Office de la Propriété Intellectuelle du Canada
Un organisme d'Industrie Canada

Canadian Intellectual Property Office
An agency of Industry Canada

CA 2558029 C 2013/05/07

(11)(21) 2 558 029

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(86) Date de dépôt PCT/PCT Filing Date: 2005/03/30
(87) Date publication PCT/PCT Publication Date: 2005/10/20
(45) Date de délivrance/Issue Date: 2013/05/07
(85) Entrée phase nationale/National Entry: 2006/08/30
(86) N° demande PCT/PCT Application No.: US 2005/010978
(87) N° publication PCT/PCT Publication No.: 2005/097081
(30) Priorités/Priorities: 2004/03/30 (US10/814,527); 2004/03/30 (US10/813,872); 2004/03/30 (US10/814,749); 2004/10/13 (US10/965,274)

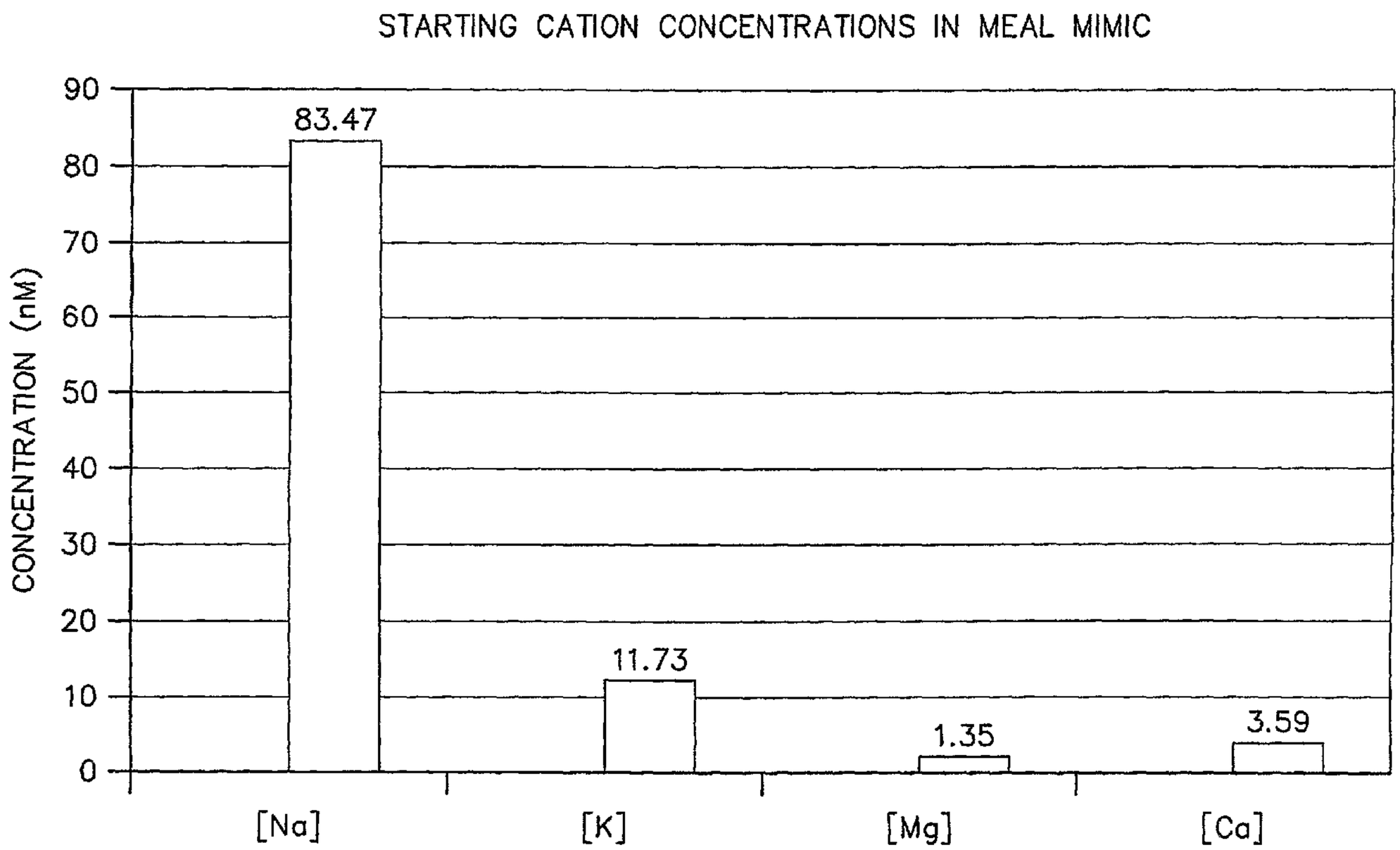
(51) Cl.Int./Int.Cl. *A61K 31/78* (2006.01), *A61P 3/12* (2006.01), *A61P 39/04* (2006.01), *A61P 7/08* (2006.01)

(72) Inventeurs/Inventors:
CHARMOT, DOMINIQUE, US;
CHANG, HAN TING, US;
KLAERNER, GERRIT, US;
COPE, MICHAEL JAMES, US;
LIU, MINGJUN, US;
LIU, FUTIAN, US;
MONG, TONY KWOK-KONG, US

(73) Propriétaire/Owner:
RELYPSA, US

(74) Agent: RIDOUT & MAYBEE LLP

(54) Titre : POLYMERES DE LIAISON IONIQUE ET LEURS UTILISATIONS
(54) Title: ION BINDING POLYMERS AND USES THEREOF



(57) Abrégé/Abstract:
The present invention provides methods and compositions for the treatment of ion imbalances. In particular, the invention provides compositions comprising potassium binding polymers and pharmaceutical compositions thereof. Methods of use of the polymeric and pharmaceutical compositions for therapeutic and/or prophylactic benefits are disclosed herein. Examples of these methods include the treatment of hyperkalemia, such as hyperkalemia caused by renal failure and/or the use of hyperkalemia causing drugs.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
20 October 2005 (20.10.2005)

PCT

(10) International Publication Number
WO 2005/097081 A1

(51) International Patent Classification[7]: A61K 9/32, 47/30

(21) International Application Number:
PCT/US2005/010978

(22) International Filing Date: 30 March 2005 (30.03.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

10/814,749	30 March 2004 (30.03.2004)	US
10/813,872	30 March 2004 (30.03.2004)	US
10/814,527	30 March 2004 (30.03.2004)	US
10/965,274	13 October 2004 (13.10.2004)	US

(71) Applicant (*for all designated States except US*): **ILYPSA, INC.** [US/US]; 3410 Central Expressway, Santa Clara, CA 95051 (US).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **CHARMOT, Dominique** [FR/US]; 1238 Bracebridge Court, Campbell, CA 95008 (US). **CHANG, Han, Ting** [—/US]; 220 Garnet Drive, Livemore, CA 94550 (US). **KLAERNER, Gerrit** [DE/US]; 5456 Fern Drive, San Jose, CA 95124 (US). **COPE, Michael, James** [IE/US]; 1111 Russell Street, Berkeley, CA 94702 (US). **LIU, Mingjun** [CN/US]; 2250 Monroe Street, Apt. 393, Santa Clara, CA 95050 (US). **LIU, Futian** [CA/US]; 1025 Boranda Avenue, Apt. 2, Mountain View, CA 94040 (US). **MONG, Tony, Kwok-Kong** [CN/US]; 955 Escanon Avenue, Apt. 512, Sunnyvale, CA 94085 (US).

(74) Agents: **ROCHE, Anie, K.** et al.; Wilson, Sonsini, Goodrich & Rosati, 650 Page Mill Road, Palo Alto, CA 94306-1050 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2005/097081 A1

(54) Title: ION BINDING POLYMERS AND USES THEREOF

(57) Abstract: The present invention provides methods and compositions for the treatment of ion imbalances. In particular, the invention provides compositions comprising potassium binding polymers and pharmaceutical compositions thereof. Methods of use of the polymeric and pharmaceutical compositions for therapeutic and/or prophylactic benefits are disclosed herein. Examples of these methods include the treatment of hyperkalemia, such as hyperkalemia caused by renal failure and/or the use of hyperkalemia causing drugs.

ION BINDING POLYMERS AND USES THEREOF

BACKGROUND OF THE INVENTION

[0002] Potassium (K^+) is the most abundant intracellular cation, comprising ~ 35-40mEq/kg in humans. See Agarwal, R, et al. (1994) Gastroenterology 107: 548-571; Mandal, AK (1997) Med Clin North Am 81: 611-639. Only 1.5-2.5% of this is extracellular. Potassium is obtained through the diet, mainly through vegetables, fruits, meats and dairy products, with certain food such as potatoes, beans, bananas, beef and turkey being especially rich in this element. See Hunt, CD and Meacham, SL (2001) J Am Diet Assoc 101: 1058-1060; Hazell, T (1985) World Rev Nutr Diet 46: 1-123. In the US, intake is ~80mEq/day. About 80% of this intake is absorbed from the gastrointestinal tract and excreted in the urine, with the balance excreted in sweat and feces. Thus, potassium homeostasis is maintained predominantly through the regulation of renal excretion. Where renal excretion of K^+ is impaired, elevated serum K^+ levels will occur. Hyperkalemia is a condition wherein serum potassium is greater than about 5.0 mEq/L.

[0003] While mild hyperkalemia, defined as serum potassium of about 5.0-6mEq/L, is not normally life threatening, moderate to severe hyperkalemia (with serum potassium greater than about 6.1 mEq/L) can have grave consequences. Cardiac arrythmias and altered ECG waveforms are diagnostic of hyperkalemia. See Schwartz, MW (1987) Am J Nurs 87: 1292-1299. When serum potassium levels increases above about 9mEq/L, atrioventricular dissociation, ventricular tachycardia, or ventricular fibrillation can occur.

[0004] Hyperkalemia is rare in the general population of healthy individuals. However, certain groups definitely exhibit a higher incidence of hyperkalemia. In patients who are hospitalized, the incidence of hyperkalemia ranges from about 1-10%, depending on the definition of hyperkalemia. Patients at the extremes of life,

either premature or elderly, are at high risk. The presence of decreased renal function, genitourinary disease, cancer, severe diabetes, and polypharmacy can also predispose patients to hyperkalemia.

[0005] Most of the current treatment options for hyperkalemia are limited to use in hospitals. For example, exchange resins, such as Kayexalate, are not suitable for outpatient or chronic treatment, due to the large doses necessary that leads to very low patient compliance, severe GI side effects and significant introduction of sodium (potentially causing hypernatremia and related fluid retention and hypertension). Diuretics that can remove sodium and potassium from patients via the kidneys are often limited in their efficacy due to underlying kidney disease and frequently related diuretic resistance. Diuretics are also contraindicated in patients where a drop in blood pressure and volume depletion are undesired (e.g. CHF patients that in addition to suffering from low blood pressure are often on a combination of drugs such as ACE inhibitors and potassium sparing diuretics such as spironolactone that can induce hyperkalemia).

[0006] Overall, it would be desirable to obtain higher binding capacity materials for the treatment of hyperkalemia, such materials preferably having a greater binding in the physiological pH range for potassium, which are also non-degradable, non-absorbable and have decreased toxic effects.

SUMMARY OF THE INVENTION

[0007] The present invention provides compositions and methods for the removal of potassium ions from the gastro-intestinal tract. In one embodiment, an effective amount of a potassium binding polymer is administered to an animal subject, such as a human, the polymer being capable of binding and removing an average of 1.5 mmol or higher of potassium per gm of polymer. In another embodiment, the polymer has an average *in vitro* binding capacity of greater than about 5 mmol/gm of polymer at a pH of greater than about 5.5. In another embodiment, the potassium binding polymer further comprises a shell that is physically or chemically attached to the polymer.

[0008] The potassium binding polymer is preferably a poly-fluoroacrylic acid polymer, a poly-difluoromaleic acid polymer, poly-sulfonic acid, or a combination thereof. In other embodiments the polymer comprises 2-fluoroacrylic acid crosslinked with divinylbenzene, ethylene bisacrylamide, N,N'-bis(vinylsulfonylacetyl) ethylene diamine, 1,3-bis(vinylsulfonyl) 2-propanol,

vinylsulfone, N,N'-methylenebisacrylamide polyvinyl ether, polyallylether, or a combination thereof. Preferably, the shell comprises of copolymers of a vinylamine, ethyleneimine, propyleneimine, allylamine, methallylamine, vinylpyridines, alkyaminoalkyl(meth)acrylates, alkyaminoalkyl(meth)acrylamides, aminomethylstyrene, chitosan, adducts of aliphatic amine or aromatic amine with electrophile such as epichlorhydrine, alkylhalides or epoxides, and wherein the amine is optionally a quarternized form. Optionally, the shell can be crosslinked by epoxides, halides, esters, isocyanate, or anhydrides such as epichlorohydrine, alkyl diisocyanates, alkyl dihalides, or diesters.

[0009] In a preferred embodiment, the potassium binding polymer is a α-fluoroacrylate polymer crosslinked with divinyl benzene. A preferred core-shell composition comprises a core of polystyrene sulfonate or α-fluoroacrylate polymer crosslinked with divinyl benzene and a shell of Eudragit™ RL 100, Eudragit RS 100, a combination thereof, benzylated polyethyleneimine, or N-dodecyl polyethyleneimine. Preferably, the core shell compositions are synthesized by a Wurster fluid bed coating process or a controlled coating precipitation process. Suitable controlled coating precipitation process includes solvent coacervation process, a pH triggered precipitation process, or temperature triggered precipitation process.

[0010] The compositions described herein are suitable for therapeutic and/or prophylactic use in the treatment of hyperkalemia. In one embodiment, the potassium binding compositions are used in combination with drugs that cause potassium retention such as potassium-sparing diuretics, angiotensin-converting enzyme inhibitors (ACEIs), Angiotensin receptor blockers (ARBs), non-steroidal anti-inflammatory drugs, heparin, or trimethoprim.

[0011] A preferred method for removing potassium from an animal subject comprises administering a potassium-binding polymer an α-fluoroacrylate polymer crosslinked with divinyl benzene. In another method, potassium is removed from a patient with a core-shell composition comprising a core of polystyrene sulfonate or α-fluoroacrylate polymer crosslinked with divinyl benzene and a shell of Eudragit RL 100, Eudragit RS 100, a combination thereof, benzylated polyethyleneimine, or N-dodecyl polyethyleneimine.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] Figure 1 depicts starting cation concentrations in a meal mimic.

[0013] Figure 2 depicts binding of cations by resins in a meal mimic.

[0014] Figure 3 depicts the original concentrations of cations in the feces of two subjects.

[0015] Figure 4 depicts the binding of cations in human fecal extracts to cation exchange resins.

[0016] Figure 5 depicts the membrane preparation for determination of ion permeability.

[0017] Figure 6 depicts the binding data of different polyethyleneimine coated beads for different cations.

[0018] Figure 7 depicts the effect of a Eudragit RL 100 shell on magnesium and potassium binding.

[0019] Figure 8 depicts binding of magnesium on benzylated polyethyleneimine coated Dowex (K) beads.

[0020] Figure 9 depicts the stability of Ben(84)-PEI coated Dowex (K) beads under acid conditions representative of the acidic conditions in the stomach.

[0021] Figure 10 depicts potassium and magnesium binding by Dowex beads coated with benzylated polyethyleneimine.

[0022] Figure 11 depicts magnesium binding by fluoroacrylic acid beads with benzylated polyethylene imine shell.

[0023] Figure 12 depicts a setup for determining membrane permeability.

[0024] Figure 13 depicts the permeability of benzylated polyethyleneimine membrane.

[0025] Figure 14 depicts the permeability and permselectivity of membranes comprising of mixtures of Eudragit RL100 and Eudragit RS 100.

[0026] Figure 15 depicts the effects of bile acids on potassium binding by Dowex(Li) coated with polyethyleneimine.

[0027] Figure 16 depicts the effect of pH on α-fluoroacrylate –acrylic acid copolymer.

[0028] Figure 17 depicts levels of excretion of cations in rats following administration of fluoroacrylate polymer and Kayexalate.

DETAILED DESCRIPTION OF THE INVENTION

[0029] The present invention provides methods, polymeric pharmaceutical compositions, and kits for the treatment of animal subjects. The terms "animal

subject" and "animal" as used herein includes humans as well as other mammals. In particular, the present invention provides polymeric compositions for the removal of potassium ions. Preferably, these compositions are used for the removal of potassium ions from the gastrointestinal tract of animal subjects.

[0030] One aspect of the invention is a method of removing potassium ions with a potassium-binding polymeric composition. In one embodiment, the potassium-binding polymeric composition has high capacity and/or selectivity for binding potassium and does not significantly release the bound potassium in the gastrointestinal tract. It is preferred that the polymeric composition exhibit selective binding for potassium ions.

[0031] It is preferred that the polymeric compositions of the present invention exhibit high capacity and/or selectivity for potassium ions. The term "high capacity" as used herein encompasses an average *in vivo* binding of about 1.5 mmol or more of potassium per gm of polymer. Typically, this *in vivo* binding capacity is determined in a human. Techniques for determining *in vivo* potassium binding capacity in a human are well known in the art. For example, following administration of a potassium-binding polymer to a patient, the amount of potassium in the feces can be used to calculate the *in vivo* potassium binding capacity. The average *in vivo* binding is preferably calculated in a set of normal human subjects, this set being about 5 human subjects, preferably about 10 human subjects, even more preferably about 25 human subjects, and most preferably about 50 human subjects.

[0032] In some embodiments, the average *in vivo* potassium binding capacity can be equal to or more than about 1.5 mmol per gm of polymer in a human. Preferably the *in vivo* potassium binding capacity in a human is about 2 mmol or more per gm, more preferred is about 3 mmol or more per gm, even more preferred is about 4 mmol or more per gm, and most preferred is about 6 mmol or more per gm. In a preferred embodiment, the average *in vivo* potassium binding capacity in a human is about 2 mmol to about 6 mmol per gm in a human.

[0033] The capacity of the potassium binding polymers can also be determined *in vitro*. It is preferred that the *in vitro* potassium binding capacity is determined in conditions that mimic the physiological conditions of the gastro-intestinal tract, in particular the colon. In some embodiments, the *in vitro* potassium binding capacity is determined in solutions with a pH of about 5.5 or more. In various embodiments, *in vitro* potassium binding capacity in a pH of about 5.5 or more is equal to or more than

6 mmol per gm of polymer. A preferred range of *in vitro* potassium binding capacity in a pH of about 5.5 or more is about 6 mmol to about 12 mmol per gm of polymer. Preferably the *in vitro* potassium binding capacity in a pH of about 5.5 or more is equal to about 6 mmol or more per gm, more preferred is about 8 mmol or more per gm, even more preferred is about 10 mmol or more per gm, and most preferred is about 12 mmol or more per gm.

[0034] The higher capacity of the polymeric composition enables the administration of a lower dose of the composition. Typically the dose of the polymeric composition used to obtain the desired therapeutic and/or prophylactic benefits is about 0.5 gm/day to about 25 gm/day. Most preferred is about 15 gm/day or less. A preferred dose range is about 5 gm/day to about 20 gm/day, more preferred is about 5 gm/day to about 15 gm/day, even more preferred is about 10 gm/day to about 20 gm/day, and most preferred is about 10 gm/day to about 15 gm/day. Preferably the dose is administered about three times a day with meals, most preferably the dose is administered once a day.

[0035] It is also preferred that the compositions described herein retain a significant amount of the bound potassium. Preferably, the potassium is bound by the polymer in the colon and not released prior to excretion of the polymer in the feces. The term "significant amount" as used herein is not intended to mean that the entire amount of the bound potassium is retained. It is preferred that at least some of the bound potassium is retained, such that a therapeutic and/or prophylactic benefit is obtained. Preferred amounts of bound potassium that can be retained range from about 5% to about 100%. It is preferred that the polymeric compositions retain about 25% of the bound potassium, more preferred is about 50%, even more preferred is about 75% and most preferred is retention of about 100% of the bound potassium. The period of retention is preferred to be during the time that the composition is being used therapeutically and/or prophylactically. In the embodiment in which the composition is used to bind and remove potassium from the gastrointestinal tract, the retention period is the time of residence of the composition in the gastro-intestinal tract and more particularly the average residence time in the colon.

[0036] Preferably the potassium binding polymers are not absorbed from the gastro-intestinal tract. The term "non-absorbed" and its grammatical equivalents is not intended to mean that the entire amount of administered polymer is not absorbed. It is expected that certain amounts of the polymer may be absorbed. It is preferred that

about 90% or more of the polymer is not absorbed, preferably about 95% or more is not absorbed, even more preferably about 97% or more is not absorbed, and most preferably about 98% or more of the polymer is not absorbed.

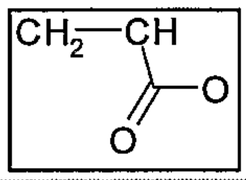
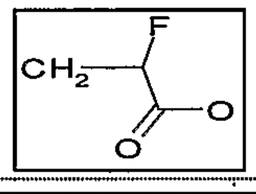
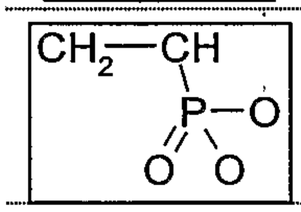
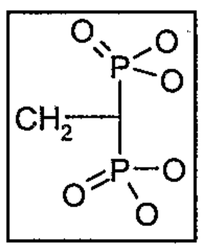
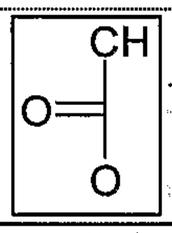
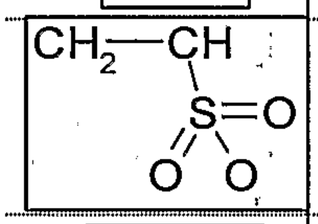
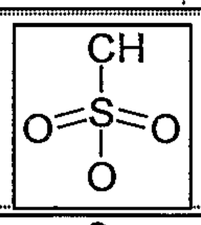
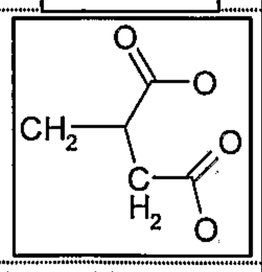
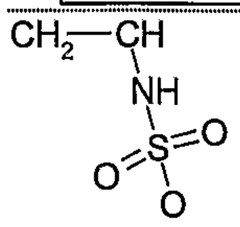
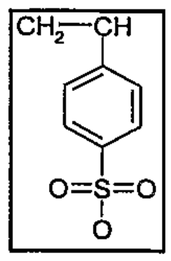
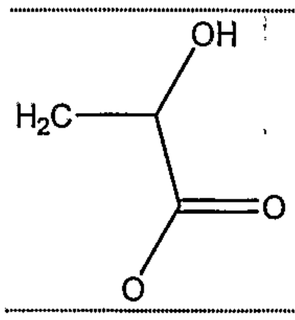
Potassium-Binding Polymers

[0037] In some embodiments, the potassium-binding polymers comprise acid groups in their protonated or ionized form, such as sulfonic ($-SO_3^-$), sulfuric ($-OSO_3^-$), carboxylic ($-CO_2^-$), phosphonic ($-PO_3^{--}$), phosphoric ($-(OPO_3^{--}$), or sulfamate ($-NHSO_3^-$). Preferably, the fraction of ionization of the acid groups is greater than about 75% at the physiological pH in the colon and the potassium binding capacity is greater than about 5 mmol/gm. Preferably the ionization of the acid groups is greater than about 80%, more preferably it is greater than about 90%, and most preferably it is about 100%. In certain embodiments the acid containing polymers contain more than one type of acid groups. In certain embodiments the acid containing polymers are administered in their anhydride form and generate the ionized form when contacted with physiological fluids.

