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(54) **PHOSPHATE-BINDING POLYMERS FOR ORAL ADMINISTRATION**

PHOSPHATBINDENDE POLYMERE FÜR ORALE VERABREICHUNG

POLYMERES FIXANT LES PHOSPHATES POUR ADMINISTRATION ORALE

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- **PATENT ABSTRACTS OF JAPAN vol. 17, no. 708 (C-1147), 24 December 1993 (1993-12-24) & JP 05 244915 A (NITTO BOSEKI CO LTD.), 24 September 1993 (1993-09-24)**
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EP 0 716 606 B1

Description

[0001] This invention relates to phosphate-binding polymers for oral administration.

[0002] People with inadequate renal function, hypoparathyroidism, or certain other medical conditions often have hyperphosphatemia, meaning serum phosphate levels of over 6 mg/dL. Hyperphosphatemia, especially if present over extended periods of time, leads to severe abnormalities in calcium and phosphorus metabolism, often manifested by aberrant calcification in joints, lungs, and eyes.

[0003] Therapeutic efforts to reduce serum phosphate include dialysis, reduction in dietary phosphate, and oral administration of insoluble phosphate binders to reduce gastrointestinal absorption. Dialysis and reduced dietary phosphate are usually insufficient to adequately reverse hyperphosphatemia, so the use of phosphate binders is routinely required to treat these patients. Phosphate binders include calcium or aluminum salts, or organic polymers such as ion exchange resins.

[0004] Calcium salts have been widely used to bind intestinal phosphate and prevent absorption. The ingested calcium combines with phosphate to form insoluble calcium phosphate salts such as $Ca_3(PO_4)_2$, $CaHPO_4$, or $Ca(H_2PO_4)_2$. Different types of calcium salts, including calcium carbonate, acetate (such as the pharmaceutical "PhosLo® "), citrate, alginate, and ketoacid salts have been utilized for phosphate binding. The major problem with all of these therapeutics is the hypercalcemia which often results from absorption of the high amounts of ingested calcium. Hypercalcemia causes serious side effects such as cardiac arrhythmias, renal failure, and skin and visceral calcification. Frequent monitoring of serum calcium levels is required during therapy with calcium-based phosphate binders.

[0005] Aluminum-based phosphate binders, such as the aluminum hydroxide gel "Amphojel®", have also been used for treating hyperphosphatemia. These compounds complex with intestinal phosphate to form highly insoluble aluminum phosphate; the bound phosphate is unavailable for absorption by the patient. Prolonged use of aluminum gels leads to accumulations of aluminum, and often to aluminum toxicity, accompanied by such symptoms as encephalopathy, osteomalacia, and myopathy.

[0006] Organic polymers that have been used to bind phosphate have typically been ion exchange resins. Those tested include Dowex® anion-exchange resins in the chloride form, such as XF 43311, XY 40013, XF 43254, XY 40011, and XY 40012. These resins have several drawbacks for treatment of hyperphosphatemia, including poor binding efficiency, necessitating use of high dosages for significant reduction of absorbed phosphate. In addition, the ion exchange resins also bind bile salts.

Summary of the Invention

[0007] In general, the invention features removing phosphate from a patient by ion exchange, which involves oral administration of a therapeutically effective amount of a composition containing at least one phosphate-binding polymer that is non-toxic and stable once ingested. The polymers of the invention may be crosslinked with a crosslinking agent. Examples of preferred crosslinking agents include epichlorohydrin, 1,4 butanedioldiglycidyl ether, 1,2 ethanedioldiglycidyl ether, 1,3-dichloropropane, 1,2-dichloroethane, 1,3-dibromopropane, 1,2-dibromoethane, succinyl dichloride, dimethylsuccinate, toluene diisocyanate, acryloyl chloride, and pyromellitic dianhydride. The crosslinking agent is present in an amount ranging from about 0.5% to about 75% by weight, more preferably from about 2% to about 20% by weight.

[0008] By "non-toxic" it is meant that when ingested in therapeutically effective amounts neither the polymers nor any ions released into the body upon ion exchange are harmful.

[0009] By "stable" it is meant that when ingested in therapeutically effective amounts the polymers do not dissolve or otherwise decompose to form potentially harmful by-products, and remain substantially intact so that they can transport bound phosphate out of the body.

[0010] By "therapeutically effective amount" is meant an amount of the composition which, when administered to a patient, causes decreased serum phosphate.

[0011] According to a first aspect of the present invention there is provided a composition as defined in claim 1.

[0012] According to a second aspect of the present invention there is provided the use of claim 5.

[0013] According to a third aspect of the present invention there is provided the use of claim 6.

[0014] In all aspects, the negatively charged counterions may be organic ions, inorganic ions, or combination thereof. The inorganic ions suitable for use in this invention include the halides (especially chloride), phosphate, phosphite, carbonate, bicarbonate, sulfate, bisulfate, hydroxide, nitrate, persulfate, sulfite, and sulfide. Suitable organic ions include acetate, ascorbate, benzoate, citrate, dihydrogen citrate, hydrogen citrate, oxalate, succinate, tartrate, taurocholate, glycocholate, and cholate.

[0015] The invention provides an effective treatment for decreasing the serum level of phosphate by binding phosphate in the gastrointestinal tract, without comcomittantly increasing the absorption of any clinically undesirable materials, particularly calcium or aluminum.

[0016] Other features and advantages will be apparent from the following description of the preferred embodiments and from the claims.

