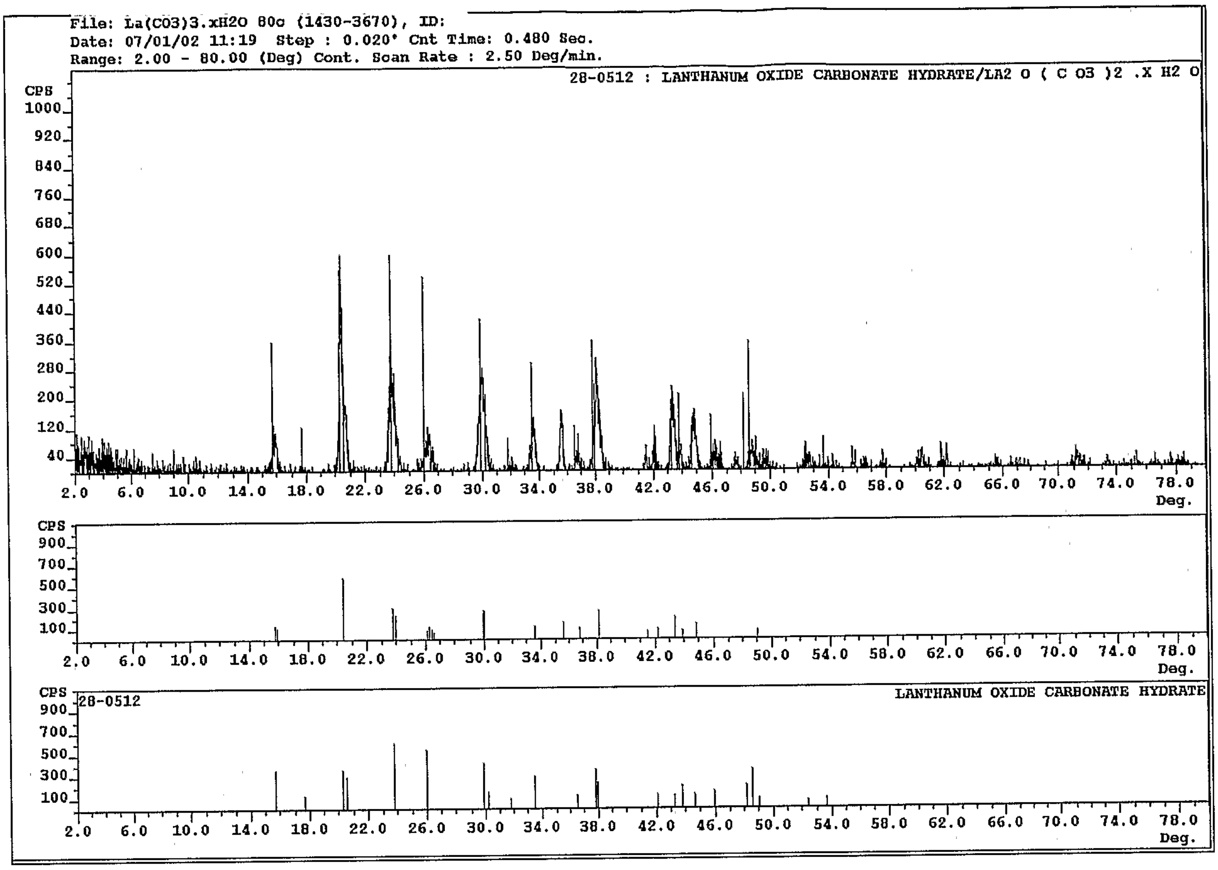

File: La(CO3)3.xH2O 80c (1430-3670), ID:
Date: 07/01/02 11:19 Step : 0.020° Cnt Time: 0.480 Sec.
Range: 2.00 - 80.00 (Deg) Cont. Scan Rate : 2.50 Deg/min.
28-0512 : LANTHANUM OXIDE CARBONATE HYDRATE/LA2 O (C O3)2 .X H2 O
CPS
Deg.
28-0512
LANTHANUM OXIDE CARBONATE HYDRATE