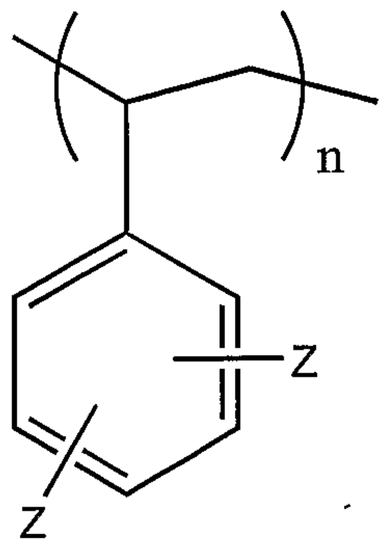
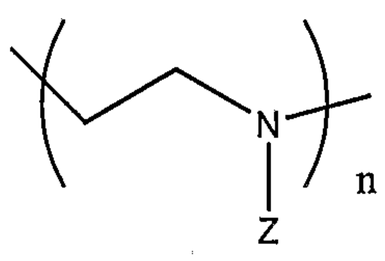
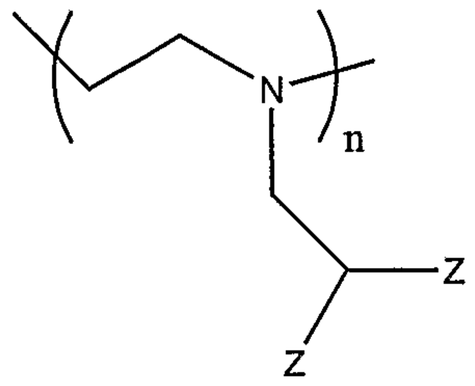
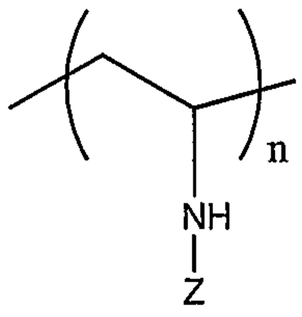
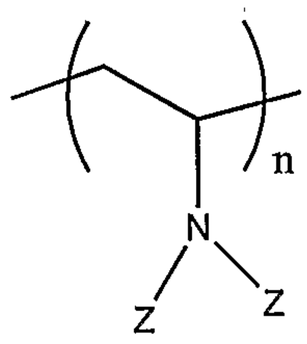
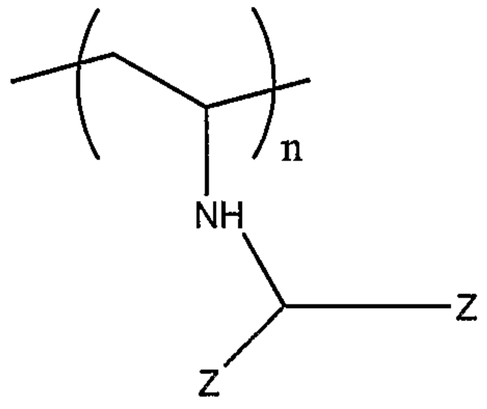
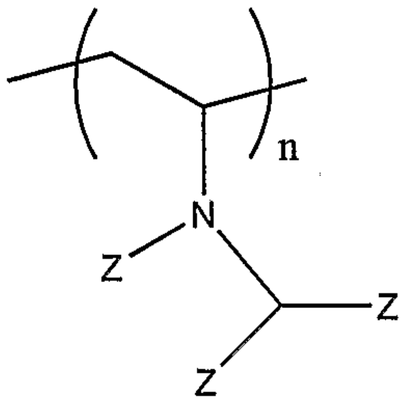
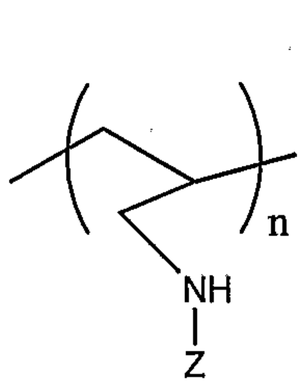
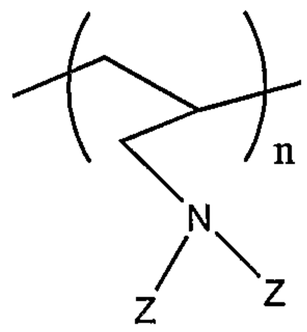
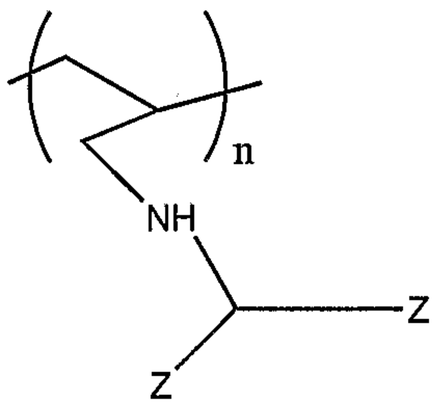
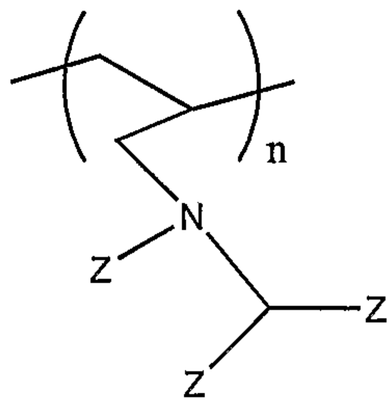
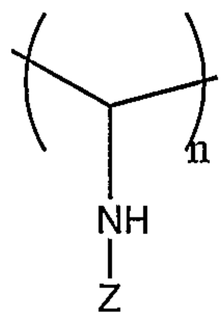
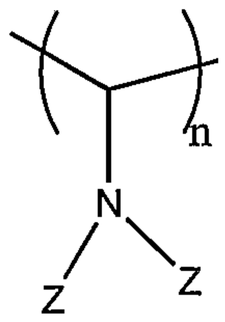
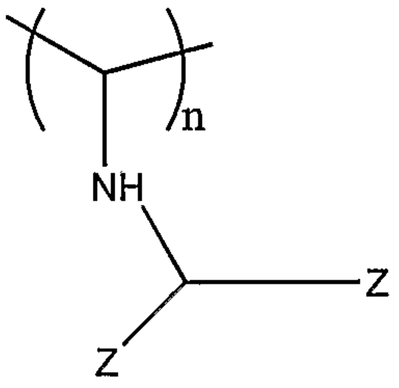
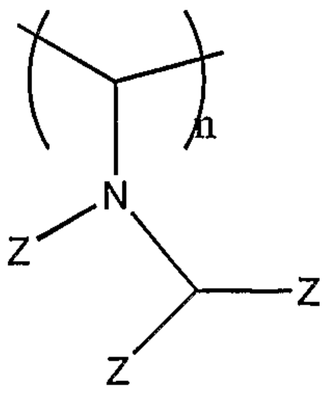
[0038] In some other embodiments, a pK_a-decreasing group, preferably an electron-withdrawing substituent, is located adjacent to the acid group, preferably it is located in the alpha or beta position of the acid group. The preferred electron-withdrawing substituents are a hydroxyl group, an ether group, an ester group, or an halide atom, and most preferably F. Preferred acid groups are sulfonic ($-SO_3^-$), sulfuric ($-OSO_3^-$), carboxylic ($-CO_2^-$), phosphonic ($-PO_3^{--}$), phosphoric ($-(OPO_3^{--}$), or sulfamate ($-NHSO_3^-$). Other preferred polymers result from the polymerization of alpha-fluoro acrylic acid, difluoromaleic acid, or an anhydride thereof.

[0039] Examples of other suitable monomers for potassium-binding polymers are included in Table 1.

TABLE 1: Examples of cation exchange moieties – structures & theoretical binding capacities

	Molar mass per charge	Theoretical capacity	Fraction of titrable H @pH 3	Fraction of titrable H @ pH 6	Expected Capacity @pH3	Expected Capacity @pH6
	71	14.1	0.05	.35	0.70	4.93
	87	11.49	0.2	0.95	2.3	10.92
	53	18.9	0.25	0.5	4.72	9.43
	47.5	21.1	0.25	0.5	5.26	10.53
	57	17.5	0.1	0.5	1.75	8.77
	107	9.3	1	1	9.35	9.35
	93	10.8	1	1	10.75	10.75
	63	15.9	0	0.4	0	6.35
	125	8	1	1	8	8
	183	5.5	1	1	5.46	5.46
	87	11.49	.1	.6	1.14	6.89

[0040] Other suitable cation exchange moieties include:

wherein n is equal to or greater than one and Z represents either SO_3H or PO_3H. Preferably n is about 50 or more, more preferably n is about 100 or more, even more preferred is n about 200 or more, and most preferred is n about 500 or more.

[0041] Suitable phosphonate monomers include vinyl phosphonate, vinyl 1,1 bis phosphonate, and ethylenic derivatives of phosphonocarboxylate esters, oligo(methylenephosphonates), and hydroxyethane-1,1-diphosphonic acid. Methods of synthesis of these monomers are well known in the art.

[0042] Sulfamic (i.e. when Z=SO_3H) or phosphoramidic (i.e. when Z= PO_3H) polymers can be obtained from amine polymers or monomer precursors treated with a sulfonating agent such as sulfur trioxide/amine adducts or a phosphonating agent such as P_2O_5, respectively. Typically, the acidic protons of phosphonic groups are exchangeable with cations, like sodium or potassium, at pH of about 6 to about 7.

[0043] Free radical polymers derived from monomers such as vinyl sulfonate, vinylphosphonate, or vinylsulfamate can also be used.

[0044] Preferred monomers for use herein are α-fluoroacrylate and difluoromaleic acid, α-fluoroacrylate being most preferred. This monomer can be prepared from a variety of routes, see for example, Gassen et al, J. Fluorine Chemistry, 55, (1991) 149-162, KF Pittman, C. U., M. Ueda, et al. (1980). *Macromolecules* 13(5): 1031-1036. Difluoromaleic acid is preferred by oxidation of fluoroaromatic compounds (Bogachev et al, Zhurnal Organisheskoi Khimii, 1986, 22(12), 2578-83), or fluorinated furans derivatives (See U.S. patent 5,112,993). A preferred mode of synthesis of α-fluoroacrylate is given in EP 415214.

[0045] Other methods comprise the step-growth polymerization from phosphonate, carboxylic, phosphate, sulfinate, sulfate and sulfonate functionals compounds. High density polyphosphonates such as Briquest, marketed by Rhodia, are particularly useful.

[0046] The polymers of the invention also include ion exchange resins synthesized from naturally occurring polymers, such as saccharide polymers and semi-synthetic polymers, optionally functionalized to create ion exchange sites on the backbone or on the pendant residues. Examples of polysaccharides of interest include materials from vegetal or animal origins, such as cellulosic materials, hemicellulose, alkyl cellulose, hydroxyalkyl cellulose, carboxymethylcellulose, sulfoethylcellulose, starch, xylan, amylopectine, chondroitin, hyarulonate, heparin, guar, xanthan, mannan, galactomannan, chitin and chitosan. Most preferred are polymers that do not degrade under the physiological conditions of the gastrointestinal tract and remain non-absorbed, such as carboxymethylcellulose, chitosan, and sulfoethylcellulose.

[0047] The potassium binding polymer can be encased in a dialysis bag, paper bag, microporous matrix, polymer gel, hollow fibers, vesicles, capsules, tablet, or a film.

[0048] The polymers can be formed by polymerization processes using either homogeneous or heterogeneous mode: in the former case a crosslinked gel is obtained by reacting the soluble polymer chains with a crosslinker, forming a bulk gel which is either extruded and micronized , or comminuted to smaller sized particles. In the former case, the particles are

obtained by emulsification or dispersion of a soluble polymer precursor, and subsequently crosslinked. In another method, the particles are prepared by polymerization of a monomer in an emulsion, suspension, miniemulsion or dispersion process. The continuous phase is either an aqueous vehicle or an organic solvent. When a suspension process is used, any suitable type of variants is possible, including methods such as "templated polymerization," "multistage'seeded suspension," all of which yielding mostly monodisperse particles. In one particular embodiment, the beads are formed using a "jetting" process (see U.S. patent 4,427,794), whereby a "tube of liquid containing a monomer plus initiator mixture is forced through a vibrating nozzle into a continuous phase. The nozzles can be arranged in spinning turret so as to force the liquid under centrifugal force.

[0049] A preferred process to produce alpha-fluoroacrylate beads is direct suspension polymerization. Typically, suspension stabilizers, such as polyvinyl alcohol, are used to prevent coalescence of particles during the process. It has been observed that the addition of NaCl in the aqueous phase decreased coalescence and particle aggregation. Other suitable salts for this purpose include salts that solubilize in the aqueous phase. In this embodiment, water soluble salts are added at a weight % comprised between about 0.1 to about 10, preferably comprised between about 2 to about 5 and even more preferably between about 3 and about 4.

[0050] It has been observed that in the case of alpha-fluoroacrylate esters (e.g. MeFA) suspension polymerization, the nature of the free radical initiator plays a role in the quality of the suspension in terms of particle stability, yield of beads, and the conservation of a spherical shape. Use of water-insoluble free radical initiators, such as lauryl peroxide, led to the quasi absence of gel and produced beads in a high yield. It was found that free radical initiators with water solubility lower than 0.1 g/L preferably lower than 0.01 g/L led to optimal results. In preferred embodiments, polyMeFA beads are produced with a combination of a low water solubility free radical initiator and the presence of salt in the aqueous phase, such as NaCl.

[0051] In some embodiments wherein the potassium binding polymer is used without a shell, the potassium binding polymer is not Kayexalate, sodium polystyrene sulfonate, or an ammonium form of polystyrene sulfonate.

[0052] In some embodiments, crown ethers and crown-ether like molecules are used as potassium binding polymers. Crown ethers show selectivity for certain alkali metals over others, based on the hole-size and the size of the metal ion. See Tables 2, 3 and 4 and Pedersen, C.J. 1987. Charles J. Pederson - Nobel Lecture. The discovery of crown ethers. In

Nobel Lectures, Chemistry 1981-1990. T. Frangsmyr, editor. World Scientific Publishing Co., Singapore.

[0053] In yet another embodiment, crown ethers are used as shell materials to decrease the passage of sodium, magnesium, calcium and other interfering molecules to the core and as a result, increase the *in vivo* binding capacity of a core polymer.

Table 2: Diameters of holes in Sample Crown Ethers, in Angstrom units

Macrocyclic Polyethers	Diameters
All 14-crown-4	1.2-1.5
All 15-crown-5	1.7-2.2
All 18-crown-6	2.6-3.2
All 21-crown-7	3.4-4.3

Table 3: Complexable cations and their diameters in Angstrom units

Group I		Group II		Group III		Group IV	
Li	1.36						
Na	1.94						
K	2.66	Ca	1.98				
Cu(I)	1.92	Zn	1.48				
Rb	2.94	Sr	2.26				
Ag	2.52	Cd	1.94				
Cs	3.34	Ba	2.68	La	2.30		
Au(I)	2.88	Hg(II)	2.20	Tl(I)	2.80	Pb(II)	2.40
Fr	3.52	Ra	2.80				
NH_4	2.86						

Table 4: Relative binding of sample alkali metal ions by sample crown ethers

Polyether	Li^+	Na^+	K^+	Cs^+
Dicyclohexyl-14-crown-4	1.1	0	0	0
Cyclohexyl-15-crown-5	1.6	19.7	8.7	4.0
Dibenzo-18-crown-6	0	1.6	25.2	5.8
Dicyclohexyl-18-crown-6	3.3	25.6	77.8	44.2
Dicyclohexyl-21-crown-7	3.1	22.6	51.3	49.7
Dicyclohexyl-24-crown-8	2.9	8.9	20.1	18.1

[0054] The potassium binding polymers typically include cationic counterions. The cations can be metallic, non-metallic, or a combination thereof. Examples of metallic ions include, but are not limited to, Ca^{2+}-form, H^+-form, NH^{4+}-form, Na^+-form, or a combination thereof. Examples of non-metallic ions include, but are not limited to, alkylammonium, hydroxyalkylammonium, choline, taurine,carnitine, guanidine, creatine, adenine, and aminoacids or derivatives thereof.

[0055] In preferred embodiments, the potassium binding polymers described herein have a decreased tendency to cause side-effects such as hypernatremia and acidosis due to the release of detrimental ions. The term "detrimental ions" is used herein to refer to ions that are not desired to be released into the body by the compositions described herein during their period of use. Typically, the detrimental ions for a composition depend on the condition being treated, the chemical properties, and/or binding properties of the composition. For example, the detrimental ion could be H^+ which can cause acidosis or Na^+ which can cause hypernatremia. Preferably the ratio of potassium bound to detrimental cations introduced is 1: about 2.5 to about 4.

Core–Shell Compositions

[0056] In one aspect of the invention, a core-shell composition is used for the removal of potassium. Typically in the core-shell compositions, the core comprises a potassium-binding polymer, preferably the polymer being capable of binding potassium with a high binding capacity. The various potassium-binding polymers described herein can be used as the core component of the core-shell compositions. In some embodiments, the shell modulates the entry of competing solutes such as magnesium and calcium across the shell to the core component. In one embodiment, the permeability of the membrane to divalent cations is diminished by decreasing the porosity to large hydrated cations such as alkaline-earth metals

ions, and by incorporating positive charges that create electrostatic repulsion with said multivalent cations. It is preferred that the shell of the core-shell composition is essentially not disintegrated during the period of residence and passage through the gastro-intestinal tract.

[0057] The term "competing solute" as used herein means solutes that compete with potassium for binding to a core component, but that are not desired to be contacted and/or bound to the core component. Typically, the competing solute for a core-shell composition depends on the binding characteristics of the core and/or the permeability characteristics of the shell component. A competing solute can be prevented from contacting and/or binding to a core-shell particle due to the preferential binding characteristics of the core component and/or the decreased permeability of the shell component for the competing solute from the external environment. Typically, the competing solute has a lower permeability from the external environment across the shell compared to that of potassium ions. Examples of competing solutes include, but are not limited to, Mg^{++}, Ca^{++}, and protonated amines.

[0058] In some embodiments, the shell is permeable to both mono- and di-valent cations. In some of the embodiments in which the shell is permeable to both mono- and di-valent cations, the core binds preferably mono-valent cations, preferably potassium, due to the binding characteristics of the core. In other embodiments, the shell exhibits preferred permeability to potassium ions.

[0059] It is particularly preferred that the core-shell compositions and the potassium binding polymeric compositions described herein bind potassium in the parts of the gastro-intestinal (GI) tract which have a relatively high concentration of potassium, such as in the colon. This bound potassium is then preferred to remain bound to the compositions and be excreted out of the body.

[0060] In one embodiment, the shell material protects the core component from the external GI environment. The shell material in some embodiments protects the acid groups of the core polymer and prevents their exposure to the GI environment. In one embodiment, the core component is protected with a shell component comprising of an enteric coating. Suitable examples of enteric coatings are described in the art. For example, see Remington: The Science and Practice of Pharmacy by A.R. Gennaro (Editor), 20th Edition, 2000.

[0061] In another embodiment the shell material is engineered to impose a lower permeability to higher valency cations. The permeability of the shell to alkaline-earth cations is altered by changing the average pore size, charge density and hydrophobicity of the membrane. Mg^{++} and Ca^{++} hydrated ions have a large size compared with monovalent

cations such as K^+ and Na^+ as indicated below in Table 5 (Nightingale E.R., J. Phys. Chem., 63, (1959), 1381-89).

TABLE 5

Metal ions	Hydrated radii (angstroms)
K^+	3.31
NH_4^+	3.31
Na^+	3.58
Mg^{++}	4.28
Ca^{2+}	4.12

[0062] Methods to reduced permeabilities to divalent cations are known from previous studies on cation-exchange membranes for electrodialysis (e.g. Sata et al, J.Membrane Science, 206 (2002), 31-60). Such methods are usually based on pore size exclusion and electrostatic interaction and combination thereof.

[0063] Accordingly, in some embodiments, several characteristics of the shell component are tuned so that a permeation difference is established. For example, when the mesh size of the shell material is in the same size range as the solute dimensions, the random walk of a bulkier divalent cation through the shell component is significantly slowed down. For example, experimental studies (Krajewska, B., Reactive and Functional polymers 47, 2001, 37-47) report permeation coefficients in cellulose ester or crosslinked chitosan gel membranes for both ionic and non-ionic solutes shows slowing down of bulkier solutes when mesh size nears solute dimensions. The polymer volume fraction in the swollen resin is a good indicator of the mesh size within the composition; theoretical studies have shown, for example, that mesh size usually scales with $\phi^{-3/4}$, ϕ being the polymer volume fraction in the shell component when swollen in a solution. The membrane swelling ratio depends on the hydrophobicity, crosslinking density, charge density, and solvent ionic strength.

[0064] For instance polypyrrole layered on the cation exchange materials by in-situ polymerization of pyrrole, is shown to induce permselectivity by creating a very tightly porous membrane that hinders large divalent cation diffusion relatively to monovalent cations.

[0065] Alternatively, a thin layer of a cationic polyelectrolyte is physically adsorbed to create a strong electrical field that repel highly charged cations such as Mg^{++} and Ca^{++}. Suitable cationic polyelectrolytes include, but are not limited to, copolymers with a repeat unit

selected from vinylamine, ethyleneimine, propyleneimine, allylamine, vinylpyridines, alkyaminoalkyl(meth)acrylates, alkyaminoalkyl(meth)acrylamides, aminomethylstyrene, chitosan, adducts of aliphatic amine or aromatic amine with electrophiles such as epichlorhydrine, alkylhalides or epoxydes, and wherein the amine is optionally a quarternized form. Adducts of aliphatic amine or aromatic amine with alkyldihalides are also referred to as ionenes. The polymeric permselectivity can also be controlled by pH, whereupon the polymer charge density and swelling ratio varies with the rate of (de)protonation.

[0066] pH-controlled binding selectivity is an important lever when the counter-ion initially loaded in the polymer has to be displaced and eventually replaced by potassium. If the polymer is first conditioned with Ca^{++}, a divalent cation with a high binding constant to carboxylic or sulfonic groups, one can take advantage of the acidic environment encountered in the stomach to protonate the binding sites of the polymer so as to displace the initially loaded counter-ion (i.e. Ca^{++}). In that context, it is advantageous to design polymers with ion exchange properties varying with the local pH, more preferably polymers with a low binding capacity at gastric pH and a high capacity at pH greater than about 5.5. In one preferred embodiment, the polymers of the invention have a fraction of capacity available at pH lower than about 3, of about 0-10% of the full capacity (i.e. measure at pH about 12), and greater than about 50% at pH greater than about 4.

[0067] In some embodiments, a shell of a cationic polyelectrolyte is physically adsorbed to create a strong electrical field that repels highly charged cations such as Mg^{++} and Ca^{++}. Suitable cationic polyelectrolytes include, but are not limited to, copolymers with a repeat unit selected from vinylamine, ethyleneimine, propyleneimine, allylamine, vinylpyridines, alkyaminoalkyl(meth)acrylates, alkyaminoalkyl(meth)acrylamides, aminomethylstyrene, chitosan, adducts of aliphatic amine or aromatic amine with electrophiles such as epichlorhydrine, alkylhalides or epoxydes, and wherein the amine is optionally a quarternized form. Adducts of aliphatic amine or aromatic amine with alkyldihalides are also referred to as ionenes. The polymeric permselectivity can also be controlled by pH, whereupon the polymer charge density and swelling ratio varies with the rate of (de)protonation. The polymer is held on the core through physical bonds, chemical bonds, or a combination of both. In the former case, the electrostatic interaction between negatively charged core and positively charged shell maintains the core-shell assembly during transit in the GI tract. In the latter case a chemical reaction is carried out at the core-shell interface to prevent "delamination" of the shell material.

[0068] Preferably, the shell has a permselectivity factor (i.e. binding rate of K^+ vs. other competing ions) above a certain value during the residence time of the composition in the large bowel. Not intending to be limited to one mechanism of action, it is believed that the selectivity mechanism hinges on a kinetic effect (as opposed to a pure thermodynamic mechanism for the binding event in the core). That is, if the core-shell particles of the invention are let to equilibrate for a period of time in the colon, it is predicted that the core-shell will eventually bind cations with a similar profile to the core alone. Hence, in one embodiment the shell material keeps the rate of permeation for the target ions (e.g. K^+) high enough so that said target ions fully equilibrates during the mean average residence time in the colon, while the rate of permeation of competing cations (e.g. Mg^{2+}, Ca^{2+}) is lower. This feature is defined as the time persistence of permselectivity. In this embodiment, the time persistence can be the time needed to reach between about 20% and about 80% (i.e., t_{20}, to t_{80}) of the binding capacity at equilibrium in conditions reflecting the colon electrolyte profile. Typically, for K^+ (and monovalent cations in general), t_{80}, is preferably lower than about 5 hrs, more preferably lower than about 2hrs. While for Mg (and multivalent cations in general), t_{20}, is preferably greater than about 24 hrs, most preferably about 40 hrs.

[0069] In another embodiment, the interaction of the positively charged shell with some of the hydrophobic anions present the GI can achieve a higher level of persistence (as measured as an increase in t_{80} value for Mg^{2+} and Ca^{2+}). Such hydrophobic anions include bile acids, fatty acids and anionic protein digests. Alternatively anionic surfactants can provide the same benefit. In this embodiment the core-shell material is either administered as is, or formulated with fatty acids or bile acids salts or even synthetic anionic detergents such as, but not limited to, alkyl sulfate, alkyl sulfonate, and alkylaryl sulfonate.

[0070] In systems which combine positive charges and hydrophobicity, preferred shell polymers include amine functional polymers, such as those disclosed above, which are optionally alkylated with hydrophobic agents.

[0071] Alkylation involves reaction between the nitrogen atoms of the polymer and the alkylating agent (usually an alkyl, alkylaryl group carrying an amine-reactive electrophile). In addition, the nitrogen atoms which do react with the alkylating agent(s) resist multiple alkylation to form quaternary ammonium ions such that less than 10 mol % of the nitrogen atoms form quaternary ammonium ions at the conclusion of alkylation.

[0072] Preferred alkylating agents are electrophiles such as compounds bearing functional groups such as halides, epoxides, esters, anhydrides, isocyanate, or $\alpha\beta$-unsaturated carbonyls.

They have the formula RX where R is a C1 -C20 alkyl (preferably C4 -C20), C1-C20 hydroxy-alkyl (preferably C4 -C20 hydroxyalkyl), C6 -C20 aralkyl, C1-C20 alkylammonium (preferably C4 -C20 alkyl ammonium), or C1 -C20 alkylamido (preferably C4 -C20 alkyl amido) group and X includes one or more electrophilic groups. By "electrophilic group" it is meant a group which is displaced or reacted by a nitrogen atom in the polymer during the alkylation reaction. Examples of preferred electrophilic groups, X, include halide, epoxy, tosylate, and mesylate group. In the case of, e.g., epoxy groups, the alkylation reaction causes opening of the three-membered epoxy ring.

[0073] Examples of preferred alkylating agents include a C3 -C20 alkyl halide (e.g., an n-butyl halide, n-hexyl halide, n-octyl halide, n-decyl halide, n-dodecyl halide, n-tetradecyl halide, n-octadecyl halide, and combinations thereof); a C1 -C20 hydroxyalkyl halide (e.g., an 11-halo-1-undecanol); a C1 -C20 aralkyl halide (e.g., a benzyl halide); a C1 -C20 alkyl halide ammonium salt (e.g., a (4-halobutyl) trimethylammonium salt, (6-halohexyl)trimethyl-ammonium salt, (8-halooctyl)trimethylammonium salt, (10-halodecyl)trimethylammonium salt, (12-halododecyl)-trimethylammonium salts and combinations thereof); a C1 -C20 alkyl epoxy ammoniumn salt (e.g., a (glycidylpropyl)-trimethylammonium salt); and a C1 -C20 epoxy alkylamide (e.g., an N-(2,3-eoxypropane)butyramnide, N-(2,3-epoxypropane) hexanamide, and combinations thereof). Benzyle halide and dodecyl halide are more preferred.

[0074] The alkylation step on the polyamine shell precursor can be carried out in a separate reaction, prior to the application of the shell onto the core beads. Alternatively the alkylation can be done once the polyamine shell precursor is deposited onto the core beads. In the latter case, the alkylation is preferably performed with an alkylating agent that includes at least two electrophilic groups X so that the alkylation also induces crosslinking within the shell layer. Preferred polyfunctional alkylation agents include di-halo alkane, dihalo polyethylene glycol, and epichlorohydrine. Other crosslinkers containing acyl chlorides, isocyanate ,thiocyanate, chlorosulfonyl, activated esters (N-hydroxysuccinimide) , carbodiimide intermediates, are also suitable.

[0075] Typically, the level of alkylation is adjusted depending upon the nature of the polyamine precursor and the size of the alkyl groups used on alkylation. Some factors that play a role in the level of alkylation include:

a. Insolubility of the shell polymer under conditions of the GI tract. In particular, the low pH's prevailing in the stomach tend to solubilize alkylated polyamine polymers whose pH of ionization is 5 and above. For that purpose

higher rate of alkylation and higher chain length alkyl are preferred. As an alternative, one may use an enteric coating to protect the shell material against acidic pH's, said enteric coating is released when the core-shell beads are progressing in the lower intestine.

b. The permselectivity profile: When the alkylation ratio is low the persistence of the permselectivity for competing ions (e.g. Mg^{2+}, Ca^{2+}) can be shorter than the typical residence time in the colon. Conversely when the alkylation ratio (or the weight fraction of hydrophobes) is high then the material becomes almost impermeable to most inorganic cations, and thus, the rate of equilibration for K^{+} becomes long.

Preferably, the degree of alkylation is selected by an iterative approach monitoring the two variables mentioned above.