Description of the Preferred Embodiments

[0017] Preferred polymers have the structures set forth in the Summary of the Invention, above. The polymers are preferably crosslinked, in some cases by adding a crosslinking agent to the reaction mixture during polymerization. Examples of suitable crosslinking agents are diacrylates and dimethacrylates (e.g., ethylene glycol diacrylate, propylene glycol diacrylate, butylene glycol diacrylate, ethylene glycol dimethacrylate, propylene glycol dimethacrylate, butylene glycol dimethacrylate, polyethyleneglycol dimethacrylate, polyethyleneglycol diacrylate), methylene bisacrylamide, methylene bismethacrylamide, ethylene bisacrylamide, epichlorohydrin, toluene diisocyanate, ethylenebismethacrylamide, ethylidene bisacrylamide, divinyl benzene, bisphenol A dimethacrylate, bisphenol A diacrylate, 1,4 butanedioldiglycidyl ether, 1,2 ethanedioldiglycidyl ether, 1,3-dichloropropane, 1,2-dichloroethane, 1,3-dibromopropane, 1,2-dibromoethane, succinyl dichloride, dimethylsuccinate, acryloyl chloride, or pyromellitic dianhydride. The amount of crosslinking agent is typically between 0.5 and 75 weight %, and preferably between 1 and 25% by weight, based upon combined weight of crosslinking agent and monomer. In another embodiment, the crosslinking agent is present between 2 and 20% by weight.

[0018] In some cases the polymers are crosslinked after polymerization. One method of obtaining such crosslinking involves reaction of the polymer with difunctional crosslinkers , such as epichlorohydrin, succinyl dichloride, the diglycidyl ether of bisphenol A, pyromellitic dianhydride, toluene diisocyanate, and ethylenediamine. A typical example is the reaction of poly(ethyleneimine) with epichlorohydrin. In this example the epichlorohydrin (1 to 100 parts) is added to a solution containing polyethyleneimine (100 parts) and heated to promote reaction. Other methods of inducing crosslinking on already polymerized materials include exposure to ionizing radiation, ultraviolet radiation, electron beams, radicals, and pyrolysis.

Examples

[0019] Candidate polymers were tested by stirring them in a phosphate containing solution at pH 7 for 3 h. The solution was designed to mimic the conditions present in the small intestine.

Solution Contents
10-20 mM Phosphate 80 mM Sodium Chloride 30 mM Sodium Carbonate

The pH was adjusted to pH 7, once at the start of the test and again at the end of the test, using either aqueous NaOH or HCl. After 3 h the polymer was filtered off and the residual phosphate concentration in the test solution was determined spectrophotometrically. The difference between the initial phosphate concentration and the final concentration was used to determine the amount of phosphate bound to the polymer. This result is expressed in milliequivalents per gram of starting polymer (meq/g).

[0020] The table below shows the results obtained for several polymers. Higher numbers indicate a more effective polymer.

Polymer Phosphate Bound	(meq/g)*
Poly(allylamine/epichlorohydrin)	3.1
Poly(allylamine/butanediol diglycidyl ether)	2.7
Poly(allylamine/ethanediol diglycidyl ether)	2.3
Poly(allyltrimethylammonium chloride)	0.3

* The values apply when the residual solution phosphate levels are - 5 mM.

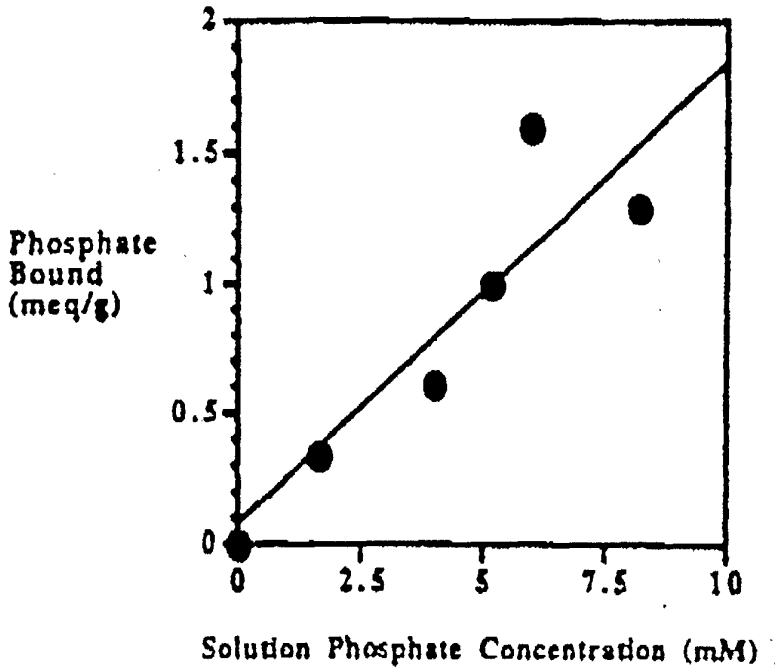
[0021] The table below shows results obtained using various other materials to bind phosphate.

Polymer (meq/g)*	Phosphate Bound
Calcium Chloride	4.0
Calcium Lactate	2.4
Ox-Absorb®	0.5
Maalox Plus®	0.3
Sephadex DEAE A-25, 40-125 m	0.2
Aluminum Hydroxide, Dried Gel	0.2

* The values apply when the residual solution phosphate levels are - 5 mM.