FIG. 17

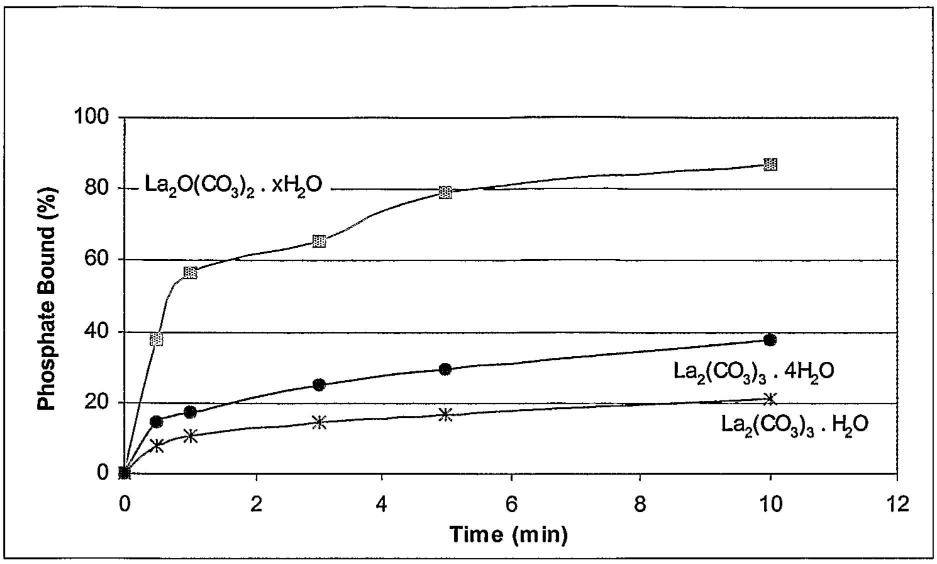

100
80
60
40
20
0
Phosphate Bound (%)
La2O(CO3)2 . xH2O
La2(CO3)3 . 4H2O
La2(CO3)3 . H2O
0
2
4
6
8
10
12
Time (min)