[0076] Methods for determining permeability coefficients are known. For example, see, W. Jost, *Diffusion in Solids, Liquids and Gases,* Acad. Press, New-York, 1960). For example, the ion permeability coefficient in a shell polymer can be measured by casting the polymer as a membrane over a solid porous material, subsequently contacted with a physiological solution (donor) containing the ions of interest, and measuring steady state permeation rates of said ions, across the membrane in the acceptor solution. Membrane characteristics can then be optimized to achieve the best cooperation in terms of selectivity and permeation rate kinetics. Structural characteristics of the membrane can be varied by modifying, for example, the polymer volume fraction (in the swollen membrane), the chemical nature of the polymer(s) and its properties (hydrophobicity, crosslinking density, charge density), the polymer blend composition (if more than one polymer is used), the formulation with additives such as wetting agents, plasticizers, and/or the manufacturing process.

[0077] The permselective membranes of the invention are optimized by studying their permselectivity profile as a function of polymer compositions and physical characteristics. Permselectivity is preferably measured in conditions close to those prevailing in the milieu of use (e.g. colon). In a typical experiment, the donor solution is a synthetic fluid with an ionic composition, osmolality, and pH mimicking the colonic fluid, or alternatively, an animal fluid collected through ileostomy or coleostomy. In another embodiment, the membrane is sequentially contacted with fluids that model the conditions found in the different parts of the GI tract, i.e. stomach, duodenum, jejunum, and ileum. In yet another embodiment, the shell is deposited on a cation exchange resin bead under the proton form by microencapsulation method and contacted with a sodium hydroxide aqueous solution. By monitoring pH or

conductivity the rate of permeation of NaOH across the membrane is then computed. In another embodiment the resin is preloaded with lithium cations and the release of lithium and absorption of sodium, potassium, magnesium, calcium and ammonium are monitored by ion chromatography. In a preferred embodiment, the permeability ratio of potassium and divalent cations such as Mg^{++} and Ca^{++}, measured in aforementioned conditions is comprised between about 1:0.5 to about 1:0.0001, preferably between about 1: 0.2 and about 1:0.01.

[0078] In another embodiment, the shell of a core-shell composition displays a permeability selectivity by passive absorption while passing through the upper GI tract. Many components present in the GI tract including components of the diet, metabolites, secretion, etc. are susceptible to adsorb onto and within the shell in a quasi-irreversible manner and can strongly modify the permeability pattern of the shell. The vast majority of these soluble materials are negatively charged and show various levels of hydrophobicity. Some of those species have a typical amphiphilic character, such as fatty acids, phospholipids, bile salts and can behave as surfactants. Surfactants can adsorb non-specifically to surfaces through hydrophobic interactions, ionic interaction and combinations thereof. In this embodiment, this phenomenon is used to change the permeability of the polymeric composition upon the course of binding potassium ions. In one embodiment fatty acids can be used to modify the permeability of the shell and in another embodiment bile acids can be used. Fatty acids and bile acids both form aggregates (micelles or vesicles) and can also form insoluble complexes when mixed with positively charged polymers (see e.g. Kaneko et al, *Macromolecular Rapid Communications* (2003), 24(13), 789-792). Both fatty acids and bile acids exhibit similarities with synthetic anionic surfactants and numerous studies report the formation of insoluble complexes between anionic surfactants and cationically charged polymers (e.g. Chen, L. et al, *Macromolecules* (1998), 31(3), 787-794). In this embodiment, the shell material is selected from copolymers containing both hydrophobic and cationic groups, so that the shell forms a complex with anionically charged hydrophobes typically found in the GI tract, such as bile acids, fatty acids, bilirubin and related compounds. Suitable compositions also include polymeric materials described as bile acids sequestering agents, such as those reported in US Patents 5,607,669; 6,294,163; and 5,374,422; Figuly et al, *Macromolecules*, 1997, 30, 6174-6184. The formation of the complex induces a shell membrane collapse which in turn can lower the diffusion of bulky divalent cations, while preferably leaving the permeation of potassium unchanged.

[0079] In yet another embodiment, the permeability of the shell of a core-shell composition is modulated by enzymatic activity in the gastro-intestinal tract. There are a number of secreted

enzymes produced by common colonic microflora. For example *Bacteroides, Prevotella, Porphyromonas,* and *Fusobacterium* produce a variety of secreted enzymes including collagenase, neuraminidase, deoxyribonuclease [DNase], heparinase, and proteinases. In this embodiment the shell comprises a hydrophobic backbone with pendant hydrophilic entities that are cleaved off *via* an enzymatic reaction in the gut. As the enzymatic reaction proceeds, the polymer membrane becomes more and more hydrophobic, and turns from a high swollen state, high permeability rate material to a fully collapsed low hydration membrane with minimal permeability to bulky hydrated cations such as Mg^{++} and Ca^{++}. Hydrophilic entities can be chosen from natural substrates of enzymes commonly secreted in the GI tract. Such entities include amino acids, peptides, carbohydrates, esters, phosphate esters, oxyphosphate monoesters, O- and S-phosphorothioates, phosphoramidates, thiophosphate, azo groups and the like. Examples of enteric enzymes susceptible to chemically alter the shell polymer include, but are not limited to, lipases, phospholipases, carboxylesterase, glycosidases, azoreductases, phosphatases, amidases and proteases. The shell can be permeable to potassium ions until it enters the proximal colon and then the enzymes present in the proximal colon can react chemically with the shell to reduce its permeability to the divalent cations.

[0080] In some embodiments, the shell thickness can be between about 0.002 micron to about 50 micron, preferably about 0.005 micron to about 20 microns. Preferably the shell thickness is more than about 0.5 micron, more preferred is more than about 2 micron, even more preferred is more than about 5 micron. Preferably the shell thickness is less than about 30 micron, more preferred is less than about 20 micron, even more preferred is less than about 10 micron, and most preferred is less than about 5 micron.

[0081] The size of the core-shell particles typically range from about 200 nm to about 2 mm, preferably being about 100 microns. Preferably the size of the core-shell particles are more than about 1 microns, more preferred is more than about 10 microns, even more preferred is more than about 20 microns, and most preferred is more than about 40 microns. Preferably the size of the core-shell particles are less than about 250 microns, more preferred is less than about 150 microns, even more preferred is less than about 100 microns, and most preferred is less than about 50 microns.

Synthesis of core-shell particles

[0082] In preferred embodiments, the shell is uniformly coated on the core material, preferably without pinholes or macroporosity and is light weight relative to the core material (for example, up to about 20 wt-%). The shell can be anchored to the core and preferably

resistant enough to sustain the mechanical constraint such as swelling and compression encountered during tablet formulation.

[0083] The shell can be formed by chemical or non-chemical processes. Non-chemical processes include spray coating, fluid bed coating, solvent coacervation in organic solvent or supercritical CO_2, solvent evaporation, spray drying, spinning disc coating, extrusion (annular jet) or layer by layer formation. Examples of chemical processes include interfacial polymerization, grafting from, grafting unto, and core-shell polymerization.

[0084] In fluid bed coating, typically the core beads are kept in a recirculating fluidized bed (Wurster type) and sprayed with a coating solution or suspension. The coating polymer can be used as a solution in alcohols, ethylacetate, ketones, or other suitable solvents or as latex. Conditions are typically optimized so as to form a tight and homogeneous membrane layer, and insure that no cracks are formed upon swelling when the particles are contacted with the aqueous vehicle. It is preferred that the membrane polymer can yield to the volume expansion and elongates so as to accommodate the dimension change. Polymer membranes have an elongation at break greater than 10%, preferably greater than 30%. Examples of this approach are reported in Ichekawa H. et al, International Journal of Pharmaceuticals, 216(2001), 67-76.

[0085] Solvent coacervation is described in the art. For example, see Leach, K. et al., J. Microencapsulation, 1999, 16(2), 153-167. In this process, typically two polymers, core polymer and shell polymer are dissolved in a solvent which is further emulsified as droplets in an aqueous phase. The droplet interior is typically a homogeneous binary polymer solution. The solvent is then slowly driven off by careful distillation. The polymer solution in each droplet undergoes a phase separation as the volume fraction of polymer increases. One of the polymer migrates to the water/droplet interface and forms a more-or less perfect core-shell particle (or double-walled microsphere).

[0086] Solvent coacervation is one of the preferred methods to deposit a controlled film of shell polymer onto the core. In one embodiment, the coacervation technique consists in dispersing the core beads in a continuous liquid phase containing the shell material in a soluble form. The coacervation process then consists of gradually changing the solvency of the continuous phase so that the shell material becomes increasingly insoluble. At the onset of precipitation some of the shell material ends up as a fine precipitate or film at the bead surface. The change in solvency can be triggered by a variety of physical chemistry means such as , but not limited to, changes in pH, ionic strength (i.e. osmolality), solvent composition (through addition of solvent or distillation), temperature (e.g when a shell

polymer with a LCST (lower critical solution temperature) is used), pressure (particularly when supercritical fluids are used). More preferred are solvent coacervation processes when the trigger is either pH or solvent composition. Typically when a pH trigger event is used and when the polymer is selected from an amine type material, the shell polymer is first solubilized at low pH. In a second step the pH is gradually increased to reach the insolubility limit and induce shell deposition; the pH change is often produced by adding a base under strong agitation. Another alternative is to generate a base by thermal hydrolysis of a precursor (e.g. thermal treatment of urea to generate ammonia). The most preferred coacervation process is when a ternary system is used comprising the shell material and a solvent/non-solvent mixture of the shell material. The core beads are dispersed in that homogeneous solution and the solvent is gradually driven off by distillation. The extent of shell coating can be controlled by on-line or off-line monitoring of the shell polymer concentration in the continuous phase. In the most common case where some shell material precipitates out of the core surface either in a colloidal form or as discrete particle, the core-shell particles are conveniently isolated by simple filtration and sieving. The shell thickness is typically controlled by the initial core to shell weight ratio as well as the extent of shell polymer coacervation described earlier. The core-shell beads can then be annealed to improve the integrity of the outer membrane as measured by competitive binding.

[0087] Supercritical CO_2 coating is described in the art. For example, see Benoit J.P. et al, J. Microencapsulation, 2003, 20(1)87-128. This approach is somewhat a variant of the solvent coacervation. First the shell coating material is dissolved in the supercritical CO_2, and then the active is dispersed in that fluid in super-critical conditions. The reactor is cooled down to liquid CO_2 conditions wherein the shell material is no longer soluble and precipitates on the core beads. The process is exemplified with shell materials selected from small molecules such as waxes and parafins. The core-shell material is recovered as a powder.

[0088] The spinning disc coating technique is based on forming a suspension of the core particles in the coating, then using a rotating disc to remove the excess coating liquid in the form of small droplets, while a residual coating remains around the core-particles. See U.S. Patent No. 4,675,140.

[0089] In the layer by layer process, a charged core material is contacted with a polyelectrolyte of opposite charge and a polymer complex is formed. This step is repeated until a multilayer is deposited on the core surface. Further crosslinking of the layers are optional.

[0090] Interfacial polymerization consists of dispersing the core material containing one reacting monomer in a continuous phase containing a co-reacting monomer. A polymerization reaction takes place at the core interface creating a shell polymer. The core can be hydrophilic or hydrophobic. Typical monomer used for that purpose can include diacylchlorides/diamines, diisocyanates/diamines, diisocyanates/diols, diacylchlorides/diols and bischloroformate and diamines or diols. Trifunctional monomers can also be used to control the degree of porosity and toughness of the membranes.

[0091] In yet another embodiment, the shell is formed by contacting the ion exchange material with a polymer dispersion of opposite charge (i.e. the core material is typically charged negatively and the shell positively), and filter the bead particles and anneal them in a fluidized bed at a temperature higher than the transition temperature (or softening point) of the shell polymer. In this embodiment the polymer dispersion is a latex or a polymer colloidal dispersion of particle size in the micron to sub-micron range.

[0092] In one further embodiment, the shell material comprises treating the acid containing core material or its derivatives such as methyl ester or acyl chloride with reactive monomer or polymer. Preferably the acid reactive material is a polymer and more preferably a polyamine: for instance a carboxylated core polymer is treated with polyethyleneimine at high temperature in an organic solvent to create amide bonds between the COOH groups and the NH and NH_2 groups. It can also be useful to activate the acid functions to facilitate the amide bond formation, e.g. by treating COOH or SO_3H groups with thionylchloride or chlorosulfonic acid to convert said groups into their acid chloride forms. See Sata et al., Die Angewandte Makromolekulare Chemie 171, (1989) 101-117 (Nr2794).

[0093] The process of "grafting from" involves an active site capable of initiating polymerization on the core surface and polymer chains are grown from the surface in monolayers. Living polymerization methods such as nitroxide-mediated living polymerizations, ATRP, RAFT, ROMP are most suitable, but non living polymerizations have also been applied.

[0094] In the process of "grafting onto" a small molecule (typically an electrophile, such as epoxy, isocyanate, anhydride, etc.) is brought in contact with the polymeric core material, said core carrying reactive species (typically nucleophile groups such as amine, alcohol, etc.). The thickness of the shell thus formed is controlled by the rate of diffusion of the shell small molecule precursor and the rate of reaction with the core. Slow-diffusing/highly reactive species tend to confine the reaction within a short distance from the core surface thus

producing a thin shell. Whereas, fast-diffusing/slow reacting species tend to invade the entire core with no defined shell and form a gradient rather than a sharp shell to core boundary.

[0095] Core-shell polymerizations can be emulsion polymerization, suspension/mini-emulsion polymerization, or dispersion polymerization. All these processes employ free radical polymerizations. In emulsion polymerization, the polymerization takes place in aqueous medium with a surfactant, monomer with a low water solubility, and a water soluble free radical initiator. Polymer particles are formed by micellar or homogeneous nucleation or both. Core shell particles can be formed theoretically by feeding the core monomer first and the shell monomer second as long as the monomer is spontaneously consumed as it is fed ("starved regime"). The potassium binding core beads are preferably made from a water insoluble monomer (e.g. alkylester of a-fluoro-acrylic acid).

[0096] In suspension/mini-emulsion polymerization, the free radical initiator is soluble with the monomer. Monomer and initiator are pre-dissolved and then emulsified in droplet stabilized with either surfactant or amphiphilic polymers. This method allows one pre-formed polymer (e.g. the shell polymer) to be dissolved as well. When the reaction proceeds, the shell polymer and the core polymer phase separate to form the desired core-shell particles.

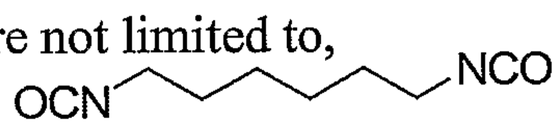
[0097] In dispersion polymerization, both the monomer and the initiator are soluble in the continuous phase (usually an organic solvent). A block copolymer is used as a steric stabilizer. The polymer particles are formed by homogenous nucleation and subsequent growth. Particle size are on the 1 to 10 microns range and mono-dispersed.

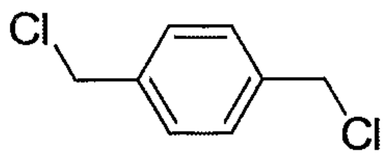
[0098] In a preferred process of dispersion, polymerization employs a refinement reported in Stover H. et al, Macromolecules, 1999, 32, 2838-2844, described thereafter: The shell monomer contains a large fraction of divinyl monomer, such as 1,4 divinylbenzene, while the core particles present some polymerizable double bond on their surface; the shell polymerization mechanism is based on the formation of short oligoradicals in the continuous phase, which are captured by the double bond present on the particle surface. The oligomers themselves contain non-reacted insaturation that replenish the surface in reactive double bonds. The net result is a formation of a crosslinked shell with a sharp boundary with the shell and the core material.

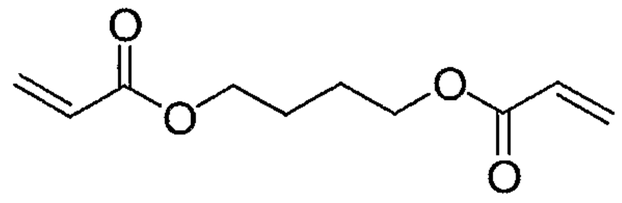
[0099] In one embodiment, a core-shell composition of the invention is synthesized by forming the cation exchange core in a conventional inverse suspension process using suitable monomers; decorating the particle surface with reactive double bonds by post-reacting with the acidic group present on the particle core; and dispersing in typical dispersion

polymerization solvent such as acetonitrile (e.g. a non-solvent for the cation-exchange core polymer) and adding a polymerizing mixture of DVB or EGDMA with a functional monomer.

[00100] In a preferred embodiment, the shell is formed with Eudragit, for example Eudragit RL 100 or RS 100 or a combination thereof, or with polyethyleneimine (PEI). These shells maybe applied by solvent coacervation technique. The PEI may be optionally benzylated and also optionally cross-linked. Examples of suitable cross-linkers include, but are not limited to,







Methods of Treatments

[00101] The methods and compositions described herein are suitable for treatment of hyperkalemia caused by disease and/or use of certain drugs.

[00102] In some embodiments of the invention, the compositions and methods described herein are used in the treatment of hyperkalemia caused by decreased excretion of potassium, especially when intake is not reduced. A common cause of decreased renal potassium excretion is renal failure (especially with decreased glomerular filtration rate), often coupled with the ingestion of drugs that interfere with potassium excretion, e.g., potassium-sparing diuretics, angiotensin-converting enzyme inhibitors (ACEIs), non-steroidal anti-inflammatory drugs, heparin, or trimethoprim. Impaired responsiveness of the distal tubule to aldosterone, for example in type IV renal tubular acidosis observed with diabetes mellitus as well as sickle cell disease and/or chronic partial urinary tract obstruction is another cause of reduced potassium secretion. Secretion is also inhibited in diffuse adrenocortical insufficiency or Addison's disease and selective hypoaldosteronism. Hyperkalemia is common when diabetics develop hypoteninemic hypoaldosteronism or renal insufficiency (Mandal, A.K. 1997. Hypokalemia and hyperkalemia. Med Clin North Am. 81:611-39).

[00103] In certain preferred embodiments, the potassium binding polymers described herein are administered chronically. Typically, such chronic treatments will enable patients to continue using drugs that cause hyperkalemia, such as potassium-sparing diuretics, ACEI's, non-steroidal anti-inflammatory drugs, heparin, or trimethoprim. Also, use of the polymeric compositions described herein will enable certain patient populations, who were unable to use hyperkalemia causing drugs, to use such drugs.

[00104] In certain chronic use situations, the preferred potassium binding polymers used are those that are capable of removing less than about 5 mmol of potassium per day or in the range of about 5 – about 10 mmol of potassium per day. In acute conditions, it is preferred that the potassium binding polymers used are capable of removing about 15 – about 60 mmol of potassium per day.

[00105] In certain other embodiments, the compositions and methods described herein are used in the treatment of hyperkalemia caused by a shift from intracellular to extracellular space. Infection or trauma resulting in cell disruption, especially rhabdomyolysis or lysis of muscle cells (a major potassium store), and tumor lysis can result in acute hyperkalemia. More often, mild-to-moderate impairment of intracellular shifting of potassium occurs with diabetic ketoacidosis, acute acidosis, infusion of argentine or lysine chloride for the treatment of metabolic alkalosis, or infusion of hypertonic solutions such as 50% dextrose or mannitol. β-receptor blocking drugs can cause hyperkalemia by inhibiting the effect of epinephrine.

[00106] In certain other embodiments, the compositions and methods described herein are used in the treatment of hyperkalemia caused by excessive intake of potassium. Excessive potassium intake alone is an uncommon cause of hyperkalemia. Most often, hyperkalemia is caused by indiscriminate potassium consumption in a patient with impaired mechanisms for the intracellular shift of potassium or renal potassium excretion. For example, sudden death among dialyzed patients who are noncompliant in diet can be attributed to hyperkalemia.

[00107] In the present invention, the potassium-binding polymers and the core-shell compositions can be co-administered with other active pharmaceutical agents. This co-administration can include simultaneous administration of the two agents in the same dosage form, simultaneous administration in separate dosage forms, and separate administration. For example, for the treatment of hyperkalemia, the potassium-binding polymers and the core-shell compositions can be co-administered with drugs that cause the hyperkalemia, such as potassium-sparing diuretics, angiotensin-convening enzyme inhibitors, non-steroidal anti-inflammatory drugs, heparin, or trimethoprim. The drug being co-administered can be formulated together in the same dosage form and administered simultaneously. Alternatively, they can be simultaneously administered, wherein both the agents are present in separate formulations. In another alternative, the drugs are administered separately. In the separate administration protocol, the drugs may be administered a few minutes apart, or a few hours apart, or a few days apart.

[00108] The term "treating" as used herein includes achieving a therapeutic benefit and/or a prophylactic benefit. By therapeutic benefit is meant eradication, amelioration, or prevention of the underlying disorder being treated. For example, in a hyperkalemia patient, therapeutic benefit includes eradication or amelioration of the underlying hyperkalemia. Also, a therapeutic benefit is achieved with the eradication, amelioration, or prevention of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the patient, notwithstanding that the patient may still be afflicted with the underlying disorder. For example, administration of a potassium-binding polymer to a patient suffering from hyperkalemia provides therapeutic benefit not only when the patient's serum potassium level is decreased, but also when an improvement is observed in the patient with respect to other disorders that accompany hyperpkalemia like renal failure. For prophylactic benefit, the potassium-binding polymers may be administered to a patient at risk of developing hyperpkalemia or to a patient reporting one or more of the physiological symptoms of hyperpkalemia, even though a diagnosis of hyperpkalemia may not have been made.

[00109] The pharmaceutical compositions of the present invention include compositions wherein the potassium binding polymers are present in an effective amount, i.e., in an amount effective to achieve therapeutic or prophylactic benefit. The actual amount effective for a particular application will depend on the patient (e.g., age, weight, etc.), the condition being treated, and the route of administration. Determination of an effective amount is well within the capabilities of those skilled in the art, especially in light of the disclosure herein.

[00110] The effective amount for use in humans can be determined from animal models. For example, a dose for humans can be formulated to achieve gastrointestinal concentrations that have been found to be effective in animals.

[00111] The dosages of the potassium binding polymers in animals will depend on the disease being, treated, the route of administration, and the physical characteristics of the patient being treated. Dosage levels of the potassium binding polymers for therapeutic and/or prophylactic uses can be from about about 0.5 gm/day to about 30 gm/day. It is preferred that these polymers are administered along with meals. The compositions may be administered one time a day, two times a day, or three times a day. Most preferred dose is about 15 gm/day or less. A preferred dose range is about 5 gm/day to about 20 gm/day, more preferred is about 5 gm/day to about 15 gm/day, even more preferred is about 10 gm/day to about 20 gm/day, and most preferred is about 10 gm/day to about 15 gm/day.

[00112] In some embodiments, the amount of potassium bound by the core-shell compositions is greater than the amount if the core component, i.e., potassium binding polymer is used in the absence of the shell. Hence, the dosage of the core component in some embodiments is lower when used in combination with a shell compared to when the core is used without the shell. Hence, in some embodiments of the core-shell pharmaceutical compositions, the amount of core component present in the core-shell pharmaceutical composition is less than the amount that is administered to an animal in the absence of the shell component.

[00113] The compositions described herein can be used as food products and/or food additives. They can be added to foods prior to consumption or while packaging to decrease levels of potassium. The compositions can also be used in fodder for animals to lower K^+ levels, which is for example desirable for example in fodders for pigs and poultry to lower the water secretion.

Formulations and Routes of Administration

[00114] The polymeric compositions and core-shell compositions described herein or pharmaceutically acceptable salts thereof, can be delivered to the patient using a wide variety of routes or modes of administration. The most preferred routes for administration are oral, intestinal, or rectal.

[00115] If necessary, the polymers and core-shell compositions may be administered in combination with other therapeutic agents. The choice of therapeutic agents that can be co-administered with the compounds of the invention will depend, in part, on the condition being treated.

[00116] The polymers (or pharmaceutically acceptable salts thereof) may be administered per se or in the form of a pharmaceutical composition wherein the active compound(s) is in admixture or mixture with one or more pharmaceutically acceptable carriers, excipients or diluents. Pharmaceutical compositions for use in accordance with the present invention may be formulated in conventional manner using one or more physiologically acceptable carriers compromising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen.

[00117] For oral administration, the compounds can be formulated readily by combining the active compound(s) with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions, wafers, and the like, for oral

ingestion by a patient to be treated. In one embodiment, the oral formulation does not have an enteric coating. Pharmaceutical preparations for oral use can be obtained as a solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, mehtyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinyl pyrrolidone (PVP). If desired, disintegrating agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

[00118] Dragee cores can be provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

[00119] For administration orally, the compounds may be formulated as a sustained release preparation. Numerous techniques for formulating sustained release preparations are known in the art.

[00120] Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for administration.

[00121] In some embodiments the polymers of the invention are provided as pharmaceutical compositions in the form of chewable tablets. In addition to the active ingredient, the following types of excipients are commonly used: a sweetening agent to provide the necessary palatability, plus a binder where the former is inadequate in providing sufficient tablet hardness; a lubricant to minimize frictional effects at the die wall and facilitate tablet ejection; and, in some formulations a small amount of a disintegrant is added to facilitate mastication. In general excipient levels in currently-available chewable tablets

are on the order of 3–5 fold of active ingredient(s) whereas sweetening agents make up the bulk of the inactive ingredients.

[00122] The present invention provides chewable tablets that contain a polymer or polymers of the invention and one or more pharmaceutical excipients suitable for formulation of a chewable tablet. The polymer used in chewable tablets of the invention preferably has a swelling ratio while transiting the oral cavity and in the esophagus of less than about 5, preferably less than about 4, more preferably less than about 3, more preferably less than 2.5, and most preferably less than about 2. The tablet comprising the polymer, combined with suitable excipients, provides acceptable organoleptic properties such as mouthfeel, taste, and tooth packing, and at the same time does not pose a risk to obstruct the esophagus after chewing and contact with saliva.

[00123] In some aspects of the invention, the polymer(s) provide mechanical and thermal properties that are usually performed by excipients, thus decreasing the amount of such excipients required for the formulation. In some embodiments the active ingredient (e.g., polymer) constitutes over about 30%, more preferably over about 40%, even more preferably over about 50%, and most preferably more than about 60% by weight of the chewable tablet, the remainder comprising suitable excipient(s). In some embodiments the polymer comprises about 0.6 gm to about 2.0 gm of the total weight of the tablet, preferably about 0.8 gm to about 1.6 gm. In some embodiments the polymer comprises more than about 0.8 gm of the tablet, preferably more than about 1.2 gm of the tablet, and most preferably more than about 1.6 gm of the tablet. The polymer is produced to have appropriate strength/friability and particle size to provide the same qualities for which excipients are often used, e.g., proper hardness, good mouth feel, compressibility, and the like. Unswelled particle size for polymers used in chewable tablets of the invention is less than about 80, 70, 60, 50, 40, 30, or 20 microns mean diameter. In preferred embodiments, the unswelled particle size is less than about 80, more preferably less than about 60, and most preferably less than about 40 microns.