[0022] Oxabsorb® is an organic polymer that encapsulates calcium such that the calcium is available to bind to such ions as phosphate, but may not be released by the polymer and thus is not supposed to be absorbed by the patient.

[0023] The amount of phosphate bound by all of these materials, both polymers and inorganic gels, is expected to vary as the phosphate concentration varies. The graph below shows the relationship between the solution phosphate concentration and the amount of phosphate bound to poly(dimethylaminopropylacrylamide). Other polymers might be expected to show a similar relationship.



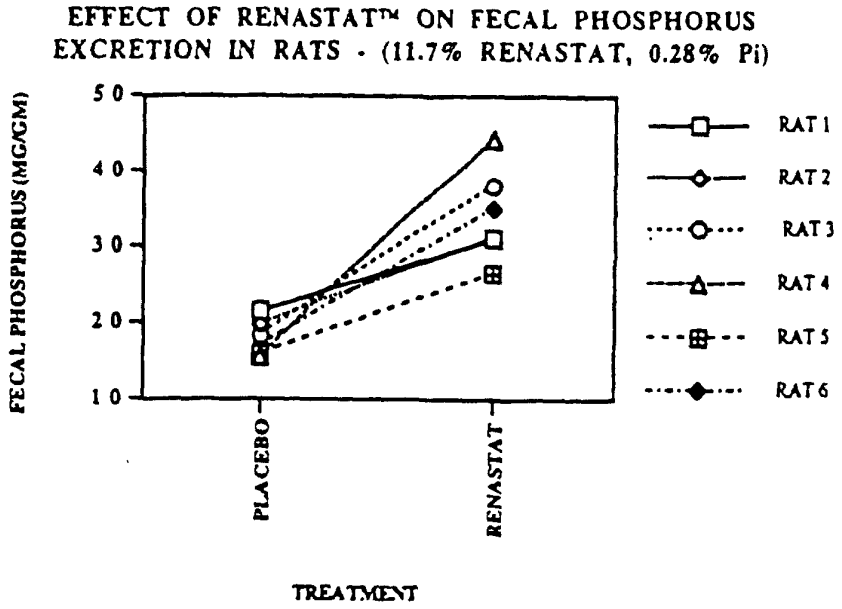
[0024] In an alternate type of test, the polymer was exposed to an acidic environment prior to exposure to phosphate as might happen in a patient's stomach. The solid (0.1 g) was suspended in 40 mL of 0.1 M NaCl. This mixture was stirred for 10 min., and the pH was adjusted to 3.0 with 1 M HCl, and the mixture was stirred for 30 min. The mixture was centrifuged, the supernatant decanted, and the solid resuspended in 40 mL of 0.1 m NaCl. This mixture was stirred for 10 min., the pH was adjusted to 3.0 with 1 M HCl, and the mixture was stirred for 30 min. The mixture was centrifuged, the supernatant decanted, and the solid residue used in the usual phosphate assay.

RAT DIETARY PHOSPHORUS EXCRETION MODEL

[0025] Six 6-8 week old Sprague-Dawley rats were placed in metabolic cages and fed semi-purified rodent chow powder containing 0.28% inorganic phosphorus. The diets were supplemented wtih 11.7% RenaStat™ (i.e., poly(allylamine/epichlorohydrin)) or micro-crystalline cellulose; the animals served as their own controls by receiving cellulose

or RenaStat™ in randomized order. The rats were fed ad libitum for three days to acclimate to the diet. Feces excreted during the next 48 hours were collected, lyophilized, and ground into powder. The inorganic phosphate content was determined according to the method of Taussky and Shorr: Microdetermination of Inorganic P. One gram of powdered feces was burned to remove carbon, then ashed in a 600°C oven. concentrated HCl was then added to dissolve the phosphorus. The phosphorus was determined with ferrous sulfate-ammonium molybdate reagent. Intensity of the blue color was determined at 700 nm on a Perkin-Elmer spectrophotometer through a 1 cm cell.

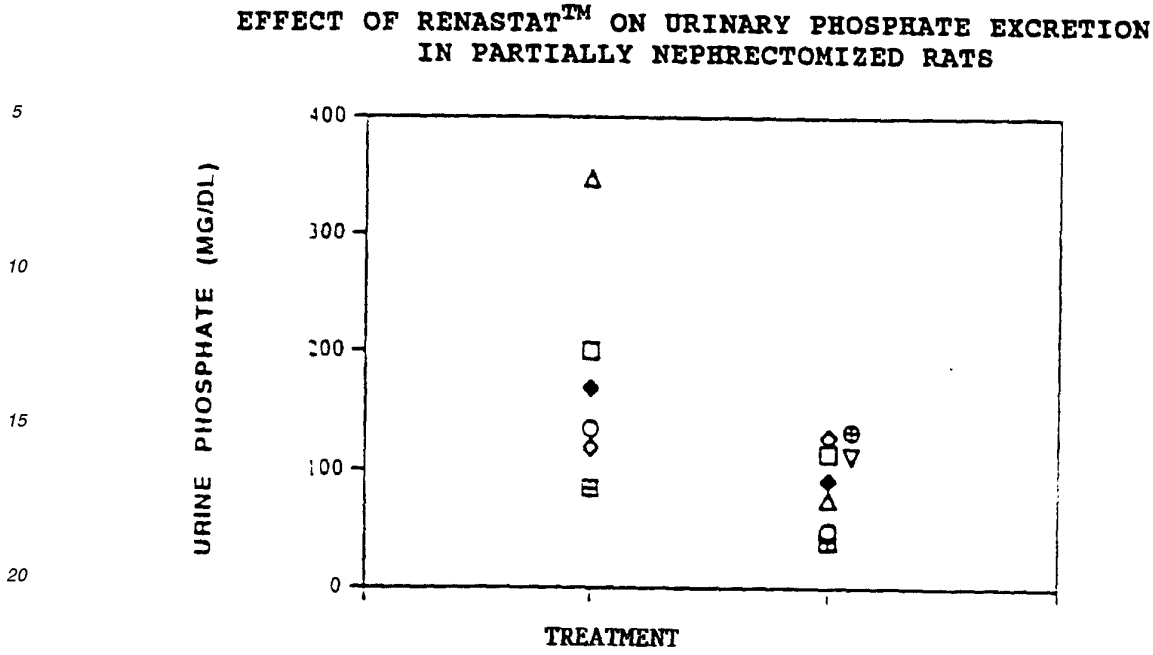
[0026] The results are shown in the following graph. Fecal phosphate concentration increased in all animals.