FIG. 18

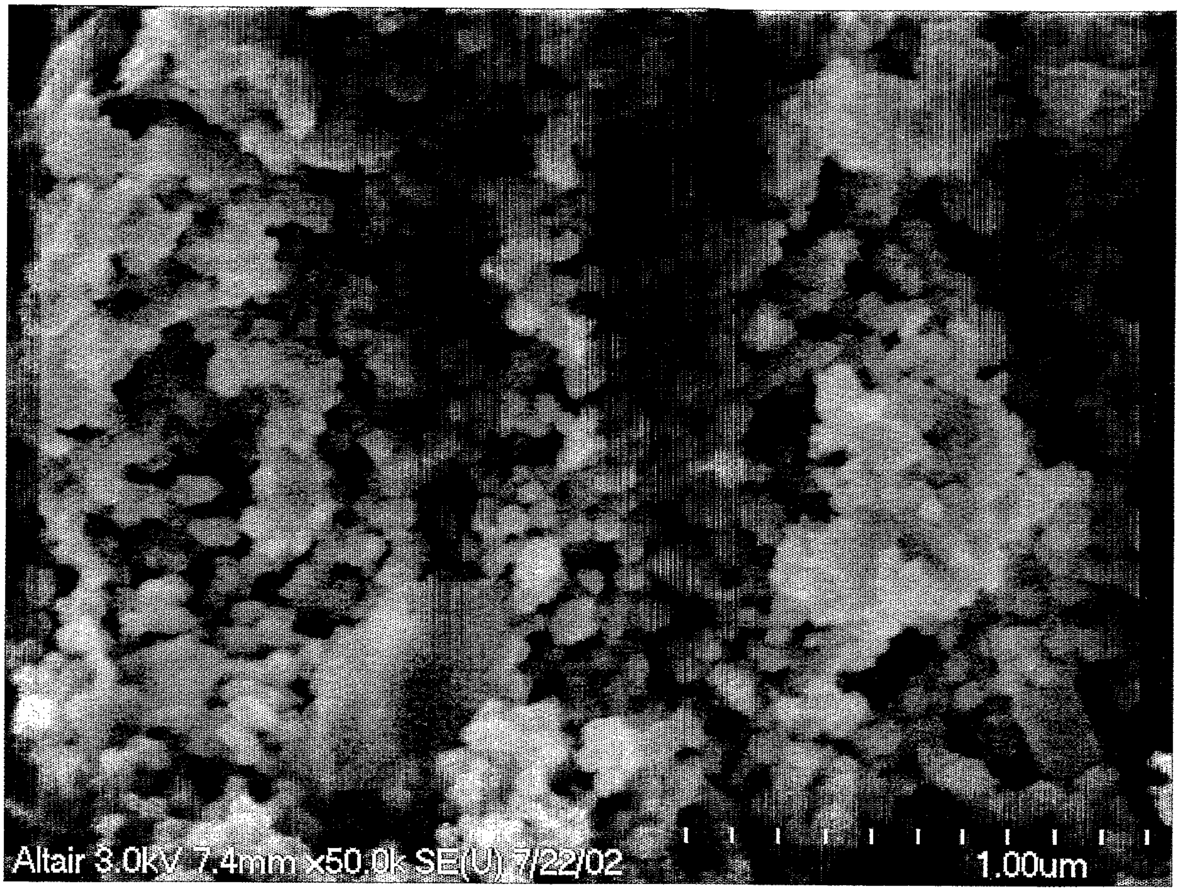


FIG. 19

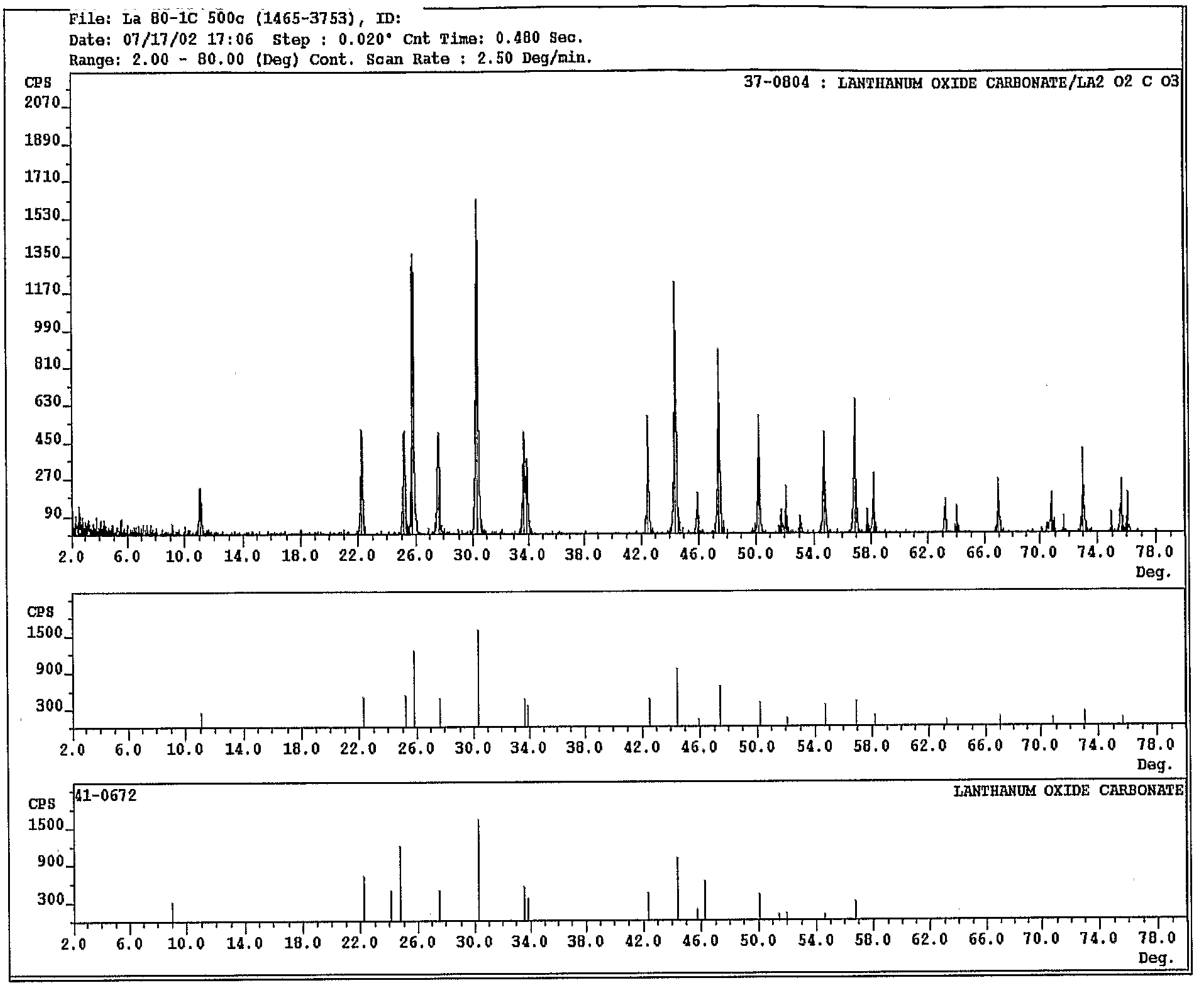
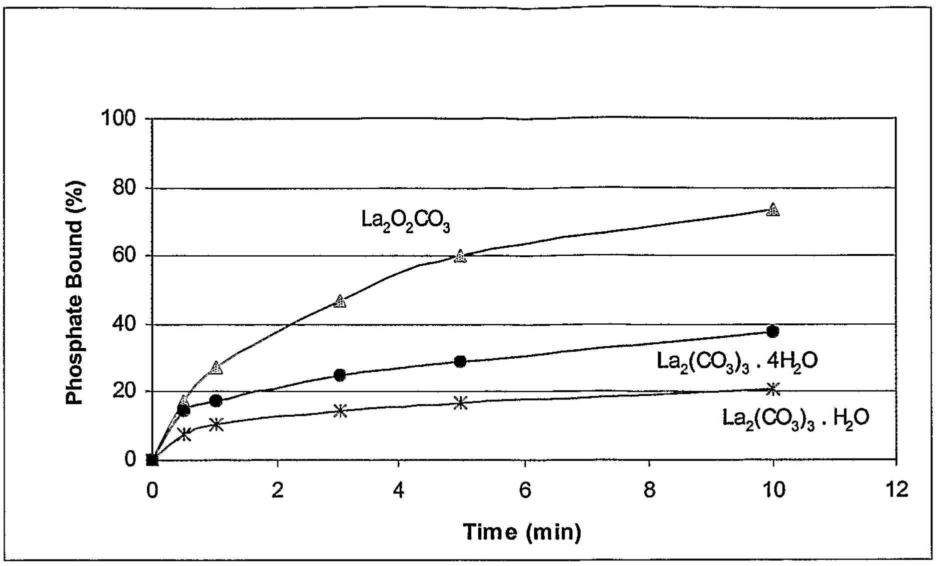