[00124] Pharmaceutical excipients useful in the chewable tablets of the invention include a binder, such as microcrystalline cellulose, colloidal silica and combinations thereof (Prosolv 90), carbopol, providone and xanthan gum; a flavoring agent, such as sucrose, mannitol, xylitol, maltodextrin, fructose, or sorbitol; a lubricant, such as magnesium stearate, stearic acid, sodium stearyl fumurate and vegetable based fatty acids; and, optionally, a disintegrant, such as croscarmellose sodium, gellan gum, low-substituted hydroxypropyl ether of cellulose, sodium starch glycolate. Other additives may include plasticizers,

pigments, talc, and the like. Such additives and other suitable ingredients are well-known in the art; see, e.g., Gennaro AR (ed), *Remington's Pharmaceutical Sciences*, 20th Edition.

[00125] In some embodiments the invention provides a pharmaceutical composition formulated as a chewable tablet, comprising a polymer described herein and a suitable excipient. In some embodiments the invention provides a pharmaceutical composition formulated as a chewable tablet, comprising a polymer described herein, a filler, and a lubricant. In some embodiments the invention provides a pharmaceutical composition formulated as a chewable tablet, comprising a polymer described herein, a filler, and a lubricant, wherein the filler is chosen from the group consisting of sucrose, mannitol, xylitol, maltodextrin, fructose, and sorbitol, and wherein the lubricant is a magnesium fatty acid salt, such as magnesium stearate.

[00126] The tablet may be of any size and shape compatible with chewability and mouth disintegration, preferably of a cylindrical shape, with a diameter of about 10 mm to about 40 mm and a height of about 2 mm to about 10 mm, most preferably a diameter of about 22 mm and a height of about 6 mm.

[00127] In one embodiment, the polymer is pre-formulated with a high Tg / high melting point low molecular weight excipient such as mannitol, sorbose, sucrose in order to form a solid solution wherein the polymer and the excipient are intimately mixed. Method of mixing such as extrusion, spray-drying, chill drying, lyophilization, or wet granulation are useful. Indication of the level of mixing is given by known physical methods such as differential scanning calorimetry or dynamic mechanical analysis.

[00128] Methods of making chewable tablets containing pharmaceutical ingredients, including polymers, are known in the art. See, e.g., European Patent Application No. EP373852A2 and U.S. Patent No. 6,475,510, and Remington's Pharmaceutical Sciences.

[00129] In some embodiments the polymers of the invention are provided as pharmaceutical compositions in the form of liquid formulations. In some embodiments the pharmaceutical composition contains an ion-binding polymer dispersed in a suitable liquid excipient. Suitable liquid excipients are known in the art; see, e.g., *Remington's Pharmaceutical Sciences.*

EXAMPLES

Example 1: Preparation of polymers with high binding capacity

Materials:

[00130] All chemicals were purchased from commercial sources and used as received. All reactions were carried out under nitrogen. Chemical structures and used abbreviations are given below in Tables 6 and 7.

Table 6: Monomer Abbreviations and Structures

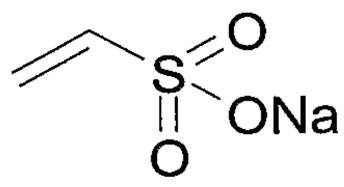
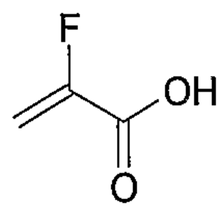
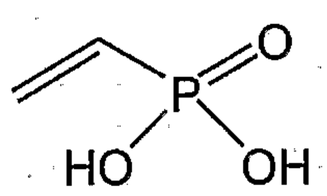
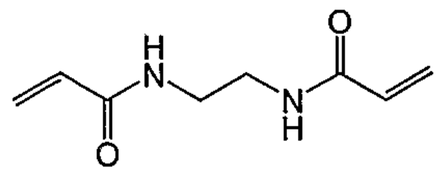
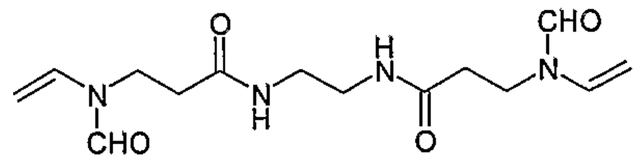
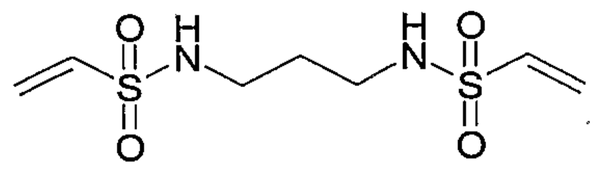
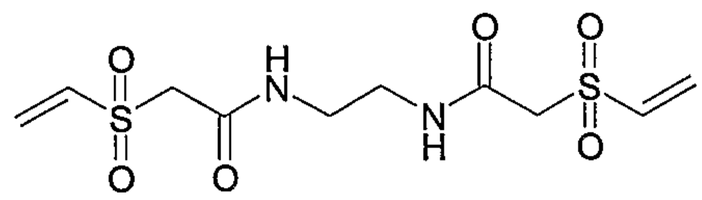
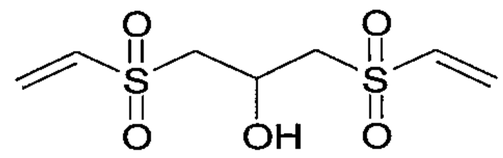
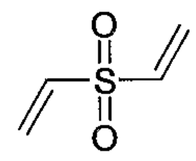
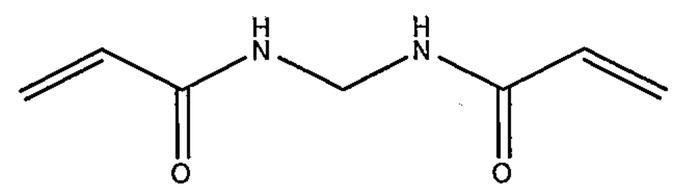
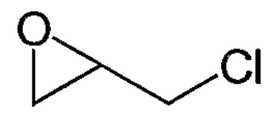
Abbreviation	Chemical name	Structure	Molecular Weight	CAS #
Na-VSA	vinylsulfonic acid sodium salt		130.1	3039-83-6
FAA	2-fluoroacrylic acid or *α*-fluoroacrylic acid or 2-fluoropropenoic acid		90.05	430-99-9
VPA	vinylphosphonic acid		108.03	1746-03-8

Table 7: Crosslinker Abbreviations and Structures

Abbreviation	Chemical name	Structure	Molecular Weight	CAS#
X-V-1	ethylenebisacrylamide		168.2	2956-58-3
X-V-2			310.36	
X-V-3			254.33	
X-V-4	N,N'-bis(vinylsulfonylacetyl) ethylene diamine		324.38	66710-66-5
X-V-5	1,3-bis(vinylsulfonyl) 2-propanol		240.3	67006-32-0
X-V-6	vinylsulfone		118.15	77-77-0
X-V-7	N,N'-methylenebisacrylamide		154.17	110-26-9
ECH	epichlorohydrin		92.52	

[00131] Initiators: VA-044: 2,2'-azobis[2-(2-imidazolin-2-yl)propane] dihydrochloride; $K_2S_2O_8$, potassium persulfate

General procedure for gel preparation from FAA:

[00132] To a 15-ml test tube were charged FAA, X-V-1, and water, followed by a magnetic stirbar. The mixture was stirred at 45°C for 20 minutes and VA-044 (100mg/ml solution in water) was added. The solution gelled and was kept at 45°C for 4 hours, then cooled to room temperature.

[00133] The gel was transferred to a 50-ml polypropylene tube and water was added to a total volume of 30 ml. The gel was crushed with a spatula, and further milled with an Ultra-Turrax. The tube was capped and centrifuged at 3000 rpm for 30 minutes and the supernatant solution was decanted off. To the gel was added 1.0M HCl to a total volume of

45 ml and tube was capped and tumbled for 30 minutes. The tube was centrifuged at 3000 rpm for 30 minutes and supernatant solution was decanted off. The same tumbling-centrifuging procedure was repeated once with 1.0M HCl and three times with nanopure water. The gel was freeze-dried for three days. The reaction solution composition and gel yield are displayed in Table 8.

Table 8: Synthesis of FAA gels

Sample #	*Reaction solution composition*				*Yield (mg)*
	FAA (mg)	X-V-1 (mg)	Water (mL)	VA-044 (mL)	
628A	757	19	0.757	0.038	740
628B	737	37	0.737	0.037	760
628C	730	73	0.730	0.037	760
628D	691	138	0.691	0.035	780

General procedure for gel preparation from NaVSA:

[00134] Commercially available NaVSA was converted into acid form and purified by vacuum distillation according to a method described by Breslow et al (*J. Am. Chem. Soc.*, 1954, 76, 6399-6401). The pure acid was then dissolved in water and neutralized with NaOH solution carefully at 0°C. The colorless salt solution was concentrated by vacuum distillation to a concentration of 56 wt. %.

[00135] To a 15-ml test tube were charged NaVSA solution, crosslinker, and a magnetic stirbar and the mixture was stirred at 45°C for 20 minutes. VA-044 (50mg/mL solution in water) or $K_2S_2O_8$ (50mg/mL solution in water) was added. The solution was stirred at 45°C (if VA-044 used) or 50°C (if $K_2S_2O_8$ used) for 16 hours, then cooled to room temperature. The gel was purified according to the same procedure as used for FAA gel. The reaction solution composition and gel yield were displayed in Table 9.

Table 9: Synthesis of NaVSA gels

Sample #	*Reaction solution composition*					*Yield*
	NaVSA (mL)	X-V-1 (mg)	X-V-5 (mg)	VA-044 (mL)	$K_2S_2O_8$ (mL)	*(mg)*
100851A1	1.493	28	0	0.056	0	0
100851A2	1.493	56	0	0.056	0	400
100851A3	1.493	112	0	0.056	0	740
100851A4	1.493	225	0	0.056	0	590
100851B1	1.493	0	28	0.056	0	550
100851B2	1.493	0	56	0.056	0	830
100851B3	1.493	0	112	0.056	0	890
100851B4	1.493	0	225	0.056	0	800
100851C1	1.493	28	0	0	0.056	0
100851C2	1.493	56	0	0	0.056	420
100851C3	1.493	112	0	0	0.056	760
100851C4	1.493	225	0	0	0.056	730
100851D1	1.493	0	28	0	0.056	390
100851D2	1.493	0	56	0	0.056	540
100851D3	1.493	0	112	0	0.056	890
100851D4	1.493	0	225	0	0.056	720

General procedure for gel preparation from copolymerization of NaVSA and FAA:

[00136] To a 15-ml test tube were charged FAA and NaVSA solution, followed by a magnetic stirbar. The mixture was stirred at room temperature for 10 minutes and all FAA dissolved. X-V-1 was added and mixture was stirred at room temperature for 10 minutes, then at 45°C for 20 minutes. VA-044 (100mg/ml solution in water) was added and the solution was stirred at 45°C for 3 hours, then cooled to room temperature. The gel was purified according to the same procedure as used for FAA gel. The reaction solution composition and gel yield were displayed in Table 10.

Table 10: Synthesis of NaVSA/FAA gels

Sample #	*Reaction solution composition*				*Yield (mg)*
	FAA (mg)	NaVSA (mL)	X-V-1 (mg)	Va-044 (mL)	
101028A1	0	1.328	100	0.100	600
101028A2	100	1.195	100	0.100	630
101028A3	200	1.062	100	0.100	720
101028A4	300	0.930	100	0.100	780
101028A5	400	0.797	100	0.100	730
101028A6	500	0.664	100	0.100	700

General procedure for gel preparation from copolymerization of AA and FAA:

[00137] To a 15-ml test tube containing a magnetic stirbar, were charged FAA, X-V-1 and water, and the mixture was stirred until all solids dissolved. AA was added, followed by VA-044 (100mg/ml solution in water). The mixture was stirred at 45°C for 3 hours, then cooled to room temperature. The gel was purified according to the same procedure as used for FAA gel. The reaction solution composition and gel yield were displayed in Table 11.

Table 11: Synthesis of FAA/AA gels

Sample #	*Reaction solution composition*					*Yield (mg)*
	FAA (mg)	AA (mL)	X-V-1 (mg)	Water (mL)	VA-044 (mL)	
100982A1	800	0	80	0.764	0.040	770
100982A2	720	0.076	80	0.764	0.040	700
100982A3	640	0.152	80	0.764	0.040	730
100982A4	560	0.228	80	0.764	0.040	740
100982A5	480	0.304	80	0.764	0.040	740
100982A6	400	0.380	80	0.764	0.040	730

General procedure for preparation of poly(vinylsulfamate) gel:

[00138] Polyvinylamine hydrochloride (PVAm.HCl) was prepared according to a literature procedure by Badesso et al (in *Hydrophilic Polymers: Performance with Environmental acceptance,* P489-504). PVAm gel was prepared by the crosslinking reaction of PVAm.HCl with epichlorohydrin. The procedure was as follows: to a 100ml of round bottom flask was charged 33 wt% PVAm.HCl aqueous solution (15 gm, 62.9 mmol), followed by 50 wt% NaOH solution (2.63gm) to neutralize 50 mol% of PVAm.HCl. Epichlorohydrin (1.0 gm) was added and the mixture was stirred magnetically until stirring stopped due to gel formation. The gel was further cured at 65^0C for 12 hours and transferred to a 50-ml polypropylene tube, and then water was added to a total volume of 30 ml. The gel was crushed with a spatula, and further milled with an Ultra-Turrax. The gel was washed with 1M HCl and nanopure water using the procedure described for FAA gel. Finally, PVAm gel was freeze dried for 3 days.

General procedure for preparing poly(vinylsulfamate) gel:

[00139] To a 20 ml vial was added 0.5 gm of PVAm gel and 10 ml of solvent. The mixture was heated at 60^0C for 1hour, then 0.5 gm of sulfur trioxide trimethylamine ($SO_3.N(CH_3)_3$) was added. Inorganic base, Na_2CO_3 or 2M NaOH solution, was added to the reaction mixture to maintain the pH above 9. The mixture was heated at 60^0C for a certain time. The mixture was centrifuged, and supernatant solution was decanted off. The gel was washed with nanopure water until pH reached 7, and freeze dried. The reaction conditions and the conversion of amine group to sulfamate group are shown in Table 12.

Table 12: Preparation of poly(vinylsulfamate) gel

Sample #	*Ratio of $(CH_3)_3.SO_3$ to NH_2*	*Base*	*Reaction time (hours)*	*Solvent*	*Conversion (%)*
001	1:1	None	3	Water	22.4
002	1:1	None	10	Water	37.1
003	1:1	None	22	Water	40.8
008	1:1.5	$(CH_3)_3N$	22	$(CH_3)_3N$ /water (20 vol%)	65.5
010	1:1.5	Pyridine	22	Pyridine/Water (20 wt%)	4.84
013	1:1	Na_2CO_3	22	Water	80.5
014	1:1.5	Na_2CO_3	22	Water	86.1
015	1:1	NaOH	22	Water	72.5
016	1.5	NaOH	22	water	73.5

Example 2: Binding Capacity Screening Protocol

[00140] All experiments were performed in duplicate. Approximately 30mg of each polymer was aliquoted in duplicate into 16x100mm glass test tubes. Dowex 50W and Amberlite CG-50 were included in each experiment as internal controls. The relevant test binding buffer (Buffer 1, Buffer 2 or Buffer 3 below) was added to a final resin concentration of 2.5mg/ml. The test tubes were sealed using a Teflon membrane and incubated at room temperature, with constant end-over-end rotation, for at least one hour to allow the cations to achieve binding equilibrium with the polymers. The test tubes were then centrifuged at 500g for thirty minutes to isolate the resins. A sample of the supernatant was taken and the equilibrium concentrations of potassium (K^+_{eq}) and sodium (Na^+_{eq}) were determined by Ion Chromatography (IC). By comparing K^+_{eq} and Na^+_{eq} with the concentration of potassium in Buffer 1, Buffer 2 or Buffer 3 in the absence of polymer (K^+_{start} and Na^+_{start}), the amount of cation (in mmoles cation/gram of polymer) was calculated. The ratio of sodium and potassium bound to the polymer was also calculated in this manner.

[00141] The capacity of each resin for Sodium and for Potassium was tested under some or all of the following conditions:

1. 75mM NaOH, 75mM KOH (pH not adjusted)
2. 50mM Citric Acid, 75mM KOH, 75mM NaOH, pH6.35 (with HCl)
3. 50mM Citric Acid, 75mM KOH, 75mM NaOH, pH 3 (with HCl)

TABLE 13: Binding capacities of phosphonic, carboxylic, and sulfonic polymers

Sample Name	Description	Total mmoles ($Na^+ + K^+$) bound/gm resin, pH12.5	$Na^+:K^+$ ratio at pH12.5	Total mmoles ($Na^+ + K^+$) bound/gm resin, pH 6.25	$Na^+:K^+$ ratio at pH 6.25	Total mmoles ($Na^+ + K^+$) bound/gm resin, pH3	Na^+: K ratio a pH3
616B3	NaVSA + 20 wt.% X-V-1						
624B	NaVSA + 5 wt.% X-V-2						
624C	NaVSA + 10 wt.% X-V-2	6.91	0.76	6.35	0.78	6.43	0.76
624D	NaVSA + 20 wt.% X-V-2	6.50	0.78	6.20	0.84	5.95	0.81
628A	FAA + 2.5 wt.% X-V-1	10.44	0.96	9.76	0.98	2.92	0.50
628A	FAA + 2.5 wt.% X-V-1			9.85	0.97	3.45	0.50
628B	FAA + 5.0 wt.% X-V-1	10.22	1.01	9.61	1.01	2.93	0.48
628C	FAA + 10 wt.% X-V-1	10.05	1.02	9.36	1.02	2.84	0.47
628C	FAA + 10 wt.% X-V-1	10.68	0.98	9.18	0.97	2.85	0.42
628C	FAA + 10 wt.% X-V-1	9.87	0.93	9.63	0.85	2.13	0.27
628D	FAA + 20 wt.% X-V-1	9.12	1.03	8.52	1.02	2.59	0.50
629A	FAA + 25mol% NaOH + 12.5 wt.% X-V-1	9.59	1.02	9.18	1.00	2.87	0.44
		10.27	0.99	9.52	0.98	2.79	0.41
629B	FAA + 50mol% NaOH + 12.5 wt.% X-V-1	9.58	1.02	9.05	1.02	2.69	0.38
629B	FAA + 50mol% NaOH + 12.5 wt.% X-V-1	10.06	0.93	9.01	0.85	1.68	0.14
629C	FAA + 75mol% NaOH + 12.5 wt.% X-V-1	9.41	0.98	9.33	1.01	3.19	0.54
629D	FAA + 100mol% NaOH + 12.5 wt.% X-V-1	9.55	0.98	9.43	1.00	3.05	0.54
636A2	NaVSA + 5 wt.% X-V-3			6.43	0.72	7.15	0.75
636A3	NaVSA + 10 wt.% X-V-3	7.93	0.77	6.70	0.76	7.07	0.77
636A4	NaVSA + 20 wt.% X-V-3	7.41	0.76	6.29	0.76	6.28	0.75

Sample Name	Description	Total mmoles ($Na^+ + K^+$) bound/gm resin, pH12.5	Na^+:K^+ ratio at pH12.5	Total mmoles ($Na^+ + K^+$) bound/gm resin, pH 6.25	Na^+:K^+ ratio at pH 6.25	Total mmoles ($Na^+ + K^+$) bound/gm resin, pH3	Na^+: K ratio a pH3
636B3	NaVSA + 10 wt.% X-V-3	9.52	0.81	6.49	0.74	7.03	0.77
636B4	NaVSA + 20 wt.% X-V-3	7.76	0.79	6.10	0.77	6.53	0.78
639A	FAA + 10 wt.% X-V-1	9.72	0.92	8.75	0.84	3.20	0.41
639A	FAA + 10 wt.% X-V-1	10.38	0.90	9.45	0.85	1.92	0.22
639B	FAA + 50mol% NaOH + 12.5 wt.% X-V-1	8.97	0.92	8.85	0.85		
639B	FAA + 50mol% NaOH + 12.5 wt.% X-V-1	9.46	0.95	8.68	0.83	1.73	0.17
639B	FAA + 50mol% NaOH + 12.5 wt.% X-V-1	8.447	0.87	8.192	0.834		
616B3	NaVSA + 20 wt.% X-V-1	5.87	0.71	6.14	0.72	6.57	0.78
100851A2	purified NaVSA + 5 wt.% X-V-1	5.92	0.67	6.68	0.70	5.58	0.69
100851A2	purified NaVSA + 5 wt.% X-V-1	7.42	0.79	7.08	0.74	5.99	
100851A2	purified NaVSA + 5 wt.% X-V-1	6.57	0.77	6.45	0.71	5.87	0.74
100851A3	purified NaVSA + 10 wt.% X-V-1	6.27	0.07	6.84	0.72	6.17	0.72
100851A3	purified NaVSA + 10 wt.% X-V-1	6.97	0.75	7.50	0.74	6.78	0.77
100851A4	purified NaVSA + 20 wt.% X-V-1	5.84	0.71	6.53	0.73	5.21	0.70
100851A4	purified NaVSA + 20 wt.% X-V-1	6.28	0.81	6.28	0.75		
100851A4	purified NaVSA + 20 wt.% X-V-1	6.22	0.76	6.82	0.75	5.48	0.74
100851B1	purified NaVSA + 2.5 wt.% X-V-5	6.42	0.65	6.50	0.65	6.09	0.65
100851B2	purified NaVSA + 5 wt.% X-V-5	5.76	0.62	6.72	0.64	6.27	0.65
100851B2	purified NaVSA + 5 wt.% X-V-5	6.77	0.73	7.27	0.67	6.48	0.71
100851B3	purified NaVSA + 10 wt.% X-V-5	5.83	0.61	7.07	0.64	5.57	0.60
100851B3	purified NaVSA + 10 wt.% X-V-5	6.66	0.80	7.27	0.69	6.05	0.68
100851B4	purified NaVSA + 20 wt.% X-V-5	6.50	0.65	6.25	0.61	5.22	0.59
100851B4	purified NaVSA + 20 wt.% X-V-5	5.50	0.66	6.59	0.66	5.82	0.66
100851C2	purified NaVSA + 5 wt.% X-V-1	6.52	0.70	6.40	0.68	5.52	0.67
100851C2	purified NaVSA + 5 wt.% X-V-1	7.23	0.78	7.03	0.75		
100851C3	purified NaVSA + 10 wt.% X-V-1	6.77	0.72	7.02	0.72	5.90	0.71

Sample Name	Description	Total mmoles ($Na^+ + K^+$) bound/gm resin, pH12.5	$Na^+:K^+$ ratio at pH12.5	Total mmoles ($Na^+ + K^+$) bound/gm resin, pH 6.25	$Na^+:K^+$ ratio at pH 6.25	Total mmoles ($Na^+ + K^+$) bound/gm resin, pH3	$Na^+: K^+$ ratio at pH3
100851C4	purified NaVSA + 20 wt.% X-V-1	6.05	0.72	6.08	0.71	4.66	0.68
100851C4	purified NaVSA + 20 wt.% X-V-1	6.51	0.78	8.07	0.80		
100851D1	purified NaVSA + 2.5 wt.% X-V-5	7.07	0.74	7.28	0.71	5.87	0.69
100851D1	purified NaVSA + 2.5 wt.% X-V-5	7.65	0.73	7.40	0.72		
100851D2	purified NaVSA + 5 wt.% X-V-5	6.83	0.66	7.17	0.71	5.42	0.64
100851D2	purified NaVSA + 5 wt.% X-V-5	7.91	0.75	7.37	0.70		
100851D3	purified NaVSA + 10 wt.% X-V-5	6.70	0.67	6.87	0.66	5.21	0.64
100851D4	purified NaVSA + 20 wt.% X-V-5	6.24	0.67	6.46	0.67	6.63	0.58
100851D4	purified NaVSA + 20 wt.% X-V-5	7.01	0.68	6.61	0.70		
100982A1	FAA + 10 wt.% X-V-1	9.66	0.89	9.02	0.86	3.40	0.50
100982A1	FAA + 10 wt.% X-V-1			8.47	0.86		
100982A2	90 wt.% FAA + 10 wt.% acrylic acid + 10 wt.% X-V-1	9.81	0.92	8.49	0.86	2.98	0.52
100982A2	90 wt.% FAA + 10 wt.% acrylic acid + 10 wt.% X-V-1			8.00	0.86		
100982A3	80 wt.% FAA + 20 wt.% acrylic acid + 10 wt.% X-V-1	10.00	0.95	7.97	0.86	2.89	0.56
100982A3	80 wt.% FAA + 20 wt.% acrylic acid + 10 wt.% X-V-1			7.74	0.87		
100982A4	70 wt.% FAA + 30 wt.% acrylic acid + 10 wt.% X-V-1	9.92	0.97	8.52	0.85	2.42	0.54
100982A4	70 wt.% FAA + 30 wt.% acrylic acid + 10 wt.% X-V-1			7.49	0.88		
100982A5	60 wt.% FAA + 40 wt.% acrylic acid + 10 wt.% X-V-1	10.00	1.00	7.48	0.86	2.01	0.53
100982A5	60 wt.% FAA + 40 wt.% acrylic acid + 10 wt.% X-V-1			7.10	0.89		
100982A6	50 wt.% FAA + 50 wt.% acrylic acid + 10 wt.% X-V-1	10.41	1.03	7.56	0.87	2.11	0.61
100982A6	50 wt.% FAA + 50 wt.% acrylic acid + 10 wt.% X-V-1			7.11	0.90		
101012A1	purified NaVSA + 2.5 wt.% X-V-2						

Sample Name	Description	Total mmoles ($Na^+ + K^+$) bound/gm resin, pH12.5	Na^+:K^+ ratio at pH12.5	Total mmoles ($Na^+ + K^+$) bound/gm resin, pH 6.25	Na^+:K^+ ratio at pH 6.25	Total mmoles ($Na^+ + K^+$) bound/gm resin, pH3	Na^+: K^+ ratio at pH3
101012A2	purified NaVSA + 5 wt.% X-V-2	7.50	0.74	7.70	0.74	6.49	0.74
101012A3	purified NaVSA + 10 wt.% X-V-2	7.04	0.74	7.31	0.74	6.27	0.74
101012A4	purified NaVSA + 20 wt.% X-V-2	6.52	0.75	6.88	0.75	6.01	0.76
101012B1	purified NaVSA + 2.5 wt.% X-V-4						
101012B2	purified NaVSA + 5 wt.% X-V-4	7.53	0.71	7.64	0.71	6.93	0.72
101012B3	purified NaVSA + 10 wt.% X-V-4	6.88	0.70	7.19	0.71	6.24	0.70
101012B4	purified NaVSA + 20 wt.% X-V-4	6.34	0.68	6.78	0.70	6.08	0.70
101012D1	purified NaVSA + 2.5 wt.% X-V-7	7.02	0.73	6.68	0.73	4.86	0.67
101012D2	purified NaVSA + 5 wt.% X-V-7	7.35	0.74	7.24	0.74	6.58	0.73
101012D3	purified NaVSA + 10 wt.% X-V-7	7.17	0.74	7.30	0.74	6.64	0.75
101012D4	purified NaVSA + 20 wt.% X-V-7	6.33	0.72	6.64	0.74	5.83	0.74
101028A1	purified NaVSA + 10 wt.% X-V-1	6.47	0.76	5.69	0.75	5.47	0.77
101028A2	90 wt.% purified NaVSA + 10 wt.% FAA +10 wt.% X-V-1	6.67	0.81	6.01	0.79	4.67	0.72
101028A3	80 wt.% purified NaVSA + 20 wt.% FAA +10 wt.% X-V-1	7.17	0.82	6.50	0.80	4.25	0.68
101028A4	70 wt.% purified NaVSA + 30 wt.% FAA +10 wt.% X-V-1	7.33	0.84	6.77	0.81	4.12	0.66
101028A5	60 wt.% purified NaVSA + 40 wt.% FAA +10 wt.% X-V-1	7.69	0.85	7.00	0.83	3.43	0.60
101028A6	50 wt.% purified NaVSA + 50 wt.% FAA +10 wt.% X-V-1	8.25	0.87	7.29	0.85	3.80	0.63
101029A2	VPA + 5 wt.% X-V-1						
101029A3	VPA + 10 wt.% X-V-1	11.38	1.49	5.70	1.00	2.37	0.89
101029A4	VPA + 20 wt.% X-V-1	10.15	1.66	4.90	1.03	2.27	0.88
101029B2	VPA + 50mol% NaOH + 5 wt.% X-V-1						
101029B3	VPA + 50 mol% NaOH + 10 wt.% X-V-1	10.97	1.50	5.27	0.98	2.63	0.91
101029B4	VPA + 50mol% NaOH + 20 wt.% X-V-1	10.23	1.62	5.10	1.01	2.06	0.88

Sample Name	Description	Total mmoles ($Na^+ + K^+$) bound/gm resin, pH12.5	Na^+:K^+ ratio at pH12.5	Total mmoles ($Na^+ + K^+$) bound/gm resin, pH 6.25	Na^+ :K^+ ratio at pH 6.25	Total mmoles ($Na^+ + K^+$) bound/gm resin, pH3	Na^+: K^+ ratio at pH3
684A	FAA + 5 wt.% X-V-1	10.7	0.91	10.30	0.84	nm	nm
684B	FAA + 5 wt.% X-V-1	9.80	0.83	9.70	0.82	nm	nm
Dowex 50WX4-200 (average of 15 experiments)		5.37	0.77	5.51	0.77	4.92	0.76
Dowex 50W (Standard deviation of 15 experiments)		0.77	0.06	0.81	0.08	0.80	0.06

nm: not measured

[00142] These examples show that the polymers of the invention display high potassium binding capacity at physiological pHs. In particular polymers prepared from 2-fluoroacrylic acid can bind up to two times more potassium than sulfonated polystyrene resins Dowex.