URINARY PHOSPHATE EXCRETION IN PARTIALLY NEPHRECTOMIZED RATS

[0027] Sprague-Dawley rats, approximately 8 weeks old, were 75% nephrectomized. One kidney was surgically removed; approximately 50% of the renal artery flow to the contralateral kidney was ligated. The animals were fed a semi-purified rodent chow containing 0.385% inorganic phosphorus and either 10% RenaStat™ or cellulose. Urine was collected and analyzed for phosphate content on specific days. Absorbed dietary phosphate is excreted into the urine to maintain serum phosphate.

[0028] The results are shown in the following graph. None of the animals became hyperphosphatemic or uremic, indicating that the residual kidney function was adequate to filter the absorbed phosphate load. The animals receiving RenaStat™ demonstrated a trend towards reduced phosphate excretion, indicative of reduced phosphate absorption.



SYNTHESES

Poly(allylamine) hydrochloride.

[0029] To a 5 L, water jacketed reaction kettle equipped with 1) a condenser topped with a nitrogen gas inlet and 2) a thermometer and 3) a mechanical stirrer was added concentrated hydrochloric acid (2590 mL). The acid was cooled to 5°C using circulating water in the jacket of the reaction kettle at 0°C. Allylamine (2362 mL; 1798 g) was added dropwise with stirring, maintaining a temperature of 5-10°C. After the addition was complete, 1338 mL of liquid was removed by vacuum distillation at 60-70°C. Azobis(amidinopropane) dihydrochloride (36 g) suspended in 81 mL water was added. The kettle was heated to 50°C under a nitrogen atmosphere with stirring for 24 h. Azobis(amidinopropane) dihydrochloride (36 g) suspended in 81 mL water was again added and the heating and stirring continued for an addition 44 h. Distilled water (720 mL) was added and the solution allowed to cool with stirring. The liquid was added dropwise to a stirring solution of methanol (30 L). The solid was then removed by filtration, resuspended in methanol (30 L), stirred 1 hour, and collected by filtration. This methanol rinse was repeated once more and the solid was dried in a vacuum oven to yield 2691 g of a granular white solid (poly(allylamine) hydrochloride).

Poly(allylamine/epichlorohydrin).

[0030] To a 5 gall bucket was added poly(allylamine) hydrochloride (2.5 kg) and water 10 L). The mixture was stirred to dissolve and the pH was adjusted to 10 with a solid NaOH. The solution was allowed to cool to room temperature in the bucket and epichlorohydrin (250 mL) was added all at once with stirring. The mixture was stirred gently until it gelled after about 15 minutes. The gel was allowed to continue curing for 18 h at room temperature. The gel was then removed and put into a blender with isopropanol (about 7.5 L). The gel was mixed in the blender with about 500 mL isopropanol for-3 minutes to form coarse particles and the solid was then collected by filtration. The solid was rinsed three times by suspended it in 9 gal of water, stirring the mixture for 1 h, and collecting the solid by filtration. The solid was rinsed once by suspending it in isopropanol (60 L), stirring the mixture for 1 h, and collecting the solid by filtration. The solid was dried in a vacuum oven for 18 h to yield 1.55 Kg of a granular, brittle, white solid.

Poly(allylamine/butanedioldiglycidyl ether).

[0031] To a 5 gallon plastic bucket was added poly(allylamine) hydrochloride (500 g) and water (2 L). The mixture was stirred to dissolve and the pH was adjusted to 10 with solid NaOH (142.3 g). The solution was allowed to cool to room temperature in the bucket and 1,4-butanedioldiglycidyl ether (130 mL) was added all at once with stirring. The mixture was stirred gently until it gelled after 4 minutes. The gel was allowed to continue curing for 18 h at room temperature. The gel was then removed and dried in a vacuum oven at 75°C for 24 h. The dry solid was ground and

sieved for -30 mesh and then suspended in 6 gallons on water. After stirring for 1 h the solid was filtered off and rinse process repeated twice more. The solid was rinsed twice in isopropanol (3 gallons), and dried in a vacuum oven at 50°C for 24 h to yield 580 g of a white solid.

Poly(allylamine/ethanedioldiglycidyl ether).