File: La 80-1C 500c (1465-3753), ID:
Date: 07/17/02 17:06 Step : 0.020° Cnt Time: 0.480 Sec.
Range: 2.00 - 80.00 (Deg) Cont. Scan Rate : 2.50 Deg/min.
37-0804 : LANTHANUM OXIDE CARBONATE/LA2 O2 C O3
CPS
Deg.
41-0672
LANTHANUM OXIDE CARBONATE

FIG. 20



100
80
60
40
20
0
Phosphate Bound (%)
$La_2O_2CO_3$
$La_2(CO_3)_3 . 4H_2O$
$La_2(CO_3)_3 . H_2O$
0
2
4
6
8
10
12
Time (min)

FIG. 21

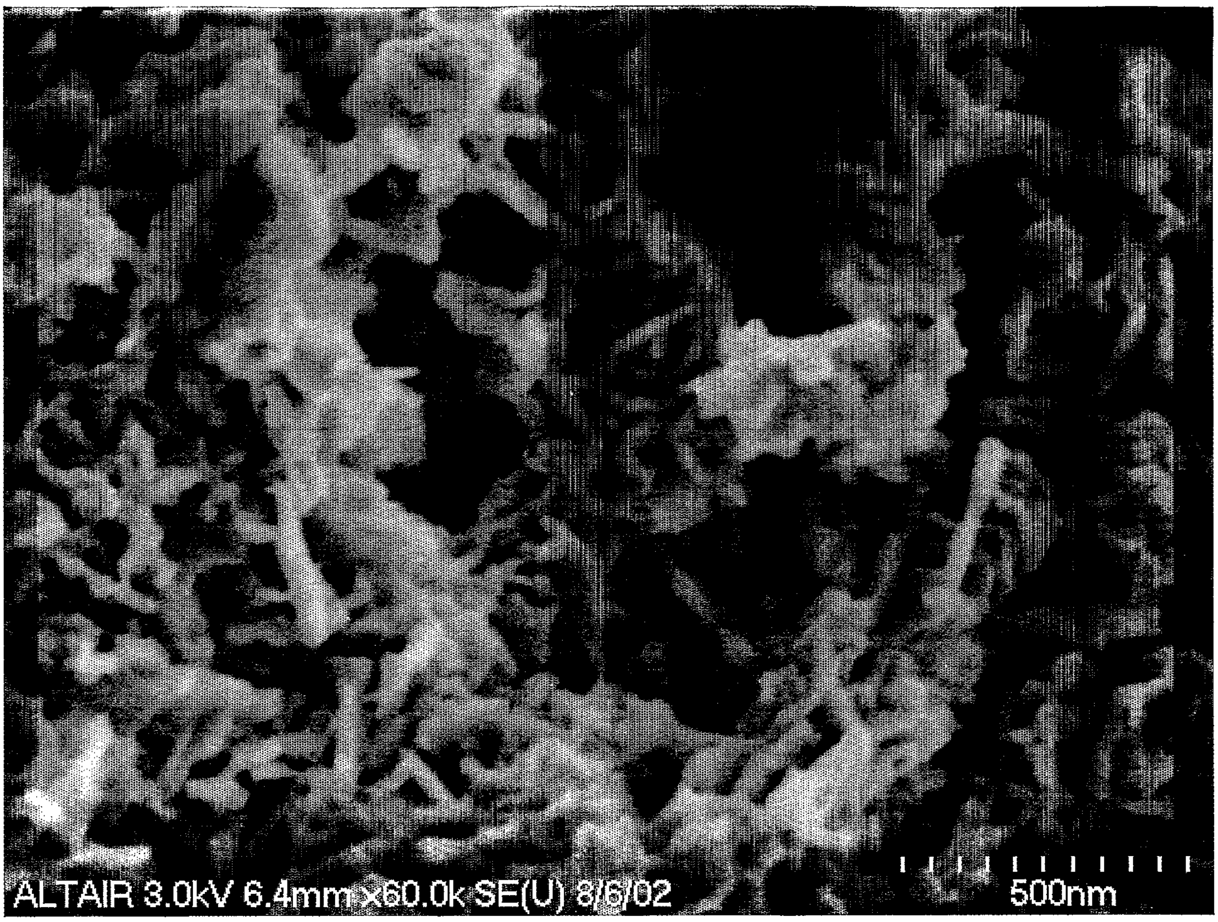


FIG. 22

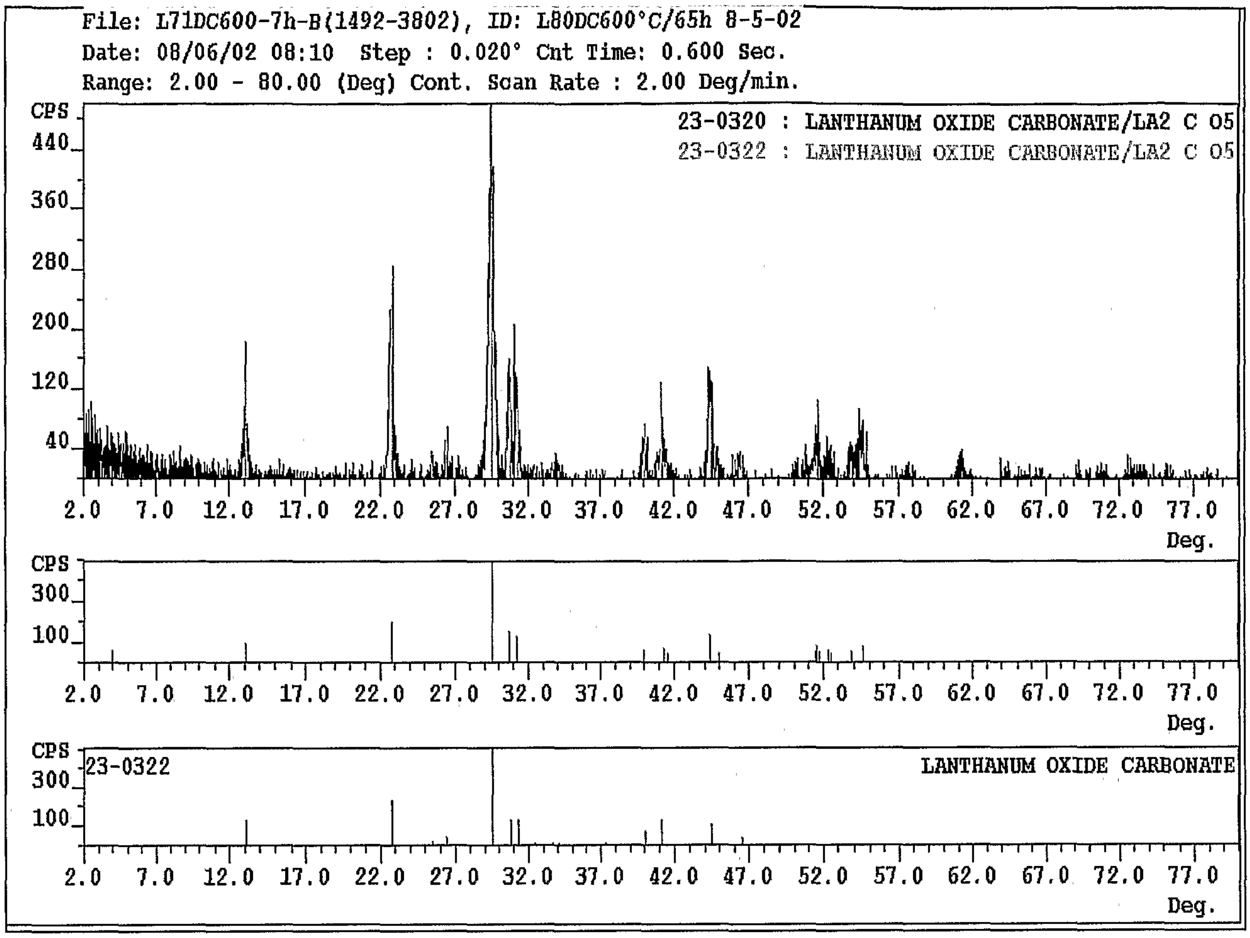
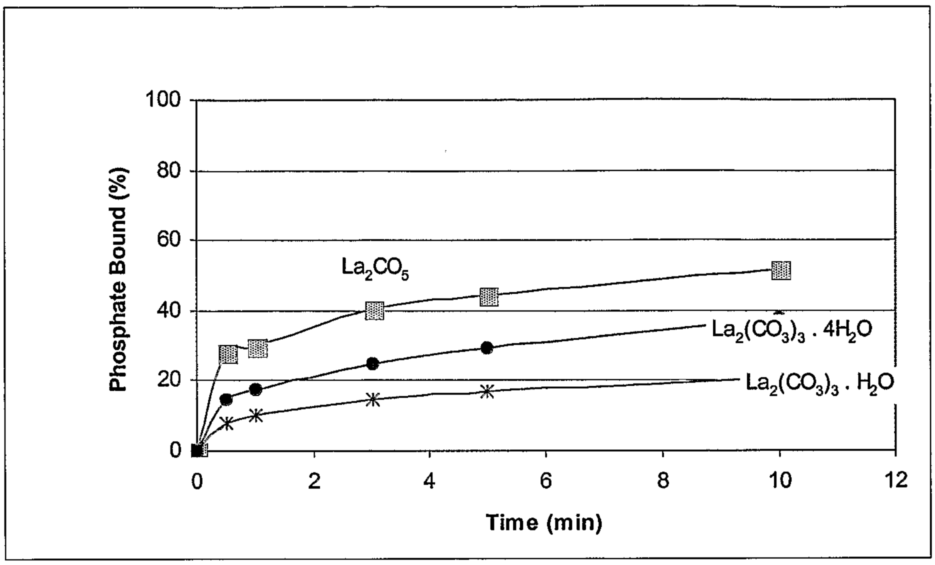
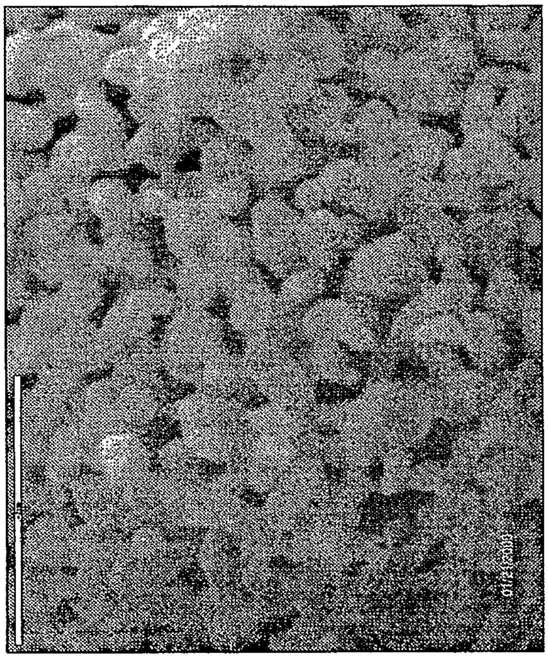