Titration curves of alpha-fluoroacrylate copolymer with acrylic acid from Table 11

[00143] The protocol was as per Helfferich, F. "Ion Exchange" (1962) McGraw-Hill, New York).

1. Approximately 50mg of polymer (acid-form) was measured into 15x100mm glass test tubes.
2. The volume of 1M NaOH required to generate the required mEq was calculated, and enough water was added to the tubes to keep the ratio of solution volume to resin weight constant.
3. The required mEq of NaOH was added to the polymer from a 1M NaOH stock.
4. The tubes were sealed and rotated for 4 days to allow to come to equilibrium
5. The equilibrated pH was measured while continuing to mix.

[00144] The results are shown in Figure 16. This example shows that polyalpha-fluoroacrylate has a lower pKa (equal to pH value at half-neutralization) than a methacrylic containing ion-exchange resin such as Amberlite CG50. The pKa value for the FAA gel material (100982A1 from Table 11) can be estimated from Figure 16 at about 5.6 versus 8 for Amberlite CG50. The incorporation of acrylic acid tends to increase pKa in proportion to the wt-% of acrylic acid in the FAA-Acrylic acid copolymer. This indicates that an electro-

withdrawing group such as fluorine in the alpha position to COOH decreases the pKa and increases the overall binding capacity within the typical physiological pH range of 5-7.

Example 3: Procedure for predicting binding of cations in the human GI

[00145] This procedure was used to model the conditions of use of a potassium binder drug and measure the binding characteristics of the polymer for potassium (target solute) in the presence of other competing cations. A meal mimic was prepared and artificially digested in the presence of pepsin and pancreatic juice. The sequence of addition of enzymes and the pH profile were controlled so that the digestion process was simulated down to the jejunum level. The test polymers, preloaded with lithium, were added to the digested meal mimic and allowed to equilibrate for a fixed period of time; the mixture was then centrifuged and the supernatant was assayed for Na^+, K^+, NH_4^+, Ca^{2+}, and Mg^{2+} by ion chromatography. The lithium released was computed as the total cation exchange, while the decrease in concentrations of the other cations was used to compute their binding variations in western diets.

Preparation of Resin

[00146] Resin (test resin, or Dowex 50WX4-200 used as a comparative), was washed extensively in 1M HCl to convert it to the H-form. It was then washed extensively in 1M LiOH. Excess LiOH was removed by washing in ddH_2O. The resins were lyophilized and stored in a desiccator.

[00147] Figure 1 depicts starting cation concentrations in meal mimic and Figure 2 depicts binding of cations by resins in meal mimic.

Measurement of binding capacities in cecal and fecal extracts

[00148] Two volumes (w/v) of ice-cold ddH_2O were added to the human feces and to normal rabbit cecal contents. These were incubated with rotation at 4°C with end-over-end rotation for at least 1hour to extract soluble cations. Fecal and cecal extracts, as well as thawed meal mimics, were centrifuged at 2000g for 10 minutes to clarify. Approximately 50mg Li-form Dowex 50W was weighed into 16x100mm glass test tubes. Control test tubes were included that contained no resin. Clarified extracts or mimics were added to a final resin concentration of 2.5mg/ml. 5-10ml of extracts or mimic were added to the control test tubes. Tubes were sealed and rotated at 4°C for 90 minutes. The tubes were centrifuged at 500g for thirty minutes to precipitate the resin. Supernatant samples were taken. The samples were then prepared for ion chromatography by spinning at 13,000g for ten minutes, taking the supernatant and rapidly passing across a 3000Da cutoff dialysis membrane by

centrifugation. Extracts were further diluted 1:5 (v/v) in ddH_2O before applying to the IC columns. Start (without resin) and equilibrium (with resin) concentrations of Li^+, Na^+, K^+, NH_4^+, Ca^{++} and Mg^{++} were determined, and the amount (in mmoles cation/gm resin) of Li^+ released, as well as Na^+, K^+, NH_4^+, Ca^{++} and Mg^{++} bound were calculated.

Procedure for measuring the binding of cations by resins in human fecal extracts

[00149] Resins and feces were prepared as follows. Resins were washed extensively in 1M HCl to convert them to the H-form. Excess HCl was removed by washing in ddH_2O. The resins were lyophilized and stored in a desiccator. Fecal samples were obtained from two human subjects, frozen immediately and stored at -80°C to minimize ammonium production *ex vivo*.

[00150] All experiments were performed in triplicate. Error bars on Figures 3 and 4 indicate standard deviations values. Fecal samples were resuspended in two volumes of ice-cold ddH_2O (w/v) and incubated overnight at 4°C to extract soluble cations. The extract was then clarified by centrifuging at 2000g for ten minutes. H-form resins were weighed into disposable 15ml-capacity columns. They were them washed extensively in 150mM LiOH to convert them to the Li-form. They were washed in ddH_2O to remove excess LiOH. Clarified fecal extract was applied to the columns to a final resin concentration of 2.5mg/ml of extract. A sample was retained for calculating resin concentrations in the absence of resin. Columns were capped and rotated at 4°C for three hours. They were then eluted by centrifugation into 50ml polypropylene tubes. The pH of eluted extracts and retained clarified fecal extracts were measured (it had not changed: Sample 1 pH was 6.75, sample 2 pH was 7.1). The samples were then prepared for ion chromatography by spinning at 13,000g for ten minutes, taking the supernatant and rapidly passing across a 3000Da cutoff dialysis membrane by centrifugation. Extracts were further diluted 1:5 (v/v) in ddH_2O before applying to the IC columns. Start (without resin) and equilibrium (with resin) concentrations of Li^+, Na^+, K^+, NH_4^+, Ca^{++} and Mg^{++} were determined, and the amount (in mmoles cation/gm resin) of Li^+ released, as well as Na^+, K^+, NH_4^+, Ca^{++} and Mg^{++} bound were calculated. In Figure 4 "Total occupied" refers to the sum of Li^+ (i.e. monovalent) binding sites occupied by the other cations, taking into account the divalent nature of Ca^{++} and Mg^{++}.

[00151] Data presented in Figure 4 demonstrate that the ex-vivo binding of potassium in human fecal extracts for the FAA based material is about twice as much that of Dowex 50WX4-200 (a material essentially identical in composition to the potassium binder Kayexalate). The ex-vivo binding of potassium by the Dowex resin is essentially the same as that reported for polystyrene sulfonate resins in human clinical studies, which establishes this

method as a good predictor for in-vivo binding performance. It also indicates that other cations, in particular Magnesium and Calcium, compete with potassium for the binding sites of the polymers. Figure 3 depicts the original concentrations of cations in the Feces of Subject 1 and Subject 2. Figure 4 depicts the binding of cations in human fecal extracts to cation exchange resins.

Example 4: Method of selection of semi-permeable membrane with high potassium binding selectivity over magnesium and calcium

[00152] This protocol describes a method to optimize polymeric materials with regards to their ion permselectivity characteristics, which then can be used as the shell component for the making of potassium selective core-shell ion-exchange particles.

Polymer synthesis and membrane preparation:

[00153] Polymeric membrane materials with different compositions were prepared by radical copolymerization of DBA (N, N'-dibutyl acrylamide) and DEAEMA (N,N'-diethylaminoethylmethacrylate) in a glove box using miniaturized reactors in a library format. AIBN was used as the initiator and ethanol as the solvent. Polymers were isolated by precipitation into water, freeze-dried, and characterized by GPC and H-NMR. The composition of the polymer (DBA mol%) ranges from 30% to 70% and molecular weight ranges from 200K to 300K as shown below:

Table 14

Polymer ID 101224	D1	D2	D3	D4	D5	D6
Mn ($x10^3$)	327	326	322	285	240	217
Mw ($x10^3$)	584	563	520	467	411	340
PDI	1.78	1.73	1.61	1.64	1.71	1.56
Composition (DBA, mol%)	31.2	37.1	48.5	56.1	64.4	68.5

[00154] Polymer membranes were prepared by casting a 2-wt% toluene solution of DBA-co-DEAEMA onto a regenerated cellulose dialysis membrane (RC membrane with MWCO of 14 K). After toluene was evaporated, a polymer membrane was formed on the top of dialysis membrane. A composite membrane of polymer membrane and RC membrane was thus prepared.

Permeability study on cations

[00155] The composite membrane was first clamped onto a glass tube with diameter of 13 mm, and then immersed into a 2 L of donor solution of cations. The tube was filled with 10 ml of acceptor solution (lactose solution with the same osmolality as the donor solution (240mM)). The acceptor solution was sampled at a specified time interval and analyzed by ion chromatography. See Figure 5.

[00156] Donor solution was prepared by mixing the aqueous solution of NaCl, KCl, $CaCl_2.2H_2O$, and $MgSO_4.7H_2O$. The solution was buffered to pH 6 by using 14 mM of MES (2-[N-morpholine]ethanesulfonic acid] solution. The concentrations of different cations determined by IC were as follows: $[Na^+]$, 40.46 mM; $[K^+]$, 31.44 mM; $[Mg^{2+}]$, 33.25 mM; $[Ca^{2+}]$, 22.324 mM.

[00157] Determination of the permeability coefficient (P) of different cations: As mentioned in the measurement set-up, the acceptor solution was sampled at a specific time interval and analyzed by IC. Assuming a Fick's first law of diffusion, P is readily obtained by linearization of the data, following a method of calculation reported in equation 1 in G. Van den Mooter, C. Samyn, and R. Kinget, International Journal of Pharmaceutics, 111, 127-136(1994). The permeability coefficients of different cations were thus calculated from the slope from this linear relationship.

$$-ln\left(\frac{C_o - C_a}{C_o}\right) = \frac{PS}{Va}t \qquad \text{.....Equation 1}$$

Where C_o is the initial concentration of the solute in the donor compartment and C_a the concentration in the acceptor compartment at time t, Va is the volume of the acceptor compartment, and S the surface of the membrane.

[00158] Permselectivity: As described above, the permeability coefficient was calculated for each cation. By normalizing the permeability coefficient of Na^+ as 1, the permselectivity for cations M1 and M2 can be calculated as follows: $P_{M1}^{M2} = P(M2)/P(M1)$

Permeability coefficients of different cations through different membranes:

[00159] Table 14 shows the permeability coefficients of different cations at different membranes. When polymers are more hydrophilic (Polymer D3 and D4 with DBA% 48.5 and 56.1%, respectively), all cations, such as Na^+, K^+, Mg^{2+}, and Ca^{2+}, are more permeable and their permeability coefficients are comparable to those through a blank dialysis membrane (RC membrane) and reflect the self-diffusivity of the cations. However, with the

increasing DBA content in polymer membrane (See Table 15 for D5 and D6), the permeability coefficients of different cations decreased as compared with blank membrane, which means that the hydrophobic nature of polymer membrane could make cations less permeable through the hydrophobic barrier.

Table 15: Permeability coefficients of cations at different membranes

Polymer ID	DBA (mol%)	PNa^+ (cm/sec)	PK^+ (cm/sec)	PMg^{2+} (cm/sec)	PCa^{2+} (cm/sec)
D3	48.5	2.41(±0.26)E-4	3.11(±0.34)E-4	6.50(±0.08)E-5	6.0(±0.07)E-5
D4	56.1	4.28(±0.44)E-5	6.11(±0.61)E-4	1.13(±0.11)E-5	1.04(±0.05)E-5
D5	64.4	4.32(±0.20)E-6	5.79(±3.59)E-6	5.42(±4.11)E-7	3.32(±3.33)E-7
D6	68.5	1.50(±0.05)E-7	-	-	-

[00160] Another characteristic for the permeability of different cations is their permselectivity. By normalizing the value of P_{Na+} as 1, the permselectivity for other cations can be calculated and the results are shown in Table 16. The permselectivity of P_{Mg}/P_{Na} and P_{Ca}/P_{Na} decreases with the increasing DBA content in polymer membranes, which implies that more hydrophobic polymer membranes may have better selectivity for different cations. For a better selectivity for different cations, two factors should be considered – the charge density and the membrane hydrophobicity.

TABLE 16

Polymer ID	DBA(%)	$P(K^+)/P(Na^+)$	$P(Ca^{2+})/P(Na^+)$	$P(Mg^{2+})/P(Na^+)$	$P(K^+)/P(Mg^{2+})$
D3	48.5	1.29	0.27	0.25	5.16
D4	56.1	1.43	0.26	0.24	5.96
D5	64.4	1.34	0.13	0.08	16.75

Example 5: Synthesis of poly-2-fluoroacrylic acid beads

[00161] Beads are prepared by a direct suspension process where a mixture of 2-fluoroacrylic methyl ester/divinylbenzene/benzoyl peroxide in a weight ratio 90/9/1 are dispersed in water under high shear with polyvinylalcohol as a suspending agent. The suspension is stirred and heated at 80°C for 10hours. The residual monomer is eliminated by

steam stripping. The beads are then filtered and treated with aqueous 3M NaOH to hydrolyze the polymer, then washed, treated with HCL, water-washed, and finally dried to form the desired polyα-fluoroacrylic acid particles. The average bead diameter is 250 microns as measured by Master Sizer (Malvern UK).

Example 6: Preparation of poly-2-fluoroacrylic acid / core- (DBA-DEAEMA) / shell particles

[00162] The core-shell particles are prepared by forming a coating of polymer D2 on the poly-2-fluoroacrylic acid beads prepared in example 5 using a Wurster coater. The shell polymer prepared in example 4 is first dissolved at 20 wt-% in toluene, and the thus obtained solution then dispersed in water in a 1: 4 weight ratio with 2 wt-% based on the organic phase of CTAB (Hexadecyltrimethyl-Ammonium Bromide) as a surfactant, using a Ultra-Turrax high-shear homogeneizer. The toluene is then driven off by evaporation under reduced pressure. The average diameter of the dispersion particles is 0.3 micrometer, as measured by Dynamic Light Scattering. The poly-2-fluoroacrylic acid beads are spray-coated with the shell polymer dispersion using a Wurster fluid bed coater 2"- 4"/6" Portable Unit. The fluidized bed unit is operated so that an average 5 microns thick coating is deposited on the core particles.

[00163] The potassium binding capacity when measured in a fecal extract as described in Example 3 is expected to be twice higher than that measured with the uncoated poly-α-fluoroacrylic acid beads.

Example 7: Preparation of polystyrene sulfonate/core- polyethyleneimine shell particles with Na+ and K+ selective-binding propertie

Procedure for coating PEI on Dowex beads

[00164] PEI (poly(ethyleneimine), Mw10,000) and Dowex beads (H-form, X4-200) were purchased from commercial sources. PEI aqueous solutions with different concentrations were prepared by dissolving PEI directly into nanopure water.

[00165] Weighed dried Dowex beads were mixed with PEI aqueous solution in library format glass tubes. After a specified reaction time, the tubes were sealed and centrifuged at 1000 rpm for 15 minutes, the supernatant solutions were then decanted off. To the beads in each tube was added nanopure water to a total volume of 10 ml and all tubes were sealed and tumbled for 30 minutes. The same tumbling-centrifuging was repeated 3 times. The beads were freeze-dried and weighted until a constant weight was obtained.

[00166] The reaction solution composition and gel weight increase are displayed in Table 17.

Table 17: Conditions for coating PEI on Dowex beads

Dowex Bead Weight (gm)	PEI Conc. (wt%)	PEI volume (ml)	Reaction time (hours)	Coated bead ID	Weight increase (Δwt%)
0.1274	2.5	10	1	DOWEX(2.5wt-1h)	*
0.2223	2.5	10	6	DOWEX(2.5wt-6h)	3.1
0.1609	1.5	10	1	DOWEX(2.5wt-1h)	*
0.2407	1.5	10	6	DOWEX(2.5wt-6h)	0.9
0.2016	0.5	10	1	DOWEX(2.5wt-1h)	*
0.2347	0.5	10	6	DOWEX(2.5wt-6h)	*

* No weight increase was observed.

Method for binding study

[00167] A mixture of NaCl, KCl, $MgCl_2$, and $CaCl_2$ was dissolved in a MES buffer (pH6.0) (MES, 2-[N-morpholine]ethanesulfonic acid]. The concentration for each cation was determined by IC. The concentrations for Na^+, K^+, Mg^{2+}, and Ca^{2+} are 26.4 mM, 9.75 mM, 4.75 mM and 4.16 mM respectively.

[00168] Weighed dried PEI-coated bead was put into a tube which contains 5-ml of MES buffer solution of NaCl, KCl, $MgCl_2$, and $CaCl_2$. The tube was sealed and tumbled. After a certain period of time as indicated in figure 6, the tube was centrifuged. 100 microliter of solution was then taken out from the supernatant for IC analysis. The binding amount of PEI coated beads for different cations were calculated from the concentration change in the solution.

The calculation is as follows:

Ion bound in beads (mmol/g) = $[V \times (C_0 - C_t) / \{[\text{weight of beads}] \times 1000\}$

C_0: initial concentration of metal ion (in mM)

C_t: concentration of metal ion after bead binding at a certain time (t hrs) (in mM)

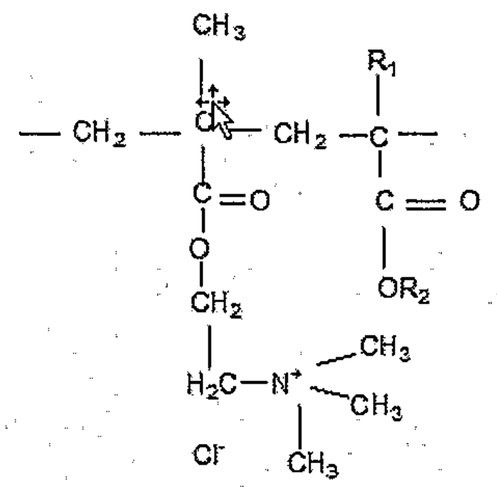
V: solution volume (5 ml)

Weight of beads (gm)

[00169] The binding data of different PEI coated beads for different cations are shown in Figure 6. PEI coated Dowex beads show higher Na^+ and K^+ binding than the uncoated beads (bare beads). The coated beads show much more selective binding than bare beads. The thicker the PEI coating (e.g. Dowex (2.5wt-6h), coated from 2.5 wt% PEI solution for 6 hours), the more selective for the different cations. The binding kinetic study shows that the binding of cations equilibrates faster for the thinner coated beads and bare beads.

Example 8: Polystyrene sulfonate beads with Eudragit shell

[00170] Shell material: Eudragit RL100 (Rohm), a copolymer of acrylic and methacrylic acid esters with 8.85-11.96% cationic ammonio methacrylate units, 10 wt% in ethanol and 10wt% triacetin. Core: Lewatit (cross-linked polystyrene sulfonate in sodium form), size – 300 μm.



RL 100

$R_1 = H, CH_3$
$R_2 = CH_3, C_2H_5$

The shell was applied using a FluidAir Wurster coater.

[00171] Binding was measured under following conditions:

Donor solution: 50 mM KCl and 50 mM $MgCl_2$

Bead concentration: 4 mg/ml

Duration: 6 hours

[00172] Figure 7 shows the effect of the shell on Mg^{2+} and K^+ binding. With increasing ratio of shell to core, Mg^{2+} binding decreased and K^+ binding increased. 20 wt% shell coating gave a K^+ binding capacity of 1.65 meq/gm, which is about 3 times higher than for uncoated Dowex.

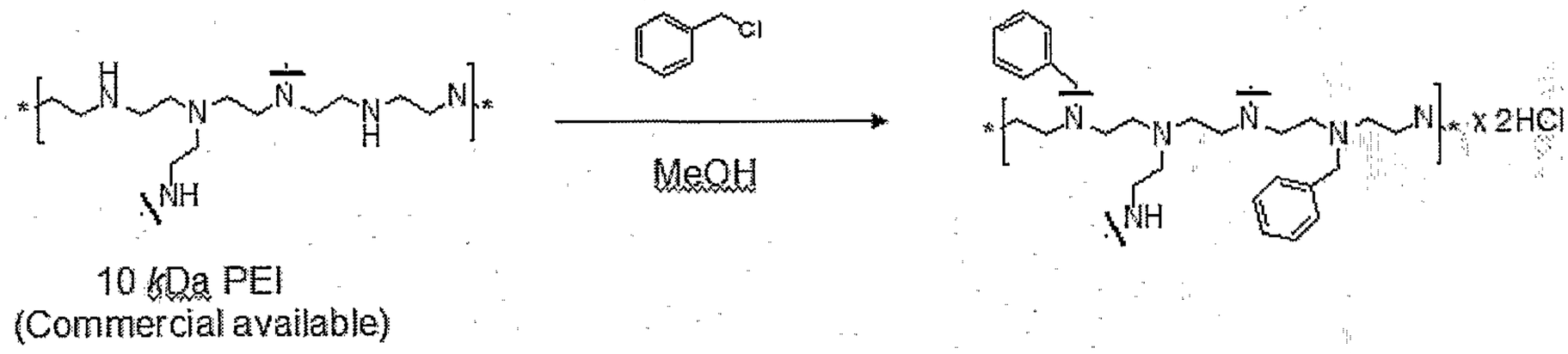
Example 9: Polystyrene sulfonate beads with benzylated polyethylene imine shell

Synthesis of benzylated polyethyleneimine (PEI)

[00173] To a 250 ml of round bottom flask were charged 15.6 g of PEI (363 mmol of $-NH_2$) and 125 ml of ethanol, this mixture was magnetically stirred until PEI was completely dissolved, then 30 g of $NaHCO_3$ (FW, 84; 256 mmol) and 40 ml of benzyl chloride (363 mmol) were subsequently added. The above mixture was reacted at 55^0C under nitrogen atmosphere overnight. Dichloromomethane was added to the slurry reaction mixture,

followed by filtration to remove inorganic salt. The solvent in filtrate was removed by vacuum. Dicholromethane was used again to re-dissolve the reaction product; inorganic salt was further removed by filtration. The solvent in the filtrate was removed again under vacuum. Finally, the product was triturated in hexane, filtered and washed with hexane, and dried under vacuum. The benzylation degree was 84% as determined by ^{1}HNMR. Similar materials with various degree of benzylation (respectively 20% and 40% for Ben(20) and Ben(40)) were prepared by adjusting the benzyl chloride to PEI ratio.

[00174] Benzylated polyethylene imine (Ben-PEI) was coated onto Dowex beads.



[00175] The shell was coated using solvent coacervation. The shell Ben(84)-PEI was dissolved in methanol and water mixture (3:1) at pH of 3. Shell and core were mixed for 5 minutes and methanol was removed by rotovap (40 minutes), isolated, washed, and dried.

[00176] Binding was measured under following conditions:

Donor solutions: 50 mM KCl and 50 mM $MgCl_2$

Bead concentration: 4 mg/ml

Duration: 6 and 24 hours

[00177] Results of the binding measurements are shown in Figure 8. Ben(84)-PEI showed selective binding for potassium after 6 and 24 hours as revealed by lower Mg^{2+} binding compared to naked beads.

[00178] Figure 9 depicts the stability of Ben(84)-PEI coated Dowex (K) beads under acid conditions representative of the acidic conditions in the stomach. The beads were exposed to pH 2 HCl for 6 hours, isolated, and dried. Binding selectivity was tested for the post-treated beads. Binding conditions were as follows:

Donor solutions: 50 mM KCl and 50 mM $MgCl_2$

Bead concentration: 4 mg/ml

Duration: 6 and 24 hours

The coating was stable and binding selectivity was maintained at 6 and 24 hours.

Example 10: FAA beads with benzylated polyethylene imine shell

[00179] The shell was applied on the FAA core by the process of solvent coacervation. The shell, Ben(84)-PEI, was dissolved in methanol and water mixture (3:1) at pH of 4.5. The shell and core were mixed for 5 minutes and methanol was removed by rotovap (40 minutes), isolated, washed, and dried.