[0032] To a 100 mL beaker was added poly(allylamine) hydrochloride (10 g) and water (40 mL). The mixture was stirred to dissolve and the pH was adjusted to 10 with solid NaOH. The solution was allowed to cool to room temperature in the beaker and 1,2 ethanedioldiglycidyl ether (2.0 mL) was added all at once with stirring. The mixture was allowed to continue curing for 18 h at room temperature. The gel was then removed and blended in 500 mL of methanol. The solid was filtered off and suspended in water (500 mL). After stirring for 1 h the solid was filtered off and the rising process repeated. The solid was rinsed twice in isopropanol (400 mL), and dried in a vacuum oven at 50°C for 24 h to yield 8.7 g of a white solid.

Poly(allylamine/dimethylsuccinate).

[0033] To a 500 mL round bottom flask was added poly(allylamine) hydrochloride (10 g), methanol (100 mL), and triethylamine (10 mL). The mixture was stirred and dimethylsuccinate (1 mL) was added. The solution was heated to reflux and stirring turned off after 30 min. After 18 h the solution was cooled to room temperature and solid was filtered off and suspended in water (1 L). After stirring for 1 h the solid was filtered off and the rinse process repeated twice more. The solid was rinsed once in isopropanol (800 mL), and dried in a vacuum oven at 50°C for 24 h to yield 5.9 g of a white solid.

Poly(allyltrimethylammonium chloride).

[0034] To a 500 mL three necked flask equipped with a magnetic stirrer, a thermometer, and a condenser topped with a nitrogen inlet, was added poly(allylamine) crosslinked with epichlorohydrin (5.0 g), methanol (300 mL), methyl iodide (20 mL), and sodium carbonate (50 g). The mixture was then cooled and water was added to total volume of 2 L. Concentrated hydrochloric acid was added until no further bubbling resulted and the remaining solid was filtered off. The solid was rinsed twice in 10% aqueous NaCl (1 L) by stirring for 1 h followed by filtration to recover the solid. The solid was then rinsed three times by suspending it in water (2 L), stirring for 1 h, and filtering to recover the solid. Finally the solid was rinsed as above in methanol and dried in a vacuum over at 50°C for 18 h to yield 7.7 g of white granular solid.

Use

[0035] The objects of the invention involve treatment of patients with hyperphosphatemia. Elevated serum phosphate is commonly present in patients with renal insufficiency, hypoparathyroidism, pseudohypoparathyroidism acute untreated acromegaly, overmedication with phosphate salts, and acute tissue destruction as occurs during rhabdomyolysis and treatment of malignancies.

[0036] The term "patient" used herein is taken to mean any mammalian patient to which phosphate binders may be administered. Patients specifically intended for treatment with the medicaments of the invention include humans, as well as nonhuman primates, sheep, horses, cattle, goats, pigs, dogs, cats, rabbits, guinea pigs, hamsters, gerbils, rats and mice.

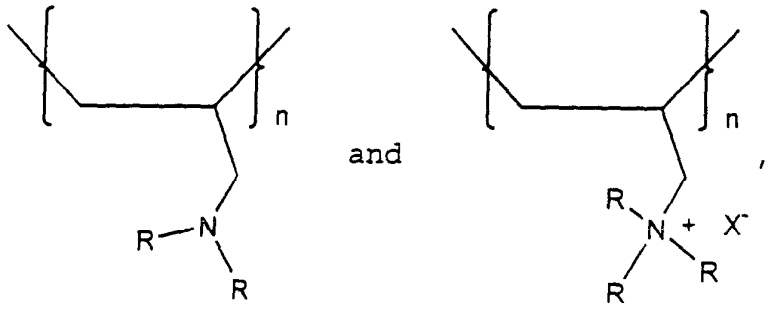
[0037] The compositions utilized in the medicaments of the inventions are orally administered in therapeutically effective amounts. A therapeutically effective amount of compound is that amount which produces a result or exerts an influence on the particular condition being treated. As used herein, a therapeutically effective amount of a phosphate binder means an amount which is effective in decreasing the serum phosphate levels of the patient to which it is administered.

[0038] The present pharmaceutical compositions are prepared by known procedures using well known and'readily available ingredients. In making the compositions of the present invention, the polymeric phosphate binder may be present alone, may be admixed with a carrier, diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, semi-solid or liquid material which acts as a vehicle, excipient or medium for the polymer. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, syrups, aerosols, (as a solid or in a liquid medium), soft or hard gelatin capsules, sterile packaged powders, and the like. Examples of suitable carriers, excipients, and diluents include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, methyl cellulose, methylhy-

droxybenzoates, propylhydroxybenzoates, propylhydroxybenzoates, and talc.

Claims

1. A crosslinked, phosphate-binding polymer characterized by repeat units selected from the group consisting of



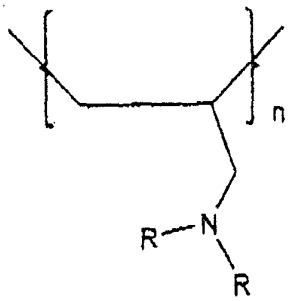
wherein n is an integer, X is an exchangeable, pharmaceutically acceptable anion and each R is H for oral administration, said polymer being non-toxic and stable once ingested.