File: L71DC600-7h-B(1492-3802), ID: L80DC600°C/65h 8-5-02
Date: 08/06/02 08:10 Step : 0.020° Cnt Time: 0.600 Sec.
Range: 2.00 - 80.00 (Deg) Cont. Scan Rate : 2.00 Deg/min.
CPS
440
360
280
200
120
40
23-0320 : LANTHANUM OXIDE CARBONATE/LA2 C O5
23-0322 : LANTHANUM OXIDE CARBONATE/LA2 C O5
2.0 7.0 12.0 17.0 22.0 27.0 32.0 37.0 42.0 47.0 52.0 57.0 62.0 67.0 72.0 77.0
Deg.
CPS
300
100
2.0 7.0 12.0 17.0 22.0 27.0 32.0 37.0 42.0 47.0 52.0 57.0 62.0 67.0 72.0 77.0
Deg.
CPS
300
100
23-0322
LANTHANUM OXIDE CARBONATE
2.0 7.0 12.0 17.0 22.0 27.0 32.0 37.0 42.0 47.0 52.0 57.0 62.0 67.0 72.0 77.0
Deg.

FIG. 23



100
80
60
40
20
0
Phosphate Bound (%)
La2CO5
La2(CO3)3 . 4H2O
La2(CO3)3 . H2O
0
2
4
6
8
10
12
Time (min)