[00180] Binding was measured under following conditions:

Donor solutions: 50 mM KCl and 50 mM $MgCl_2$

Bead concentration: 4 mg/ml

Duration: 6 hours

[00181] The potassium binding was calculated from actual magnesium uptake and overall binding capacity of polymer which was 5.74 meq/gm. The results are shown in Figure 10. Increasing the ratio of shell/core caused a decrease in magnesium binding which indicates an increase in potassium binding.

Example 11: Coating by controlled precipitation induced by pH change

[00182] The shell comprised of Benzylated PEI, Ben (~20%); and Ben (~40%) on a Dowex(K) core. Binding was measured in 50 mM KCl and 50 mM $MgCl_2$.

[00183] Figure 11 shows the results of the binding experiments. Controlled precipitation method for 40% benzylated PEI shows better coating and this combination of coating method and materials gives higher binding selectivity.

Example 12: Membrane screening of Shell Polymers

[00184] Shell polymers were screened by coating a flat membrane via solvent casting and using the coated membrane as the barrier in a diffusion cell, as depicted in Figure 15. Donor solution was 50mM 2-[N-morpholino] ethane sulfonic acid (MES) buffer at pH6.5 with 50mM K^+ and Mg^{2+}. Permeability coefficient was calculated as described in Example 4 above. Cross-linked B-PEI was tested using this method. B-PEI (35mol%) was cross-linked with 1, 4-butanediol diacrylate. The cross-linker was reacted on the top of dried B-PEI for 4 hours. The screening was performed in 50 mM KCl and 50 mM MgCl2 in 50 mM MES buffer. Cross-linker (diacrylate) reacted with B-PEI (35 mol%) membrane. As shown in Figure 13, addition of the cross-linker reduced permeability coefficient and also showed good selectivity.

[00185] Blends of Eudragit RL 100 and RS 100 were also evaluated using the method of Figure 12. The results are shown in Figure 14. Adding RS100 into RL100 can reduce the permeability and the permselectivity stays in the same range. Membranes with more than

50wt% of RS100 lost selectivity ([K^+] in the same scale, but [Mg^{2+}] much higher than other composites).

Example 13: Effects of bile acids on K^+ binding

[00186] Dowex(Li) (~100 μm) was first coated with PEI aqueous solution. The supernatant was removed and the coat was further crosslinked with 1,2-Bis-(2-iodoethoxy)-ethane (BIEE). Binding was measured in 50 mM KCl and 50 mM of MgCl2, MES buffer, pH 6.5. Bile acids extract used was 2 mg/ml (bile extract porcine with 60% bile acids and 40% unknowns, i.e., free fatty acids, phospholipids, etc.). Time: 6 and 24 hrs and Bead content: 4 mg/ml. Results are shown in Figures 15A and 15B. Enhanced performance of the shell was observed in the presence of bile acids, fatty acids, and lipids.

Example 13: Synthesis of methyl 2-fluoroacrylate beads

[00187] All chemicals were purchased from commercial sources and used as received, except as noted. Reactions were carried out under nitrogen. The monomers used were methyl 2-fluoroacrylate (MeFA); crosslinkers were divinylbenzene (DVB); initiator: azobisisobutyronitrile (AIBN) and lauroyl peroxide (LPO); suspension stabilizer polyvinylalcohol (PVA) - MW 85,000-146,000, 87-89% hydrolyzed; and salt: sodium chloride (NaCl). MeFA and DVB were vacuum distilled.

General procedure for synthesis of MeFA beads:

[00188] To a 3-neck Morton-type flask equipped with a mechanical stirrer, a water condenser and a rubber septum were charged with an aqueous solution containing PVA (and NaCl in some cases). The solution was stirred and purged with nitrogen for 20 min. An organic solution containing MeFA, DVB and an initiator was added. The mixture was stirred at room temperature for 20 min, and heated in a 70-80°C oil bath for 2-6 hrs. The reaction mixture was cooled down to room temperature and the white solid was washed with water. The solid was examined by microscope and/or Malvern Master Sizer. The solid was either isolated by freeze-drying or used directly in the next step (hydrolysis reaction).

General procedure for hydrolysis of MeFA beads to produce FAA beads:

[00189] MeFA beads were suspended in 10 wt% NaOH (or KOH) aqueous solution at a concentration of 10 wt%. The mixture was heated in a 90°C oil bath for 20 hrs, and then allowed to cool down to room temperature. Solid was washed with water and 4M HCl and then freeze-dried.

Synthesis of MeFA beads with no NaCl in aqueous phase and AIBN as initiator:

[00190] To a 250mL 3-neck Morton-type flask equipped with a mechanical stirrer, a water condenser and a rubber septum were charged 75gm aqueous solution containing 1wt% PVA. The solution was stirred at 605 rpm and purged with nitrogen for 20 min. An organic solution containing MeFA (13.5g), DVB (1.5g) and AIBN (0.075g) was added. The mixture was stirred at room temperature for 20 min and heated in a 70°C oil bath for 6 hrs. The reaction mixture was cooled down to room temperature, and the white solid was washed with water. Large irregular particles (~1mm) were observed under microscope

Synthesis of MeFA beads with NaCl in aqueous phase and AIBN as initiator:

[00191] To a 250mL 3-neck Morton-type flask equipped with a mechanical stirrer, a water condenser and a rubber septum were charged 75g aqueous solution containing 2wt% PVA and 3.75wt% NaCl. The solution was stirred at 502 rpm and purged with nitrogen for 20 min. An organic solution containing MeFA (13.5g), DVB (1.5g) and AIBN (0.075g) was added. The mixture was stirred at room temperature for 20 min, and heated in a 70°C oil bath for 6 hrs. The reaction mixture was cooled down to room temperature and the white solid was washed with water. Spherical beads (~90μm) and some large gel particles were observed under microscope

Synthesis of MeFA beads with no NaCl in aqueous phase and LPO as initiator:

[00192] To a 250mL 3-neck Morton-type flask equipped with a mechanical stirrer, a water condenser and a rubber septum were charged 75g aqueous solution containing 2wt% PVA. The solution was stirred at 503rpm and purged with nitrogen for 20 min. An organic solution containing MeFA (13.5g), DVB (1.5g) and LPO (0.15g) was added. The mixture was stirred at room temperature for 20 min and heated in a 70°C oil bath for 2 hrs. The reaction mixture was cooled down to room temperature, and solid was washed with water, and freeze-dried. A white powder (11.85g) was obtained. Large irregular particles (0.5-1mm) of aggregated beads were observed under microscope.

Synthesis of MeFA beads with NaCl in aqueous phase and LPO as initiator:

[00193] To a 1000mL 3-neck Morton-type flask equipped with a mechanical stirrer, a water condenser and a rubber septum were charged 300g aqueous solution containing 1wt% PVA and 3.75wt% NaCl. The solution was stirred at 307rpm and purged with nitrogen for 20 min. An organic solution containing MeFA (54g), DVB (6g) and LPO (0.6g) was added. The mixture was stirred at room temperature for 20 min and heated in a 70°C oil bath for 4 hrs. The reaction mixture was cooled down to room temperature, solid was washed with water,

and freeze-dried. A white powder (56g) was obtained. Spherical beads (~100μm) were observed under microscope.

Example 14: In vivo efficacy of fluoroacrylate (FAA) polymer-NH_4 form compared to Kayexalate (Polystyrene Sulfonate)

[00194] 40 male rats were acclimated for three days on Harlan Teklad Diet TD.04498, whereupon they were randomly assigned to four groups of ten rats. The four groups were then fed for a further four days an admixture of Harlan Teklad Diet TD.04498 with test or control articles according to Table 18.

TABLE 18

Group	Number of Animals	Treatment Groups	Test Article Concentration in Diet (g/kg)	Dose levels (% diet w/w)
1	10	Cellulose Control	20	2%
2	10	Kayexalate: NH_4^+-form	**21.5**	**2.15%**
3	10	FAA polymer:NH_4^+-form	**23**	**2.3%**
4	10	FAA polymer:NH_4^+-form	**11.5**	**1.15%**

[00195] 2.15% Kayexalate: NH_4^+-form corresponds to 2% Kayexalate: H^+-form and 2.3% FAA polymer:NH_4^+-form corresponds to 2% FAA polymer:H^+-form. The binding capacity values reported below correspond to the H^+-form polymers. The FAA-polymer used in this *in vivo* study was synthesized using the same procedure as shown in Table 11, for polymer number 100982A1, and the material was further ion exchanged with ammonium ions.

[00196] Feces were collected from each rat and pooled each 24hrs. Feces were lyophilized and dry weights per rat per day were recorded. Fecal cations were extracted in 1M HCl overnight and measured using Ion Chromatography. The total moles of each cation (Sodium, Ammonium, Potassium, Magnesium and Calcium) excreted into the feces of each rat per day was calculated.

[00197] It was determined that the effect of the polymers on fecal cations reached equilibrium after two days of treatment. The data for the third and fourth days were pooled and are shown in Figure 17. A statistical analysis of the data from the third and fourth days of treatment indicates that FAA polymer:NH_4^+-form binds significantly more Sodium, Ammonium, Potassium and Calcium than does Kayexalate.

[00198] The amount of each cation (in mEq) bound per gram of H^+-form polymer was calculated based on the dietary intake of polymer and the difference between the amount of cation in the feces of control animals versus the amount of cation in the feces of test animals on diets containing 2% test articles. The calculated *in vivo* binding capacities for Kayexalate and FAA polymer:NH_4^+-form are shown in Table 19.

TABLE 19: mEq cations bound *in vivo* per g resin (when present at 2% in diet)

	Na	**NH_4**	**K**	**Mg**	**Ca**	**Total mEq**
Kayexalate	1.09	0.41	0.24	0.66	0.46	**2.87**
FAA polymer:NH_4^+-form	2.11	1.10	0.44	1.13	1.30	**6.07**

[00199] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition, comprising one or more pharmaceutically acceptable carriers, excipients, and/or diluents and further comprising

- a potassium binding polymer, having acid groups selected from the group consisting of sulfonic ($-SO_3^-$), sulfuric ($-OSO_3^-$), carboxylic ($-CO_2^-$), phosphonic ($-PO_3^{--}$), phosphoric ($-OPO_3^{--}$), and sulfamate ($-NHSO_3^-$) groups, and

- an electron-withdrawing substituent located adjacent to the acid group, wherein the electron-withdrawing substituent is selected from the group consisting of a hydroxyl group, an ether group, an ester group, and a halide atom, and

- wherein the electron-withdrawing substituent is fluorine when the acid group is carboxylic.

2. The pharmaceutical composition of claim 1, wherein the polymer comprises a poly-fluoroacrylic acid or poly-difluoromaleic acid polymer, or a combination thereof.

3. The pharmaceutical composition of claim 1 or 2, wherein the polymer is an alpha-fluoroacrylic acid polymer crosslinked with divinylbenzene, ethylene bisacrylamide, N,N'- bis(vinylsulfonylacetyl) ethylene diamine, 1,3-bis(vinylsulfonyl) 2-propanol, vinylsulfone, N,N'-methylenebisacrylamide polyvinyl ether, polyallylether, or a combination thereof.

4. The pharmaceutical composition of any one of claims 1 to 3, comprising the potassium binding polymer as core component, and further comprising a shell component.

5. The pharmaceutical composition of claim 4, wherein the shell comprises copolymers, at least one repeat unit of said copolymer being a vinylamine, ethyleneimine, propyleneimine, allylamine, methallylamine, vinylpyridine, alkyaminoalkyl(meth)acrylate, alkyaminoalkyl(meth)acrylamide, aminomethylstyrene, chitosan, or adduct of aliphatic or aromatic amine with at least one electrophile selected from an epichlorhydrine, an alkylhalide, and an epoxide, wherein the amine is optionally a quarternized form.

6. The pharmaceutical composition of any one of claims 4 to 5, wherein the shell is crosslinked by epoxides, halides, esters, isocyanate, or anhydrides such as epichlorohydrine, alkyl diisocyanates, alkyl dihalides, or diesters.

7. The pharmaceutical composition of any one of claims 4 to 6, wherein the shell comprises polyethyleneimine.

8. The pharmaceutical composition of claim 7, wherein the shell comprises crosslinked and/or benzylated polyethyleneimine.

9. The pharmaceutical composition of any one of claims 4 to 6, wherein the shell comprises polyvinylamine.

10. The pharmaceutical composition of claim 3 or 4, comprising a core of alpha-fluoroacrylic acid polymer crosslinked with divinyl benzene.

11. The pharmaceutical composition of claim 10, further comprising a shell of benzylated polyethyleneimine, or N-dodecyl polyethyleneimine.

12. The pharmaceutical composition of any one of claims 1 to 11, further comprising one or more drugs selected from the group consisting of potassium-sparing diuretics, angiotensin-converting enzyme inhibitors, Angiotensin receptor blockers, non-steroidal anti- inflammatory drugs, heparin, and trimethoprim.

13. A pharmaceutical kit, comprising a pharmaceutical composition of any one of claims 1 to 12, and further comprising one or more drugs selected from the group consisting of potassium-sparing diuretics, angiotensin-converting enzyme inhibitors, Angiotensin receptor blockers, non-steroidal anti-inflammatory drugs, heparin, and trimethoprim.

14. Use of a pharmaceutical composition of any one of claims 1 to 12 for the preparation of a medicament for the treatment of hyperkalemia.

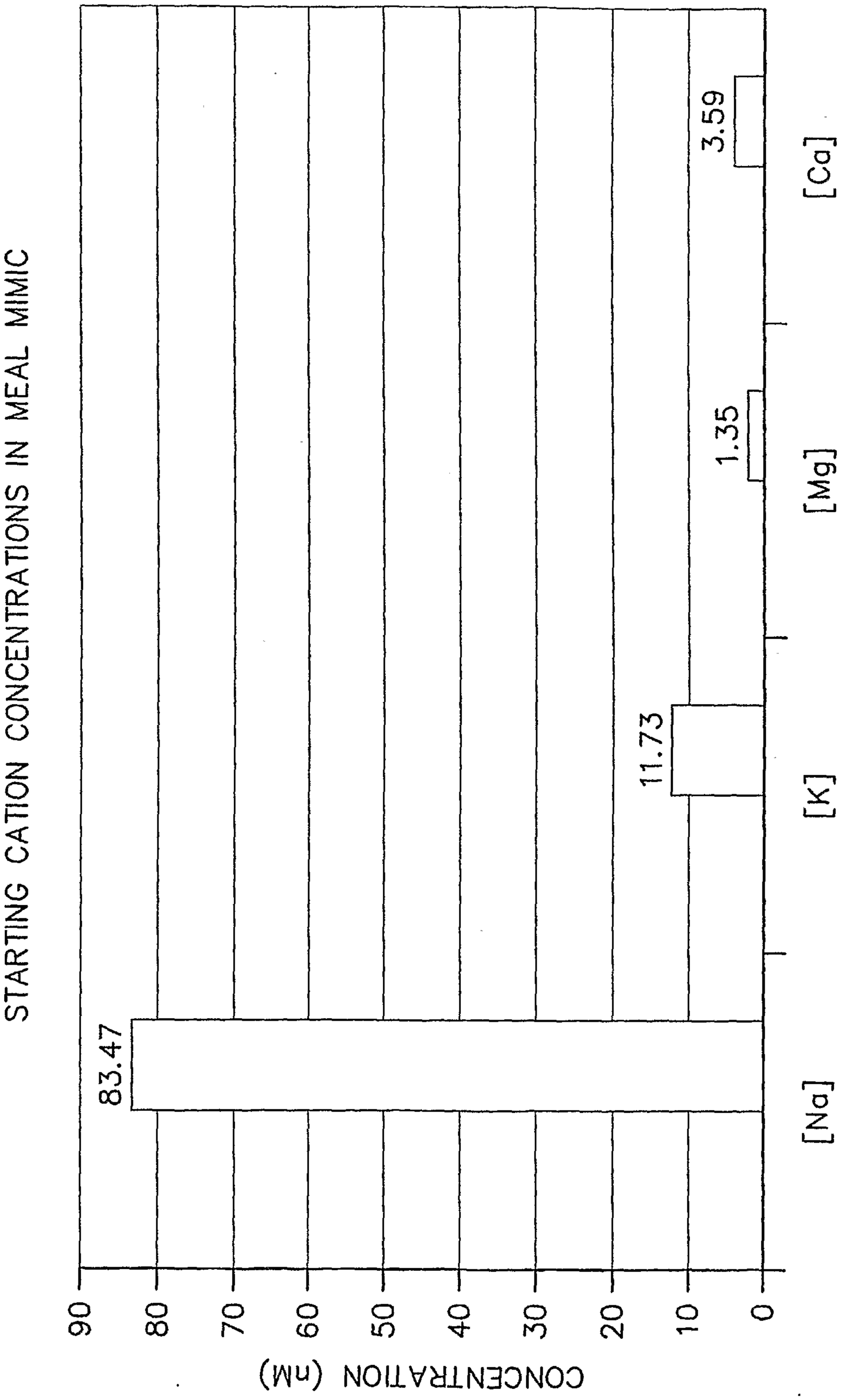

STARTING CATION CONCENTRATIONS IN MEAL MIMIC
83.47
[Na]
11.73
[K]
1.35
[Mg]
3.59
[Ca]
90
80
70
60
50
40
30
20
10
0
CONCENTRATION (nM)

FIG. 1

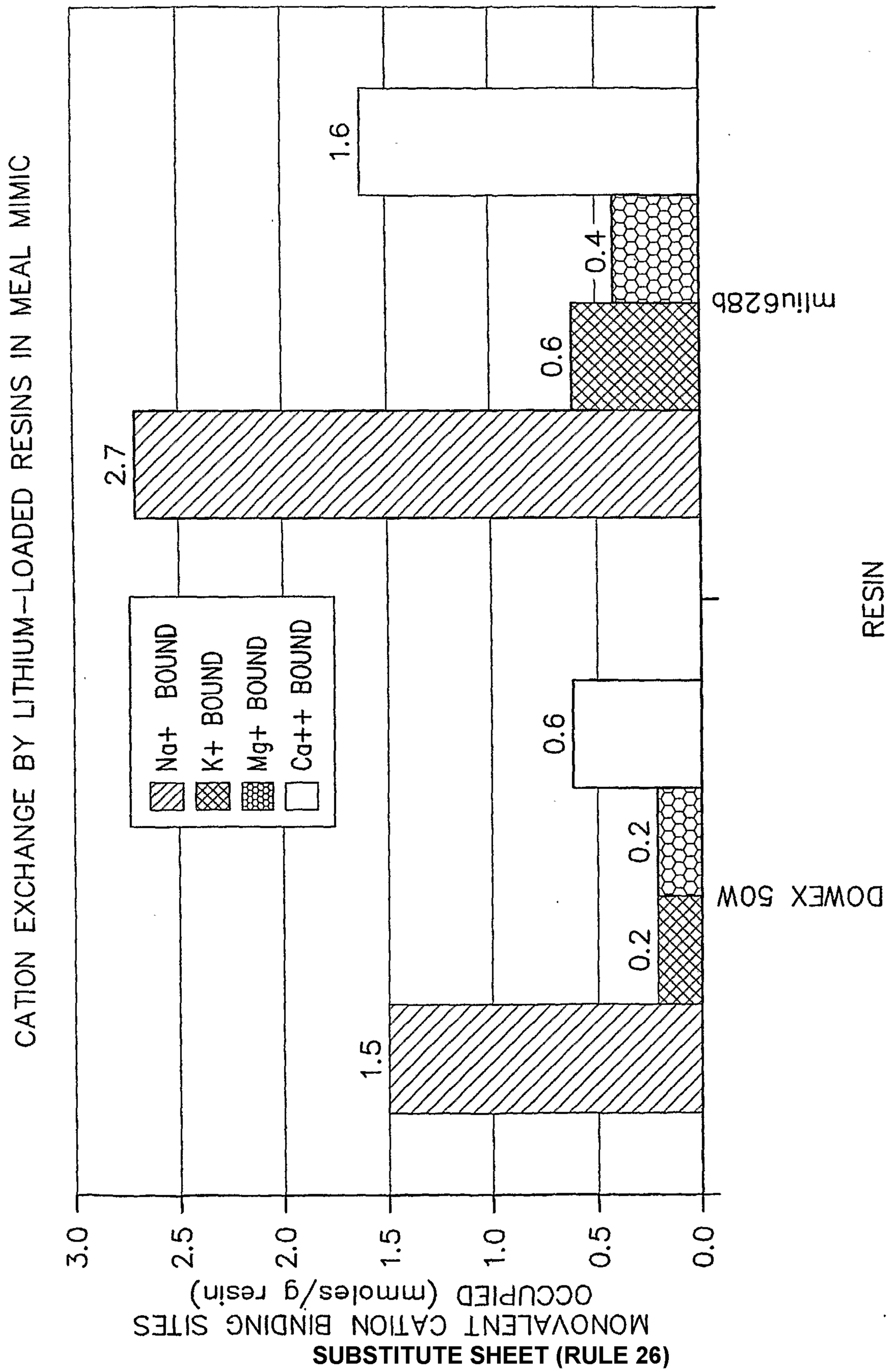

CATION EXCHANGE BY LITHIUM-LOADED RESINS IN MEAL MIMIC
Na+ BOUND
K+ BOUND
Mg+ BOUND
Ca++ BOUND
RESIN
DOWEX 50W
mlu628b
2.7
0.6
0.4
1.6
0.2
0.2
0.6
1.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
MONOVALENT CATION BINDING SITES OCCUPIED (mmoles/g resin)

FIG. 2

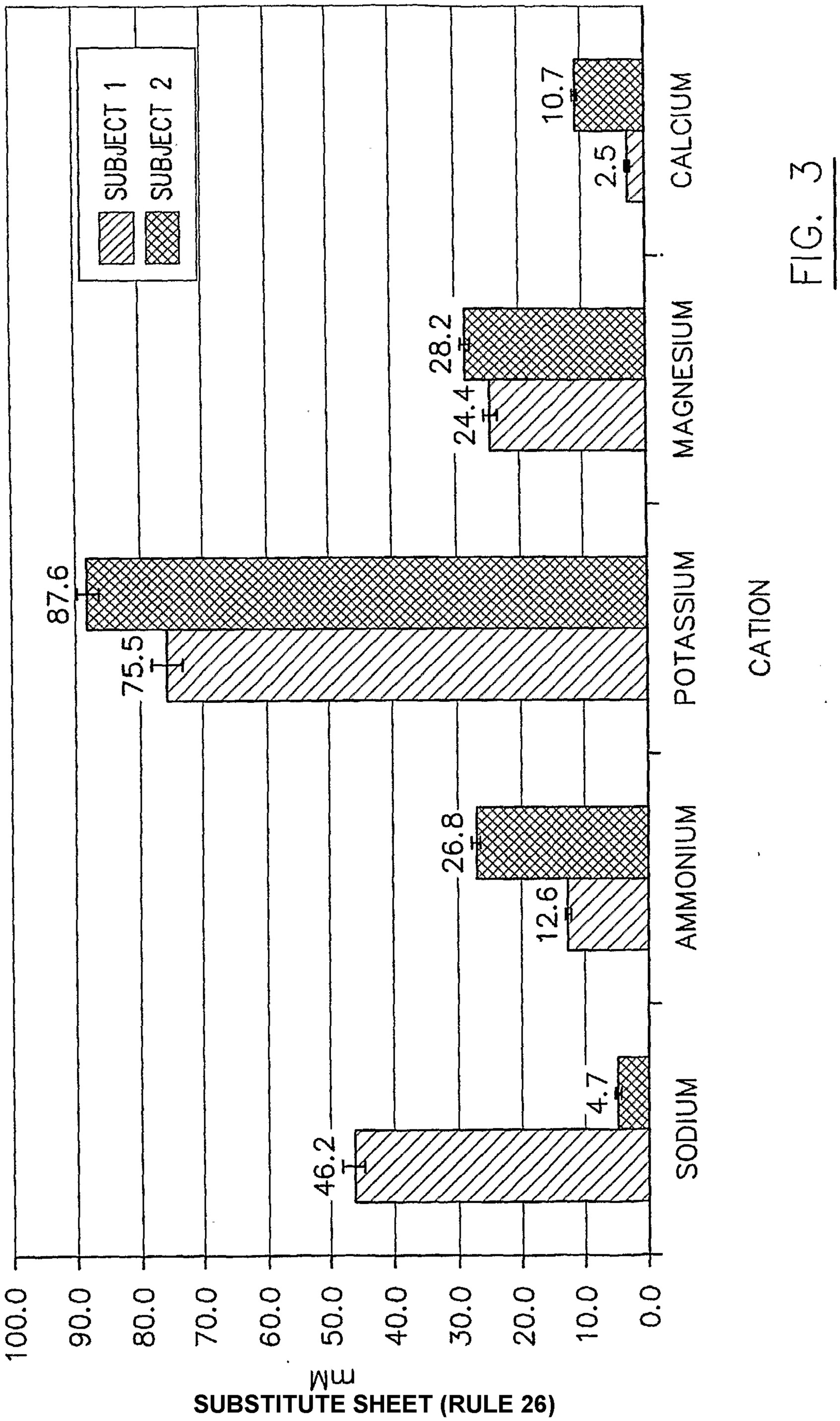

CATION CONCENTRATIONS IN FECAL EXTRACTS
SUBJECT 1
SUBJECT 2
CALCIUM
10.7
2.5
MAGNESIUM
28.2
24.4
POTASSIUM
87.6
75.5
AMMONIUM
26.8
12.6
SODIUM
46.2
4.7
CATION
mM
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0