2. The polymer of claim 1, wherein said polymer is crosslinked with a crosslinking agent selected from the group consisting of diacrylates, dimethacrylates, ethylene glycol diacrylate, propylene glycol diacrylate, butylene glycol diacrylate, ethylene glycol dimethacrylace, propylene glycol dimethacrylate, butylene glycol dimethacrylate, polyethyleneglycol dimethacrylate, polyethyleneglycol diacrylate, methylene bisacrylamide, methylene bismethacrylamide, ethylene bisacrylamide, epichlorohydrin, toluene diisocyanate, ethylenebismethacrylamide, ethylidene bisacrylamide, divinyl benzene, bisphenol A dimethacrylate, bisphenol A diacrylate, 1,4 butanedioldiglycidyl ether, 1,2 ethanedioldiglycidyl ether, 1,3-dichloropropane, 1,2-dichloroethane, 1,3-dibromopropane, 1,2-dibromoethane, succinyl dichloride, dimethylsuccinate, acryloyl chloride, or pyromellitic dianhydride wherein said crosslinking agent is present in said polymer from 0.5% to 75% by weight.

3. The polymer of claim 2, wherein said crosslinking agent is present in said composition from 2% to 20% by weight.

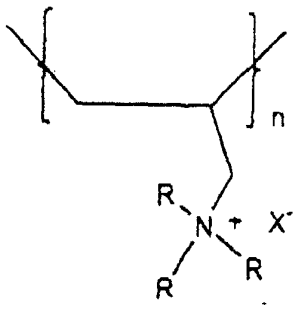
4. The polymer of claim 2 or claim 3, wherein said crosslinking agent comprises epichlorohydrin, 1,4 butanedioldiglycidyl ether, 1,2 ethanedioldiglycidyl ether, 1,3-dichloropropane,1,2-dichloroethane,1,3-dibromopropane, 1,2-dibromoethane, succinyl dichloride, dimethylsuccinate, toluene diisocyanate, acryloyl chloride, or pyromellitic dianhydride.

5. Use of a polymer characterised by a repeat unit having the formula



wherein n is an integer and each R, independently, is H or a C_1-C_5 alkyl, C_1-C_5 alkyl amino, or phenyl group, said polymer being non-toxic and stable once ingested, for the manufacture of a medicament for removing phosphate from a patient by ion exchange.

6. use of a polymer characterised by a repeat unit having the formula



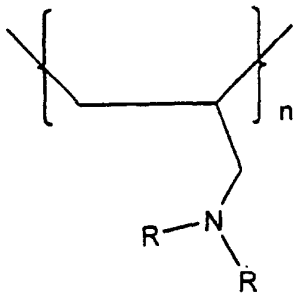
wherein n is an integer each R, independently, is H or a C_1-C_5 alkyl, C_1-C_5 alkylamino, or phenyl group, and each X is an exchangeable pharmaceutically acceptable anion, and wherein said polymer is non-toxic and stable once ingested, for the manufacture of a medicament for removing phosphate from a patient by ion exchange.

7. The use of claim 5 or claim 6, wherein said polymer is crosslinked with a crosslinking agent wherein said crosslinking agent is present in said composition from 0.5% to 75% by weight.

8. The use of claim 7 wherein said crosslinking agent is present in said composition from 2% to 20% by weight.

9. The use of claim 7 or claim 8, wherein said crosslinking agent comprises epichlorohydrin, 1,4 butanedioldiglycidyl ether, 1,2 ethanedioldiglycidyl ether, 1,3-dichloropropane,1,2-dichloroethane,1,3-dibromopropane, 1,2-dibromoethane, succinyl dichloride, dimethylsuccinate, toluene diisocyanate, acryloyl chloride, or pyromellitic dianhydride.

10. The use of claim 6 or claims dependent thereon, wherein the polymer is a copolymer comprising a second repeat unit having the formula



wherein each n, independently, is an integer and each R, independently, is H or a C_1-C_5 alkyl, C_1-C_5 alkylamino, or phenyl group.

Patentansprüche

1. ***Vernetztes, Phosphat bindendes*** Polymer, **dadurch gekennzeichnet**, dass eine oder mehrere der Wiederholungseinheiten ausgewählt werden aus der Gruppe bestehend aus

   und

   wobei n eine ganze Zahl bedeutet, X für ein austauschbares, pharmazeutisch annehmbares Anion steht, und R jeweils für H steht, zur ***oralen Verabreichung, wobei das Polymer, einmal aufgenommen, nichttoxisch und stabil ist.***

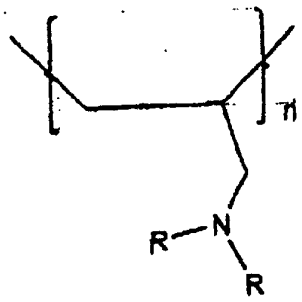
2. Polymer nach Anspruch 1, wobei das Polymer mit einem Vernetzungsmittel, ausgewählt aus der Gruppe bestehend

aus Diacrylaten, Dimethacrylaten, Ethylenglycoldiacrylat, Propylenglycoldiacrylat, Butylenglycoldiacrylat, Ethylenglycoldimethacrylat, Propylenglycoldimethacrylat, Butylenglycoldimethacrylat, Polyethylenglycoldimethacrylat, Polyethylenglycoldiacrylat, Methylenbisacrylamid, Methylenbismethacrylamid, Ethylenbisacrylamid, Epichlorhydrin, Toluoldiisocyanat, Ethylenbismethacrylamid, Ethylidenbisacrylamid, Divinylbenzol, Bisphenol A-dimethacrylat, Bisphenol A-diacrylat, 1,4-Butandioldiglycidylether, 1,2-Ethandioldiglycidylether, 1,3-Dichlorpropan, 1,2-Dichlorethan, 1,3-Dibrompropan, 1,2-Dibromethan, Succinyldichlorid, Dimethylsuccinat, Acrylsäurechlorid oder Pyromellitsäuredianhydrid vernetzt ist, und wobei das Vernetzungsmittel in dem Polymer von 0,5 bis 75 Gew.-% vorhanden ist.