FIG. 24



length of scale bar = 2 micron

FIG. 25

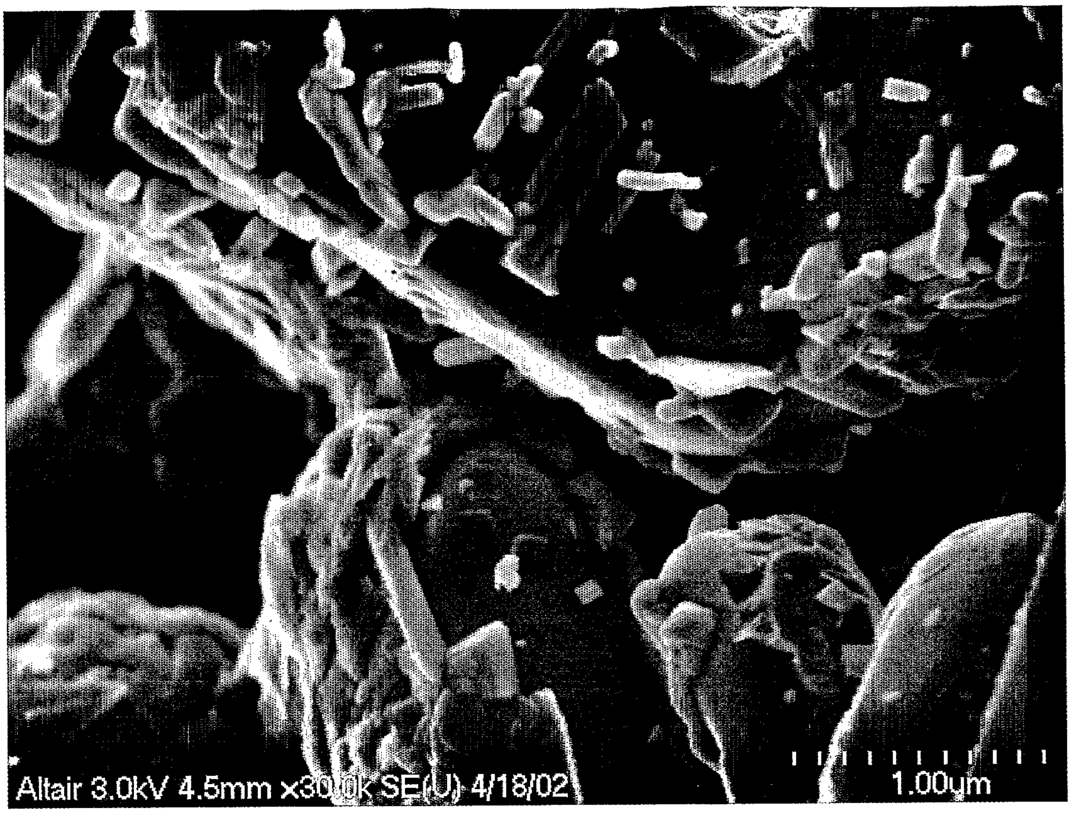


FIG. 26

FIG. 27

FIG 28

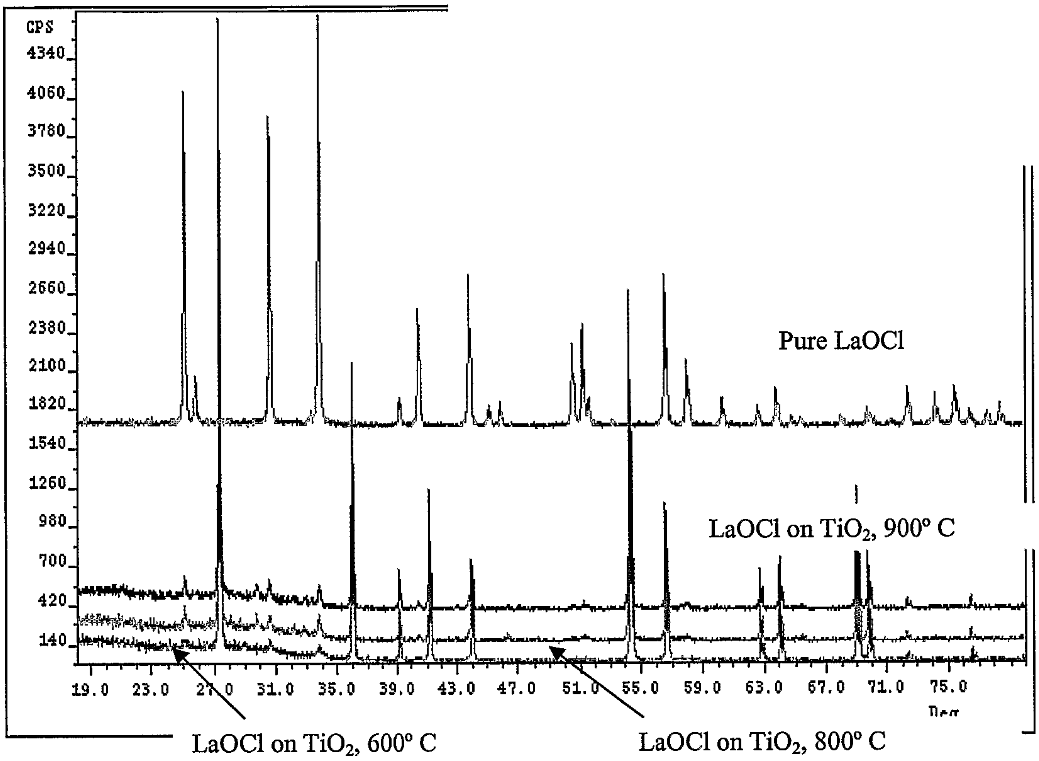

CPS
4340
4060
3780
3500
3220
2940
2660
2380
2100
1820
1540
1260
980
700
420
140
19.0 23.0 27.0 31.0 35.0 39.0 43.0 47.0 51.0 55.0 59.0 63.0 67.0 71.0 75.0
Pure LaOCl
LaOCl on TiO_2, 900° C
LaOCl on TiO_2, 600° C
LaOCl on TiO_2, 800° C