FIG. 3

4/17

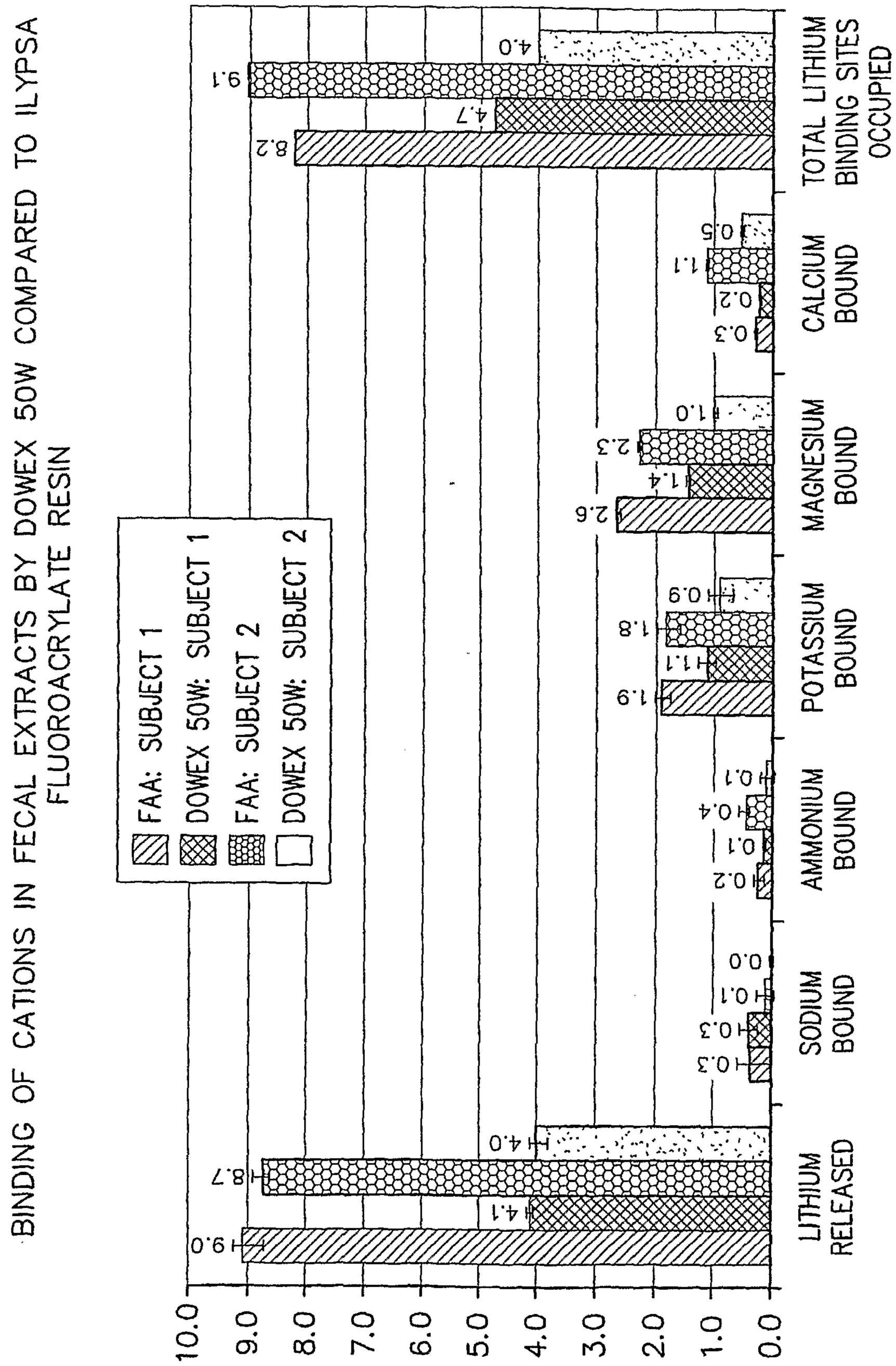
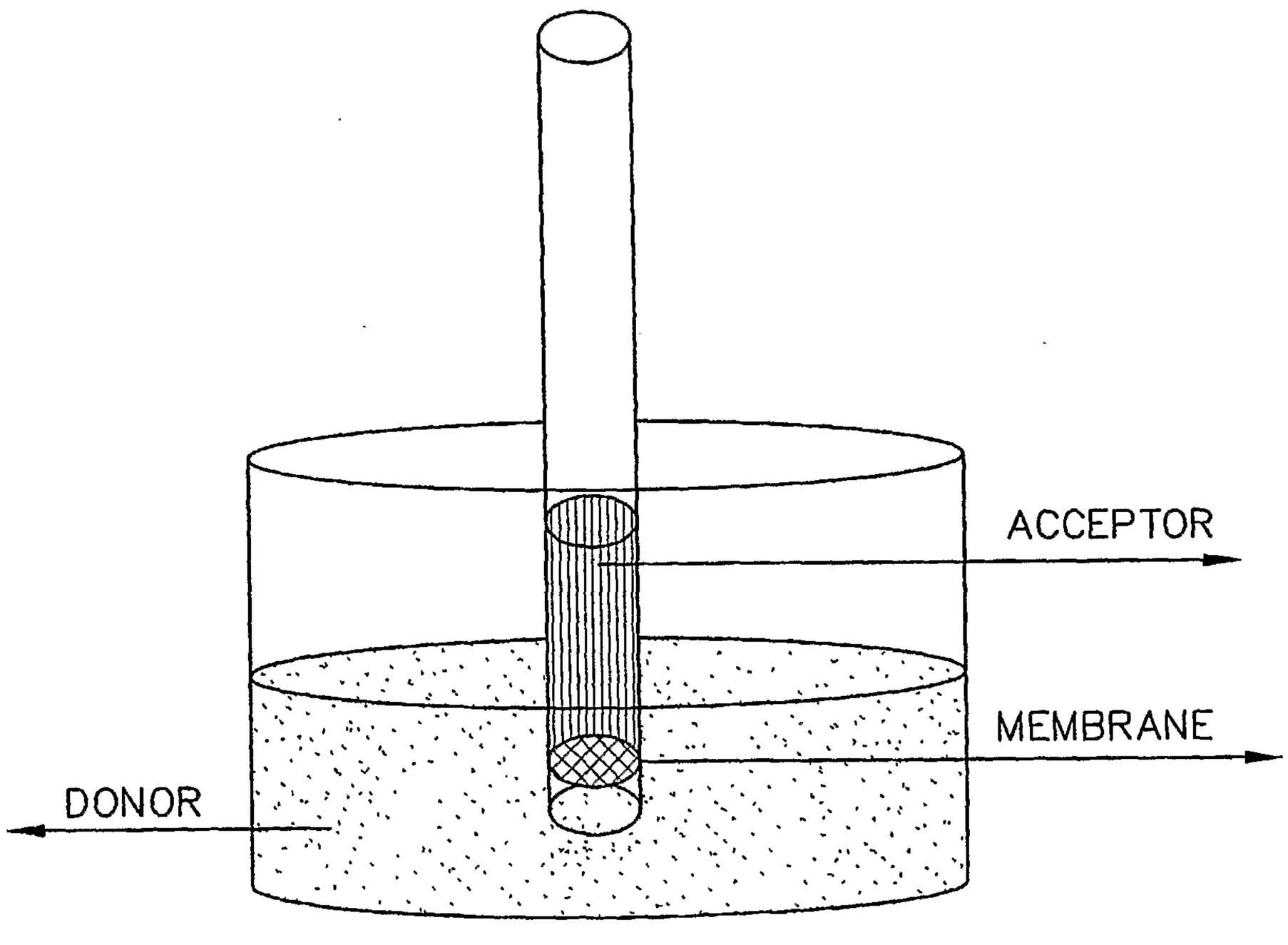

BINDING OF CATIONS IN FECAL EXTRACTS BY DOWEX 50W COMPARED TO ILYPSA FLUOROACRYLATE RESIN
FAA: SUBJECT 1
DOWEX 50W: SUBJECT 1
FAA: SUBJECT 2
DOWEX 50W: SUBJECT 2
SODIUM BOUND
AMMONIUM BOUND
POTASSIUM BOUND
MAGNESIUM BOUND
CALCIUM BOUND
TOTAL LITHIUM BINDING SITES OCCUPIED
LITHIUM RELEASED
CATION
mmoles/g resin
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
9.0
8.7
4.1
4.0
0.4
0.1
0.2
0.0
0.1
0.3
0.3
0.1
1.0
2.3
1.4
2.6
0.5
1.1
0.2
0.3
1.9
1.1
0.9
4.0
9.1
4.7
8.2

FIG. 4

FIG. 5



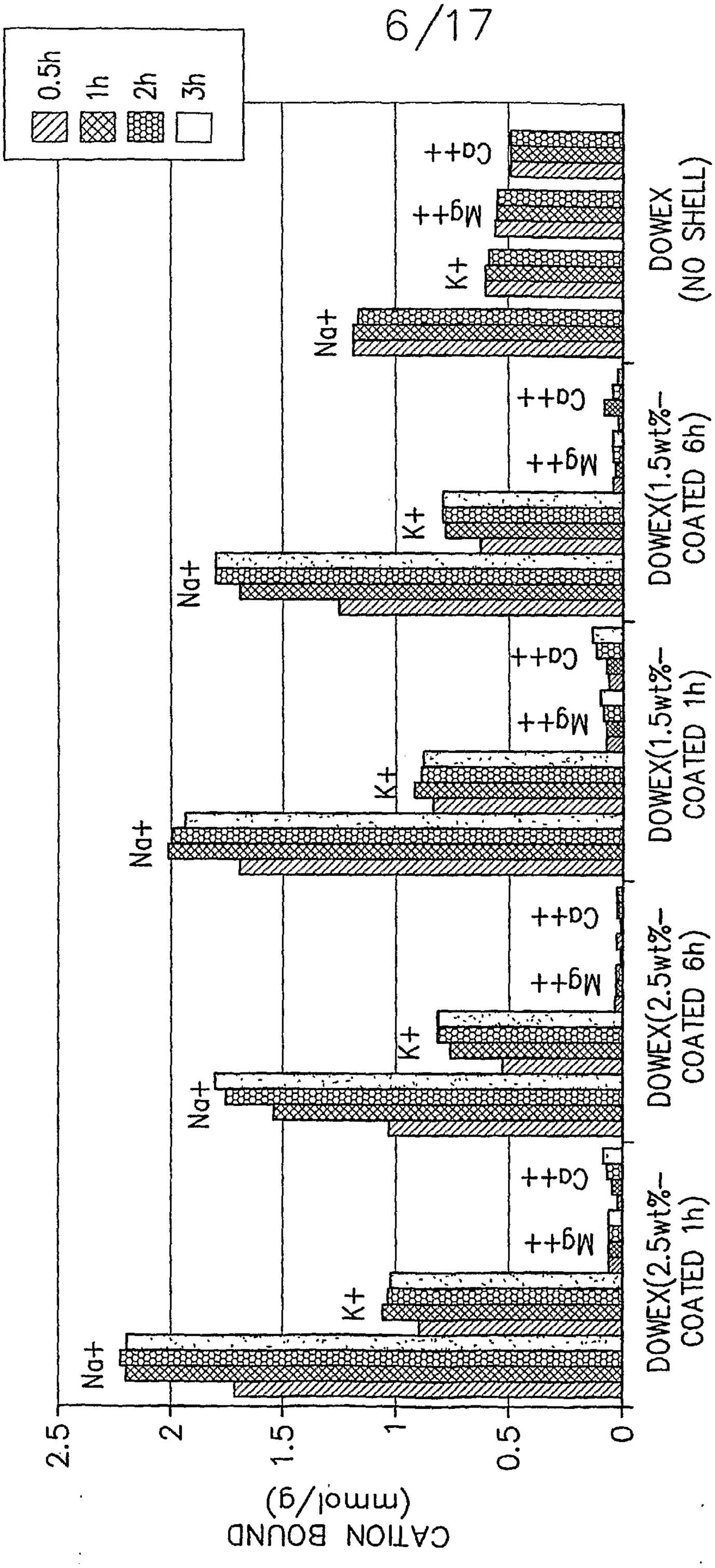


FIG. 6

PEI COATED DOWEX BEADS

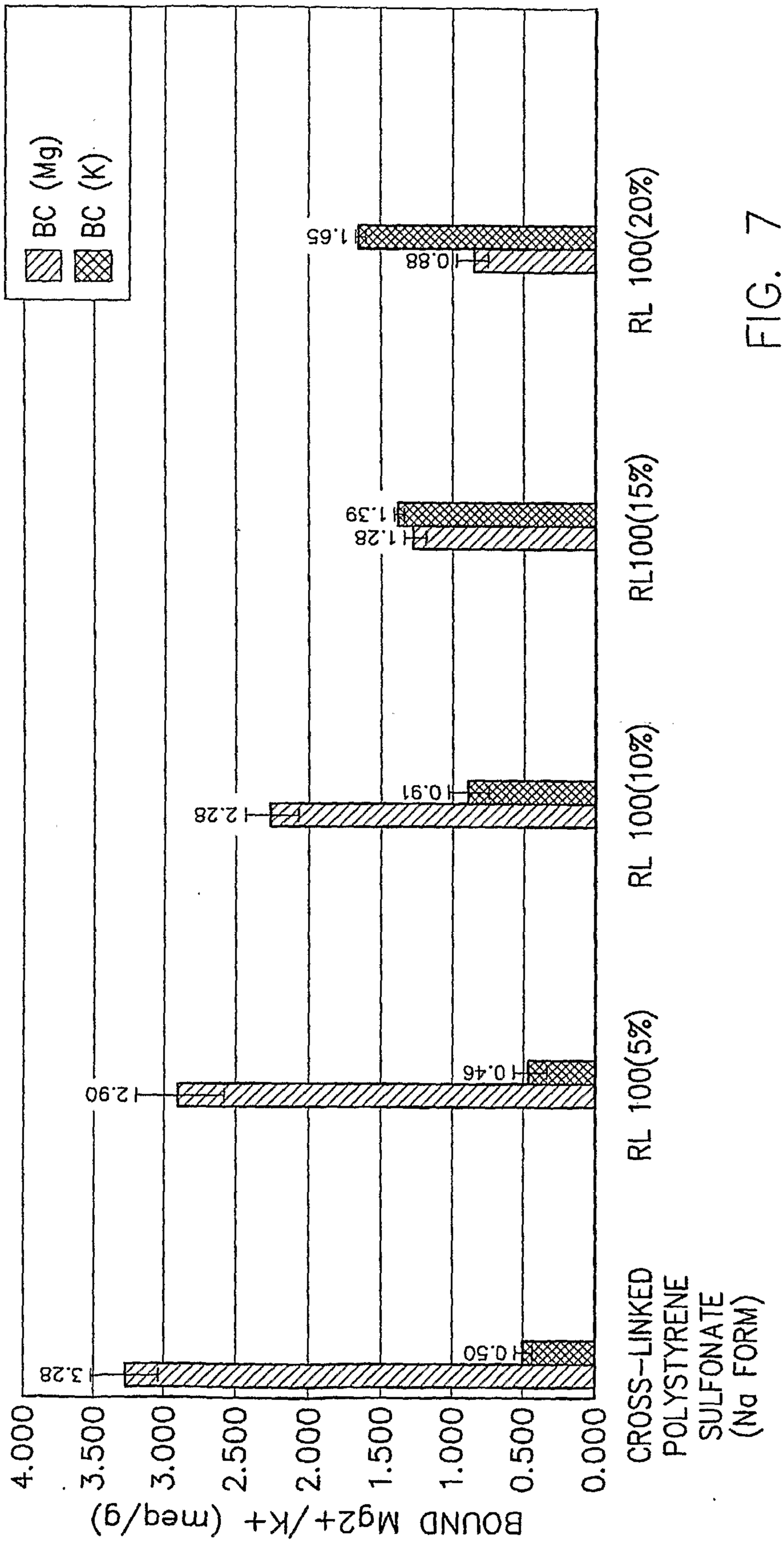

WURSTER COATING (300 um BEAD)
BC (Mg)
BC (K)
RL100(15%)
RL 100(20%)
RL 100(10%)
RL 100(5%)
CROSS-LINKED POLYSTYRENE SULFONATE (Na FORM)
1.65
0.88
1.39
1.28
0.91
2.28
0.46
2.90
0.50
3.28
4.000
3.500
3.000
2.500
2.000
1.500
1.000
0.500
0.000
BOUND Mg2+/K+ (meq/g)

FIG. 7

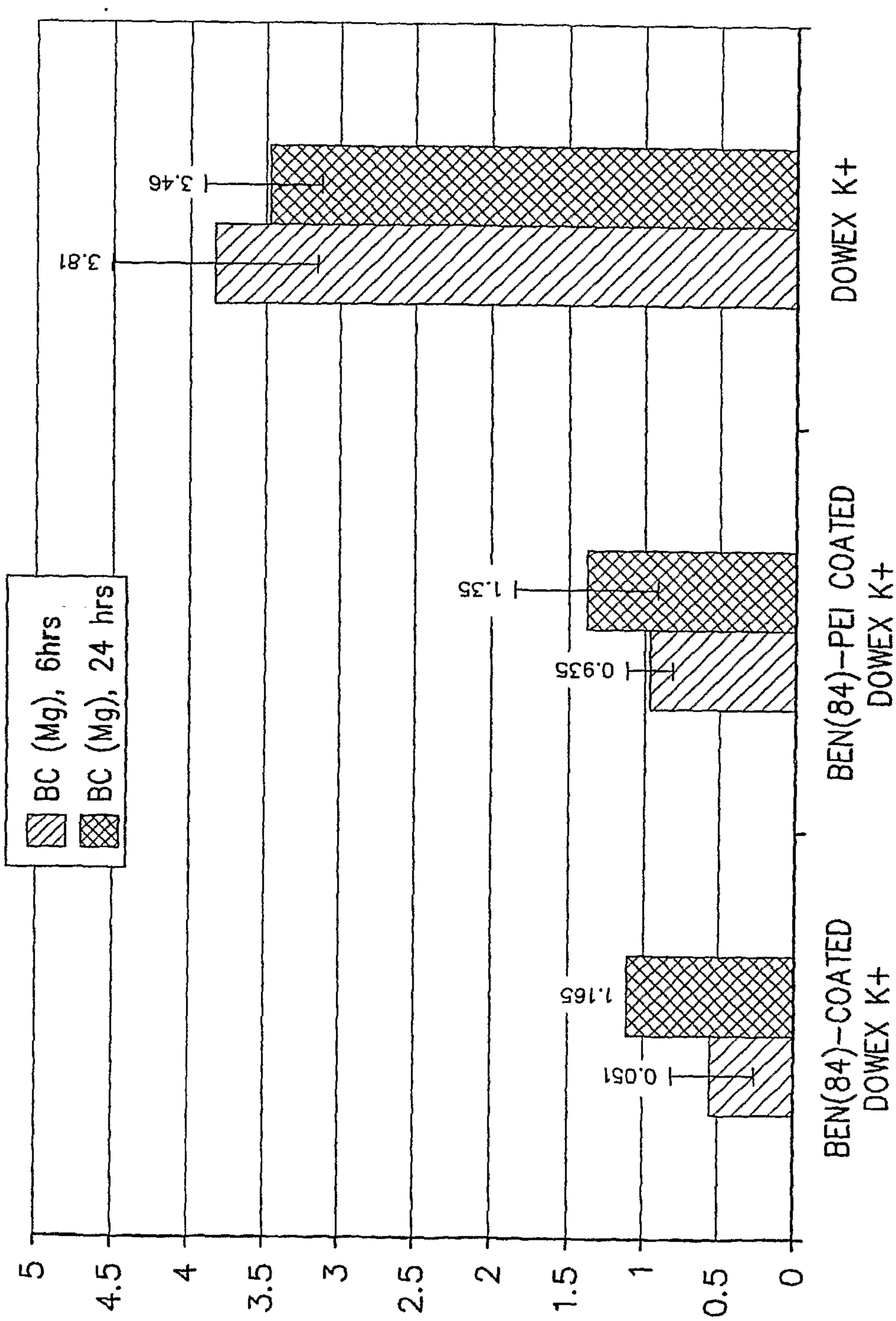

BC (Mg), 6hrs
BC (Mg), 24 hrs
3.46
3.81
1.35
0.935
1.165
0.051
DOWEX K+
BEN(84)–PEI COATED DOWEX K+
BEN(84)–COATED DOWEX K+
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
Mg(2+) BOUND (meq/g)

FIG. 8

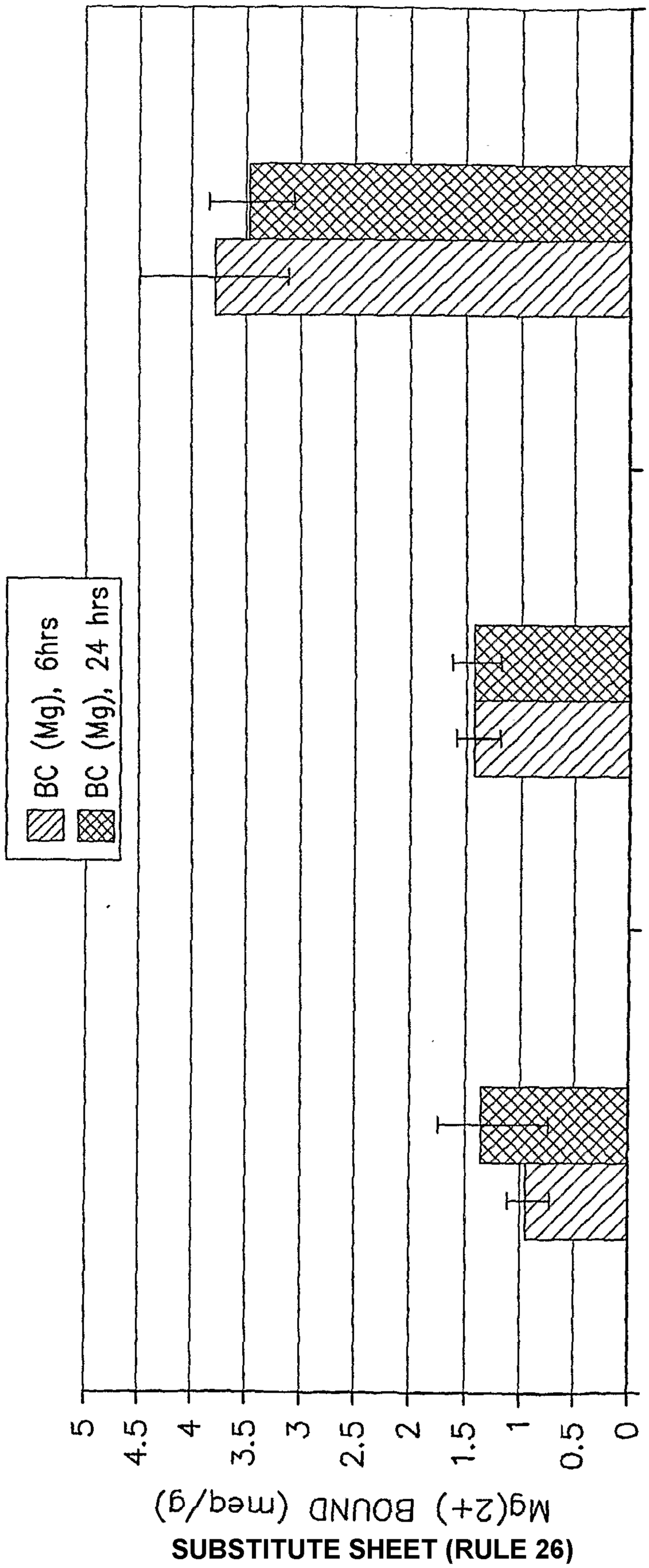
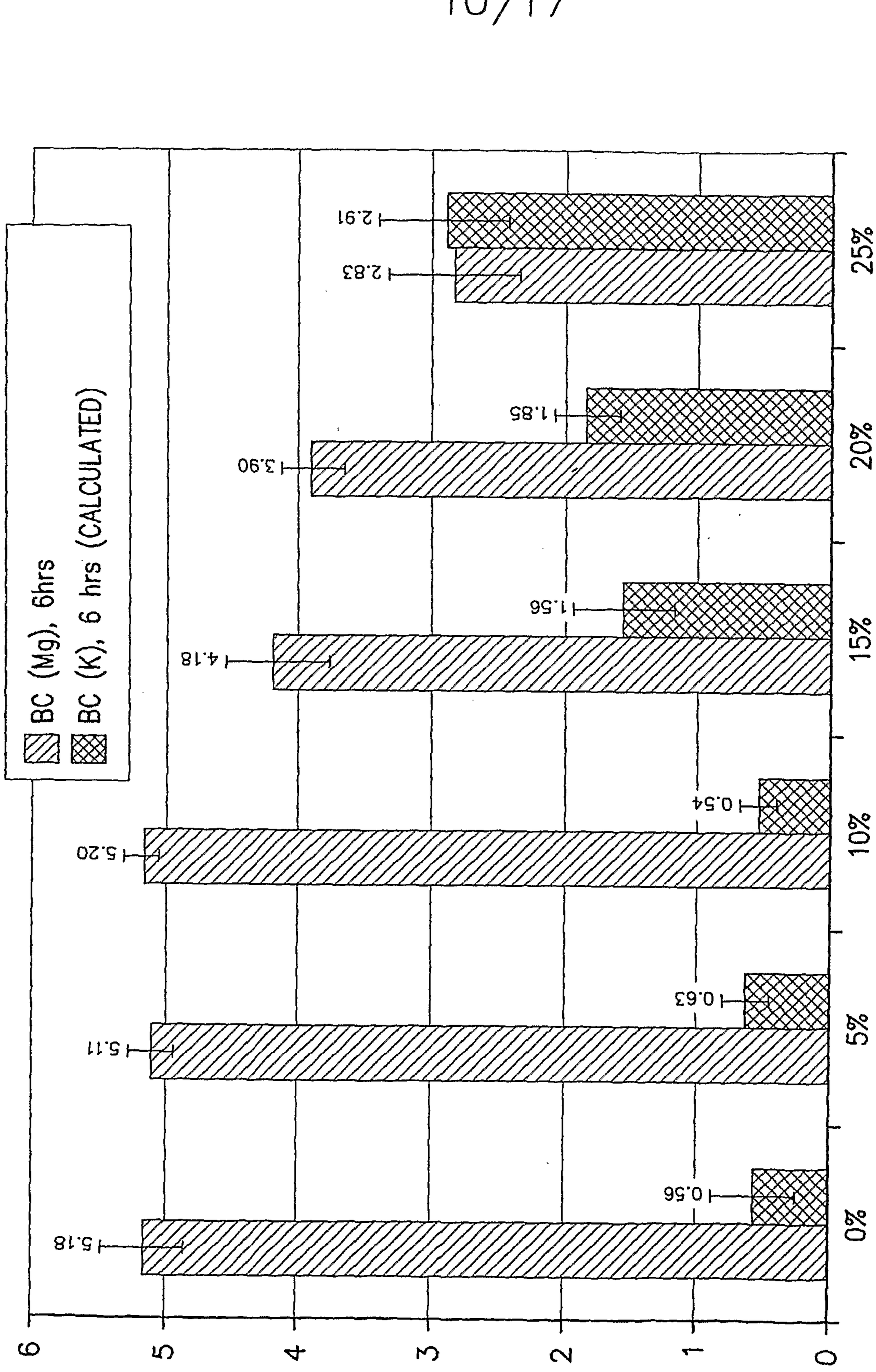

BC (Mg), 6hrs
BC (Mg), 24 hrs
BEN(84)–PEI COATED DOWEX K+ (UNTREATED)
BEN(84)–PEI COATED DOWEX K+ (TREATED WITH pH2 HCl)
DOWEX K+
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
Mg(2+) BOUND (meq/g)

FIG. 9

FIG. 10


BC (Mg), 6hrs
BC (K), 6 hrs (CALCULATED)
FEED RATIO (SHELL POLYMER/BEAD)
25%
20%
15%
10%
5%
0%
2.91
2.83
1.85
3.90
1.56
4.18
0.54
5.20
0.63
5.11
0.56
5.18
0
1
2
3
4
5
6
Mg(2+)/K+ BOUND (meq/g)