3. Polymer nach Anspruch 2, wobei das Vernetzungsmittel in der Zusammensetzung von 2 bis 20 Gew.-% vorhanden ist.

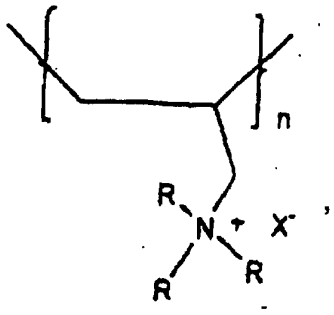
4. Polymer nach Anspruch 2 oder Anspruch 3, wobei das Vernetzungsmittel Epichlorhydrin, 1,4-Butandioldiglycidylether, 1,2-Ethandioldiglycidylether, 1,3-Dichlorpropan, 1,2-Dichlorethan, 1,3-Dibrompropan, 1,2-Dibromethan, Succinyldichlorid, Dimethylsuccinat, Toluoldiisocyanat, Acrylsäurechlorid oder Pyromellitsäuredianhydrid umfasst.

5. Verwendung eines Polymeren, gekennzeichnet durch eine Wiederholungseinheit mit der Formel



wobei n eine ganze Zahl ist und R jeweils unabhängig voneinander für H, ein C_1-C_5 Alkyl, ein C_1-C_5 Aminoalkyl, oder eine Phenolgruppe steht, und wobei das Polymer, sobald es aufgenommen wird, nicht toxisch ist und stabil, zur Herstellung eines Medikamentes zum Entfernen von Phosphat aus einem Patienten durch Ionen-Austausch.

6. Verwendung eines Polymeren, gekennzeichnet durch eine Wiederholungseinheit mit der Formel



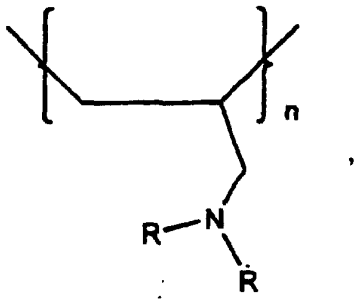
wobei n eine ganze Zahl ist und R jeweils unabhängig voneinander für H, ein C_1-C_5 Alkyl, ein C_1-C_5 Aminoalkyl, oder eine Phenylgruppe steht, und wobei X für ein austauschbares, pharmazeutisch akzeptables Anion steht, und wobei das Polymer, sobald es aufgenommmen wird, ungiftig und stabil ist, zur Herstellung eines Medikamentes zum Entfernen von Phosphat aus einem Patienten durch Ionen-Austausch.

7. Verwendung nach Anspruch 5 oder Anspruch 6, wobei das Polymer mit einem Vernetzungsmittel vernetzt ist, und wobei das Vernetzungsmittel in der Zusammensetzung in einer Menge von 0,5 bis 75 Gew.-% vorhanden ist.

8. Verwendung nach Anspruch 7, wobei das Vernetzungsmittel in der Zusammensetzung in einer Menge von 2 bis 20 Gew.-% vorhanden ist.

9. Verwendung nach Anspruch 7 oder Anspruch 8, wobei das Vernetzungsmittel Epichlorhydrin, 1,4-Butandioldiglycidylether, 1,2-Ethandioldiglydicylether, 1,3-Dichlorpropan, 1,2-Dichlorethan, 1,3-Dibrompropan, 1,2-Dibromethan, Succinyldichlorid, Dimethylsuccinat, Toluoldiisocyanat, Acrylsäurechlorid oder Pyromellitsäuredianhydrid umfasst.

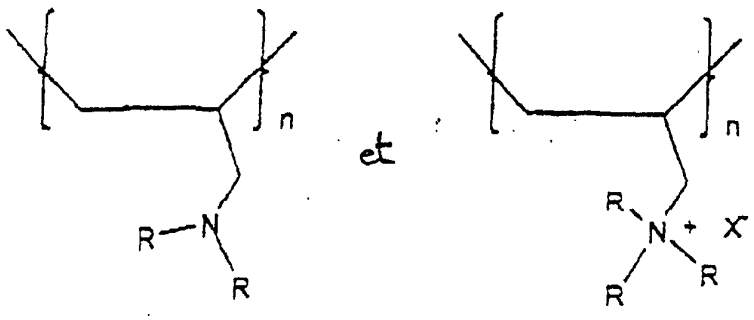
10. Verwendung nach Anspruch 6 oder davon abhängigen Ansprüchen, wobei das Polymer ein Copolymer ist, welches eine zweite Wiederholungseinheit umfasst mit der Formel



wobei jedes n unabhängig voneinander für eine gerade Zahl steht, und R unabhängig voneinander für H oder ein C_1-C_5 Alkyl, ein C_1-C_5 Aminoalkyl oder eine Phenylgruppe steht.