FIG. 29

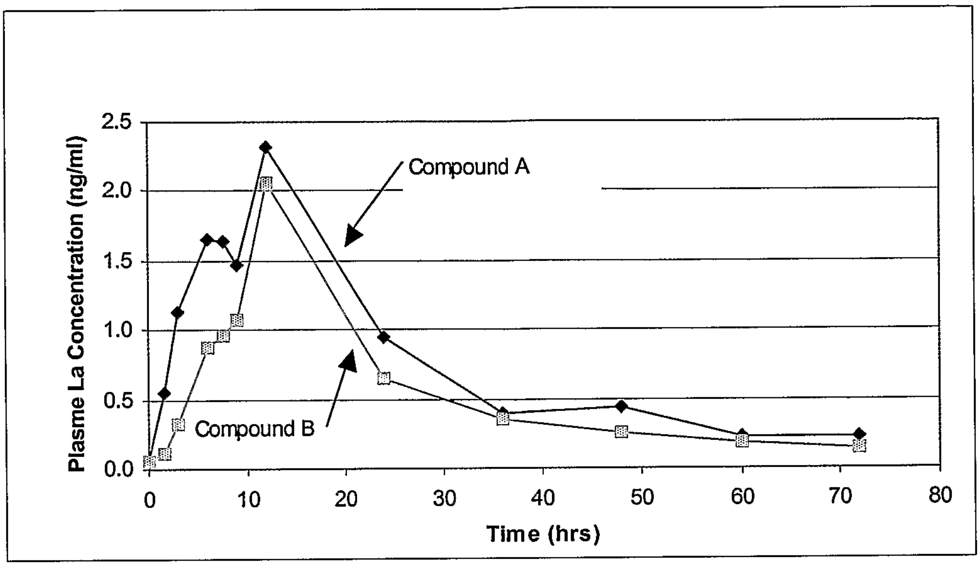
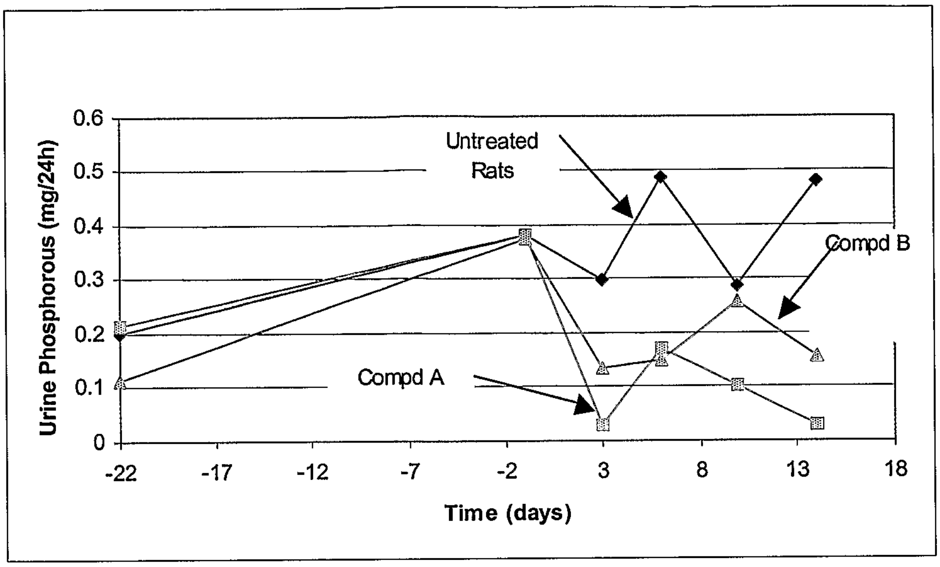

Plasme La Concentration (ng/ml)
2.5
2.0
1.5
1.0
0.5
0.0
Compound A
Compound B
0
10
20
30
40
50
60
70
80
Time (hrs)

FIG. 30


Untreated
Rats
Compd B
Compd A
Urine Phosphorous (mg/24h)
0.6
0.5
0.4
0.3
0.2
0.1
0
-22
-17
-12
-7
-2
3
8
13
18
Time (days)

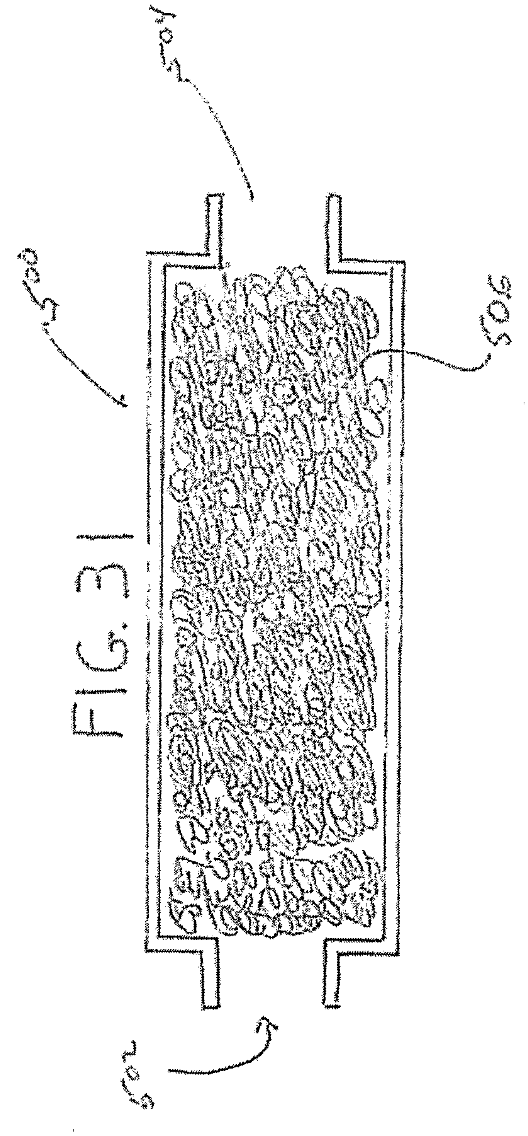


FIG. 31