Revendications

1. Polymère réticulé liant le phosphate caractérisé par un ou plusieurs motifs récurrents choisis dans le groupe constitué des motifs de formules :



dans lesquelles n est un nombre entier, X est un anion échangeable pharmaceutiquement acceptable et chaque R représente un atome d'hydrogène, pour administration orale, ledit polymère étant non toxique et stable une fois ingéré.

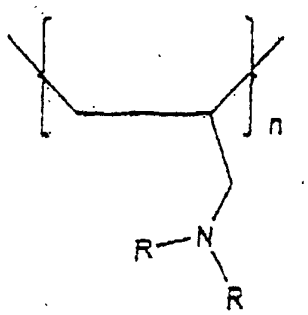
2. Polymère selon la revendication 1, dans lequel ledit polymère est réticulé à l'aide d'un agent réticulant choisi dans le groupe constitué des diacrylate, diméthacrylate, diacrylate d'éthylèneglycol, diacrylate de propylèneglycol, diacrylate de butylèneglycol, diméthacrylate d'éthylèneglycol, diméthacrylate de propylèneglycol, diméthacrylate de butylèneglycol, diméthacrylate de polyléthylèneglycol, diacrylate de polyéthylèneglycol, méthylène bisacrylamide, méthylène bisméthacrylamide, éthylène bisacrylamide, épichlorhydrine, toluène diisocyanate, éthylène bisméthacrylamide, éthylidène bisacrylamide, divinylbenzène, diméthacrylate de bisphénol A, diacrylate de bisphénol A, éther diglycidylique de 1,4-butanediol, éther diglycidylique de 1,2- éthanediol, 1,3-dichloropropane, 1,2-dichloroéthane, 1,3-dibromopropane, 1,2-dibromoéthane, dichlorure de succinyle, succinate de diméthyle, chlorure

d'acryloyle, et dianhydride pyromellique, dans lequel ledit agent réticulant est présent dans ledit polymère à raison de 0,5 à 75% en poids.

3. Polymère selon la revendication 2, dans lequel ledit agent réticulant est présent dans ladite composition à raison de 2 à 20% en poids.

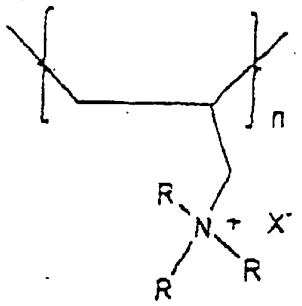
4. Polymère selon la revendication 2 ou la revendication 3, dans lequel ledit agent réticulant comprend de l'épichlorhydrine, de l'éther diglycidylique de 1,4-butanediol, de l'éther diglycidylique de 1,2-éthanediol, du 1,3-dichloropropane, du 1,2-dichloroéthane, du 1,3-dibromopropane, du 1,2-dibromoéthane, du dichlorure de succinyle, du succinate de diméthyle, du toluène-diisocyanate, du chlorure d'acryloyle ou du dianhydride pyromellique.

5. Utilisation d'un polymère caractérisé par un motif récurrent de formule :



dans lequel n est un nombre entier et chaque R représente indépendamment un atome d'hydrogène ou un groupe C_1-C_5 alkyle, C_1-C_5 alkylamino ou phényle, ledit polymère étant non toxique et stable une fois ingéré, pour la fabrication d'un médicament pour l'élimination de phosphate par échange d'ions chez un patient.

6. Utilisation d'un polymère caractérisé par un motif récurrent de formule :



dans lequel n est un nombre entier, chaque R représente indépendamment un atome d'hydrogène ou un groupe alkyle en C_1-C_5 ou un groupe alkylamino en C_1-C_5 ou un groupe phényle et chaque X représente un anion échangeable pharmaceutiquement acceptable, et dans lequel ledit polymère est non toxique et stable une fois ingéré, pour la fabrication d'un médicament pour l'élimination de phosphate par échange d'ions chez un patient.

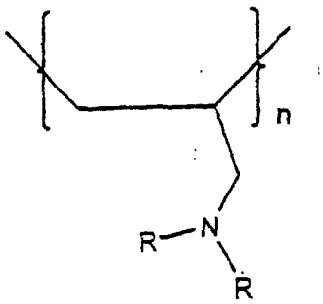
7. Utilisation selon la revendication 5 ou la revendication 6, dans laquelle ledit polymère est réticulé à l'aide d'un agent réticulant, ledit agent réticulant étant présent dans ladite composition à raison de 0,5 à 75% en poids.

8. Utilisation selon la revendication 7, dans laquelle ledit agent réticulant est présent dans ladite composition à raison de 2 à 20% en poids.

9. Utilisation selon la revendication 7 ou la revendication 8, dans laquelle ledit agent réticulant comprend de l'épichlorhydrine, de l'éther diglycidylique de 1,4-butanediol, de l'éther diglycidylique de 1,2-éthanediol, du 1,3-dichloropropane, du 1,2-dichloroéthane, du 1,3-dibromopropane, du 1,2-dibromoéthane, du dichlorure de succinyle, du

succinate de diméthyle, du toluène-diisocyanate, du chlorure d'acryloyle ou du dianhydride pyromellique.

10. Utilisation selon la revendication 6 ou selon l'une des revendications dépendantes de la revendication 6, dans lesquelles ledit polymère est un copolymère comprenant, à titre de second motif récurrent, un motif récurrent de formule :



dans laquelle chaque n, indépendamment, est un nombre entier, chaque R, indépendamment, représente H ou alkyle en C_1-C_5, alkylamino en C_1-C_5, ou un groupe phényle.