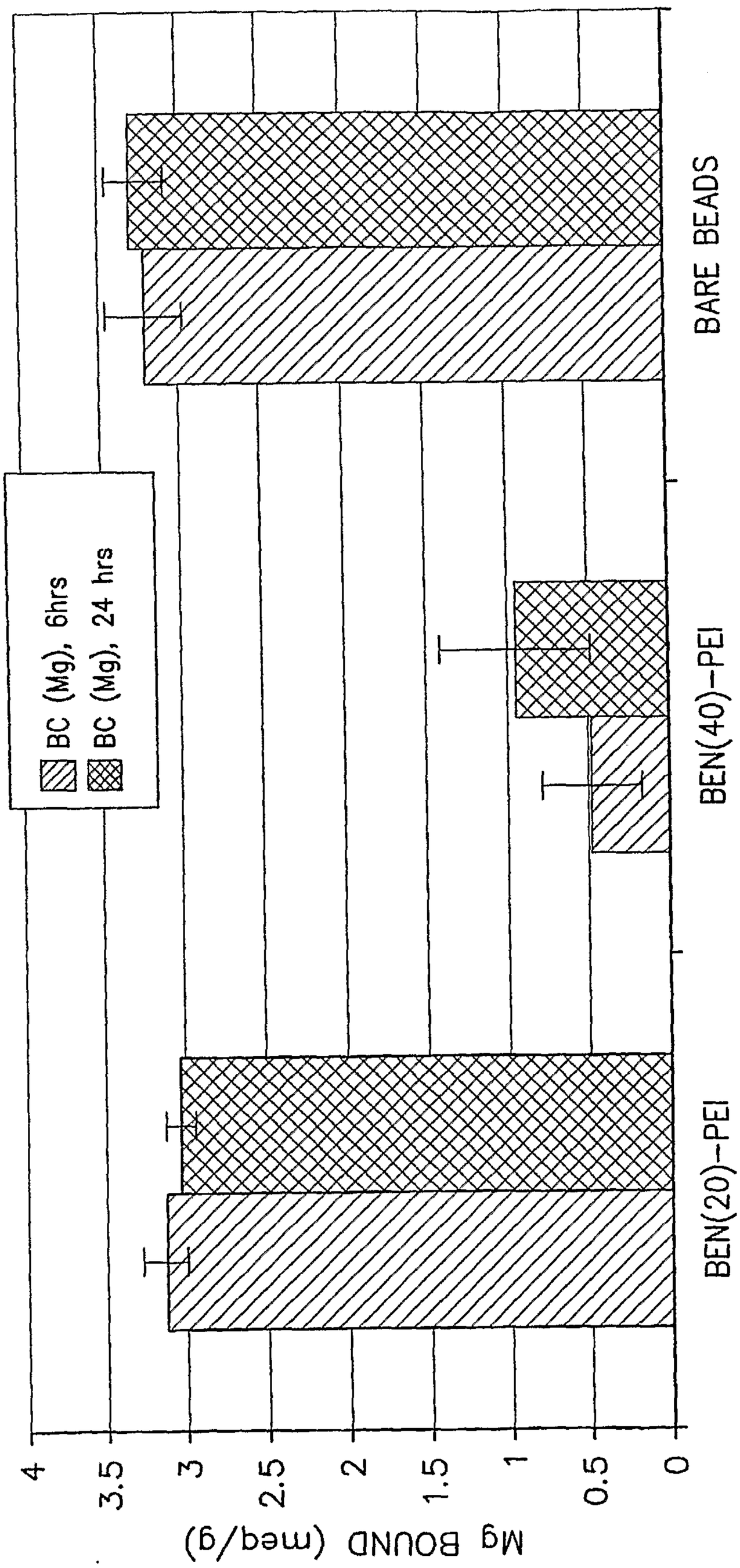

BARE BEADS
BEN(40)–PEI
BEN(20)–PEI
BC (Mg), 6hrs
BC (Mg), 24 hrs
4
3.5
3
2.5
2
1.5
1
0.5
0
Mg BOUND (meq/g)

FIG. 11

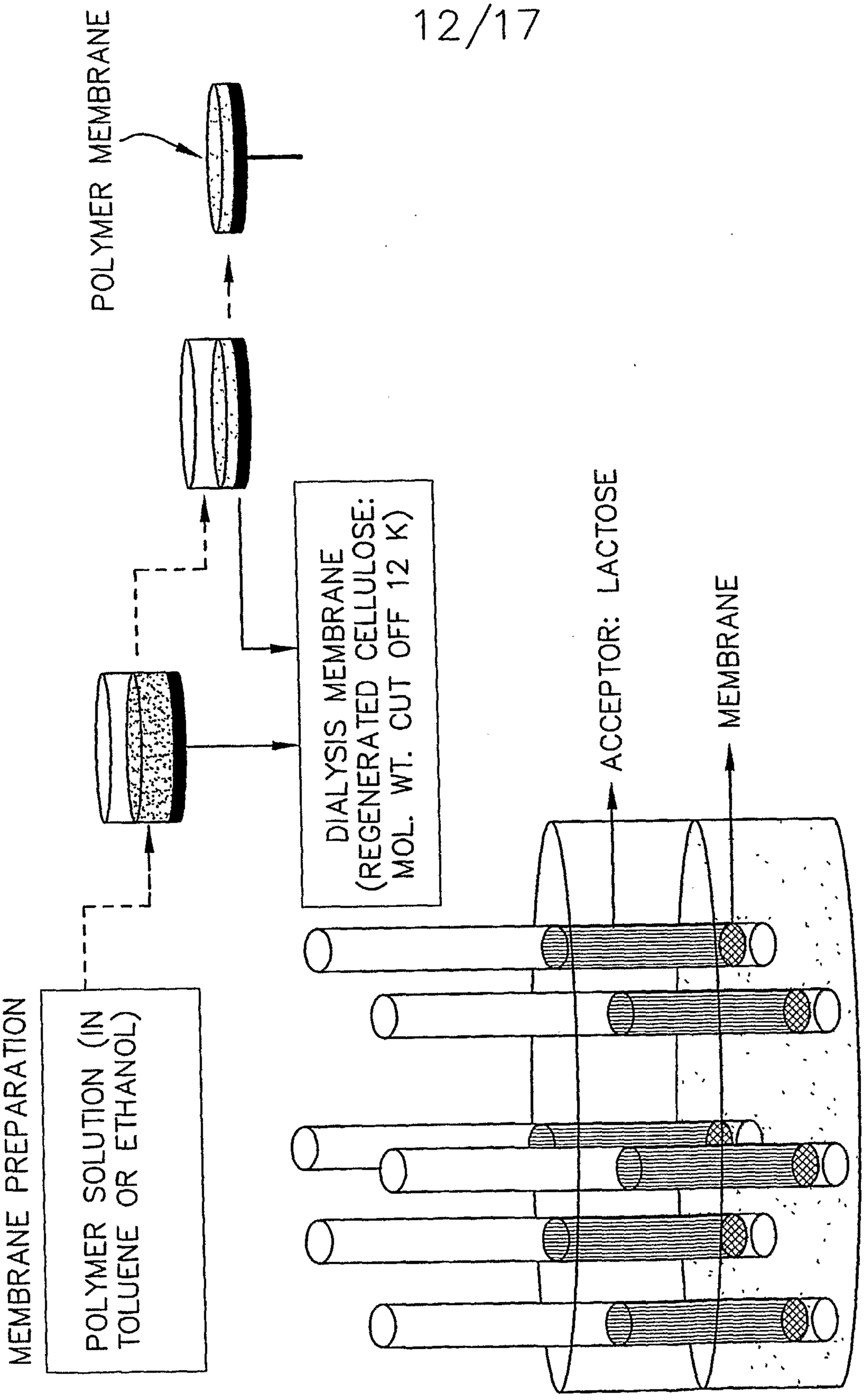

MEMBRANE PREPARATION
POLYMER SOLUTION (IN TOLUENE OR ETHANOL)
POLYMER MEMBRANE
DIALYSIS MEMBRANE (REGENERATED CELLULOSE: MOL. WT. CUT OFF 12 K)
ACCEPTOR: LACTOSE
MEMBRANE

FIG. 12

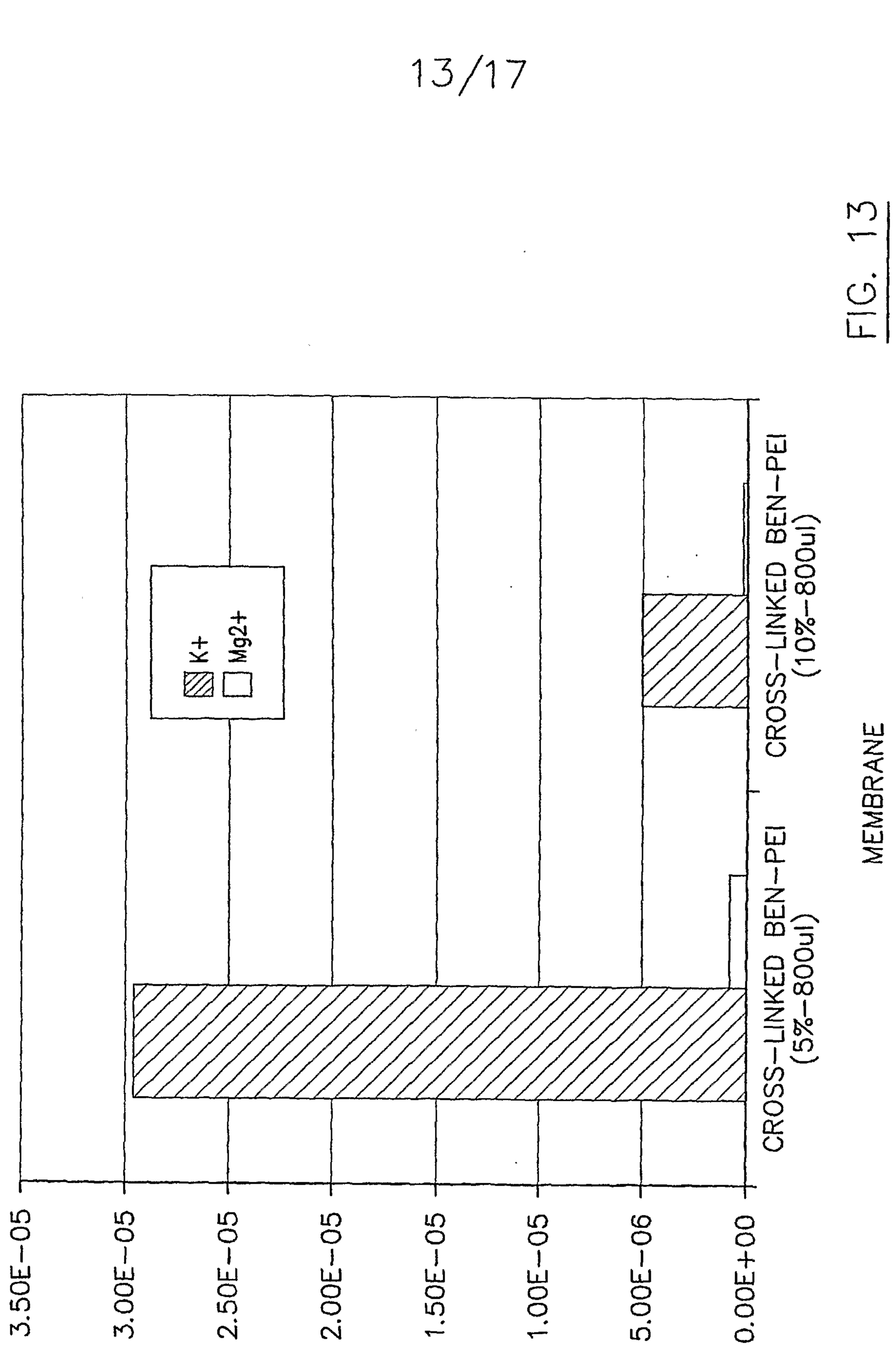

K+
Mg2+
CROSS-LINKED BEN-PEI (10%-800ul)
CROSS-LINKED BEN-PEI (5%-800ul)
MEMBRANE
3.50E-05
3.00E-05
2.50E-05
2.00E-05
1.50E-05
1.00E-05
5.00E-06
0.00E+00
PERMEABILITY (cm/s)

FIG. 13

FIG. 14A

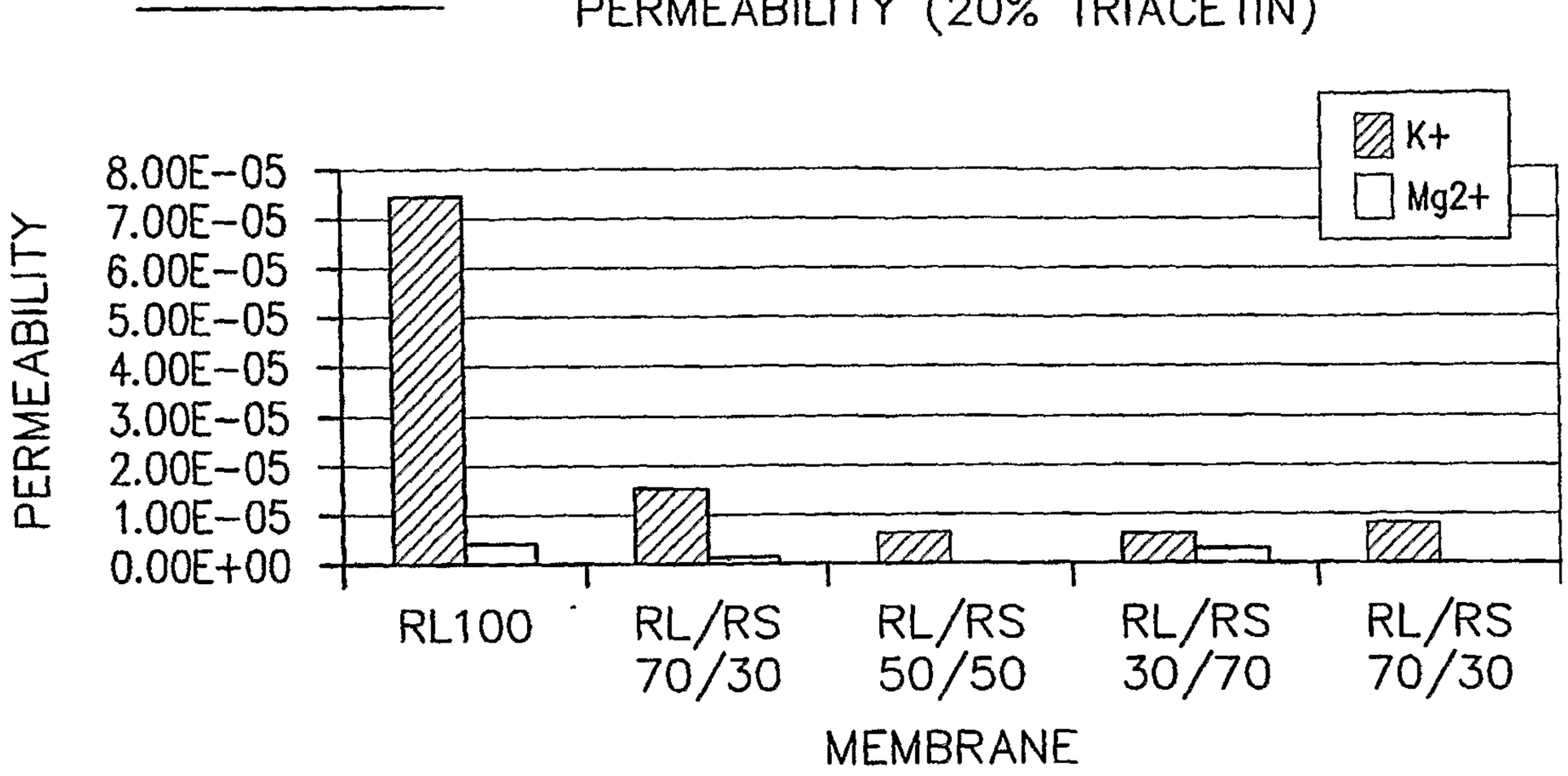


FIG. 14B

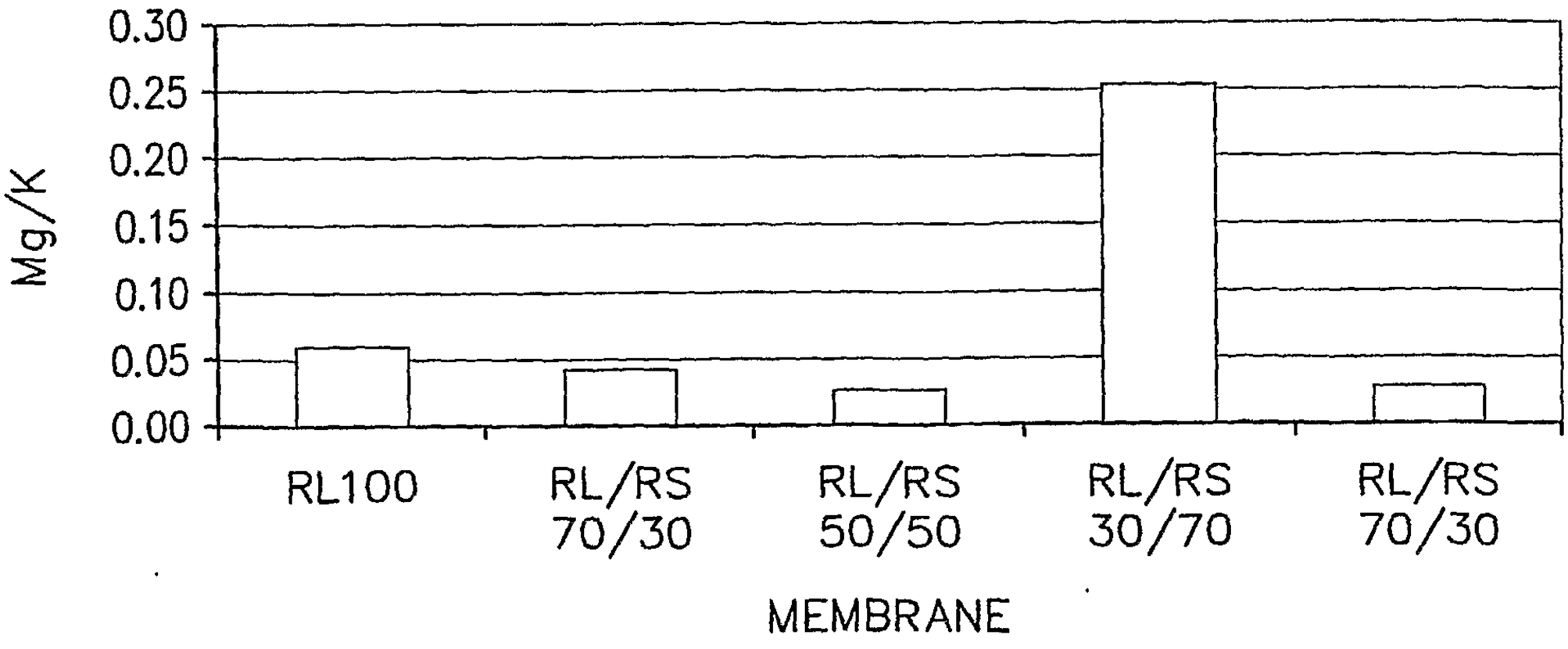


FIG. 15A

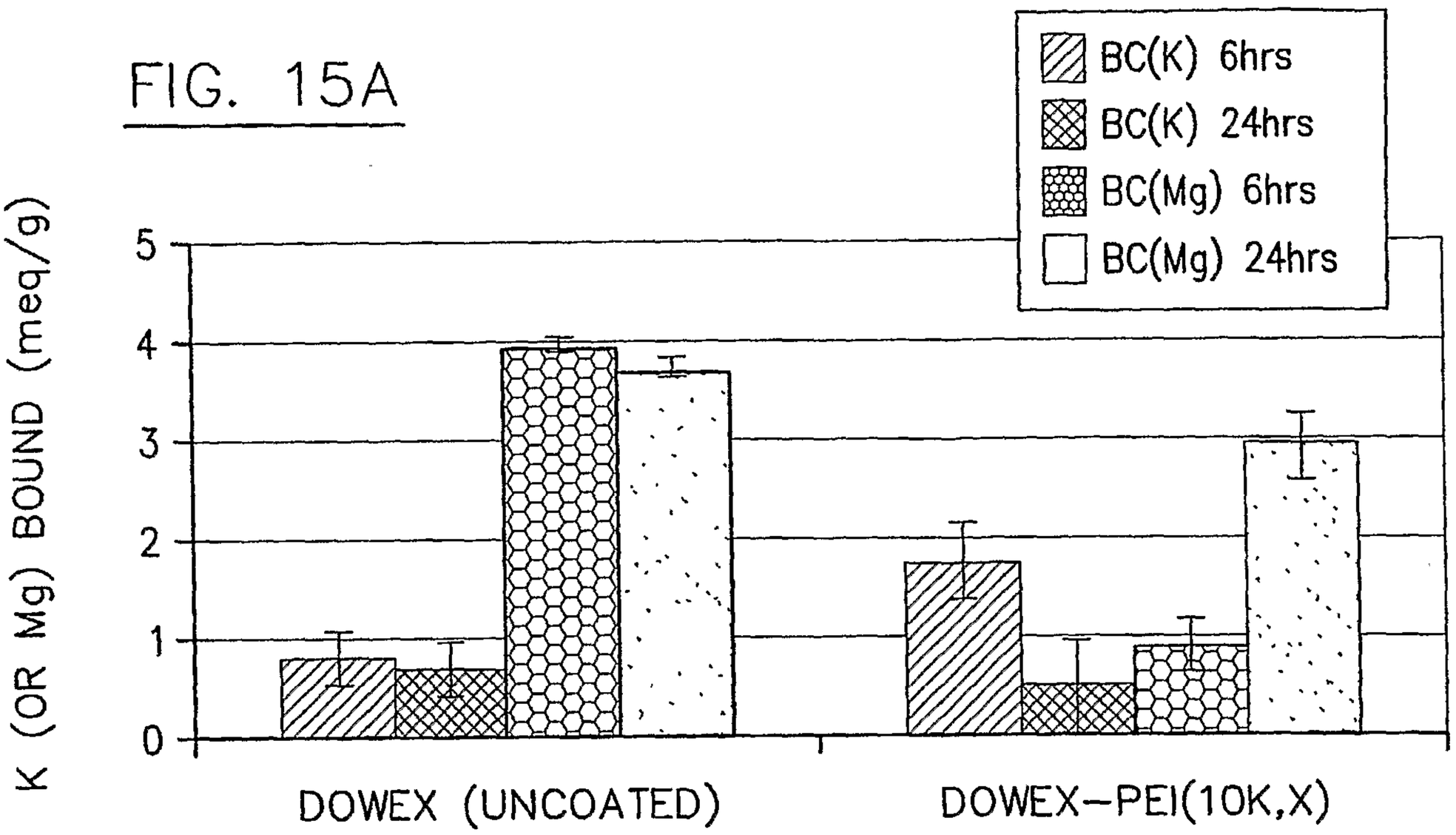
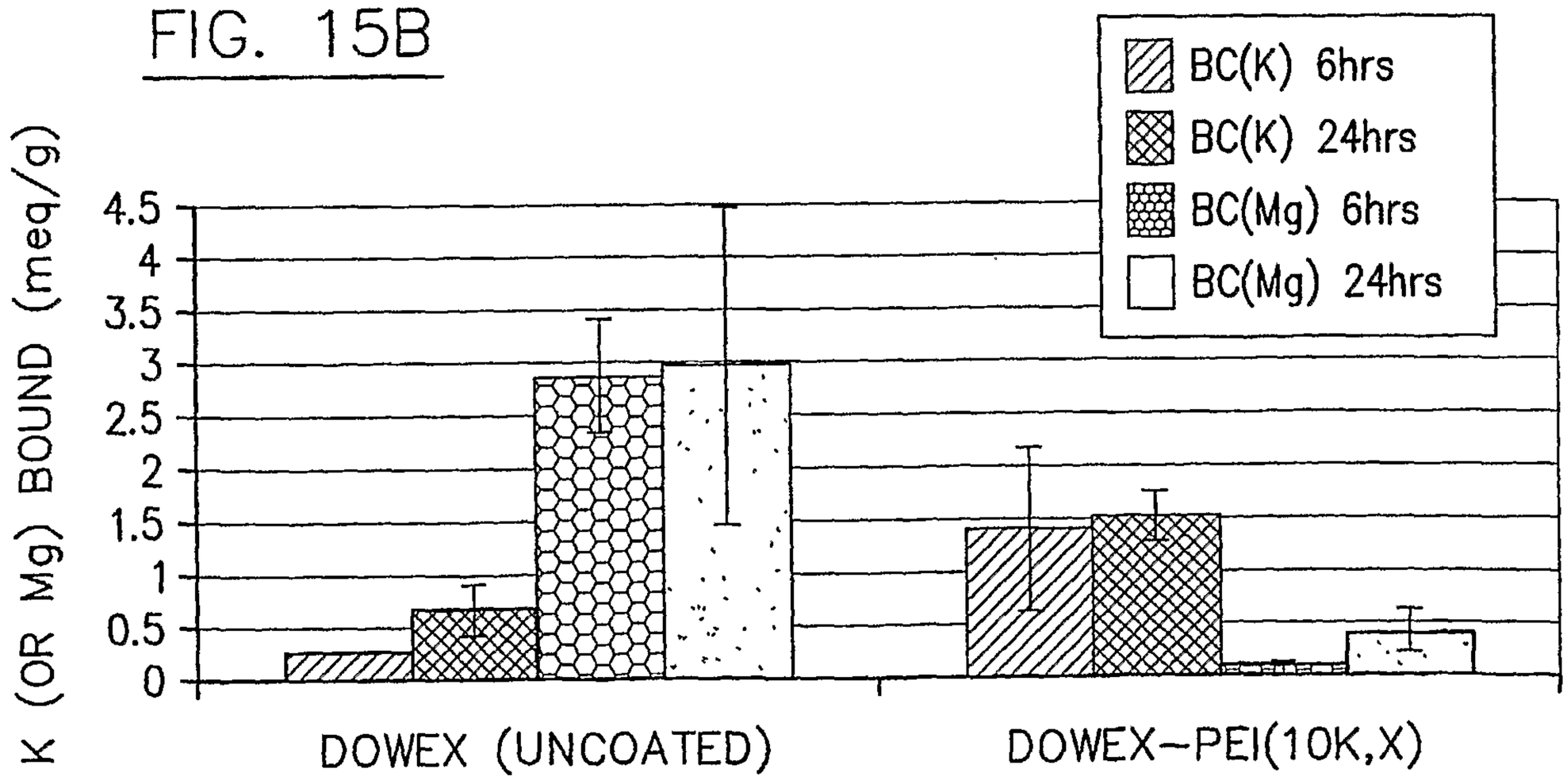


FIG. 15B



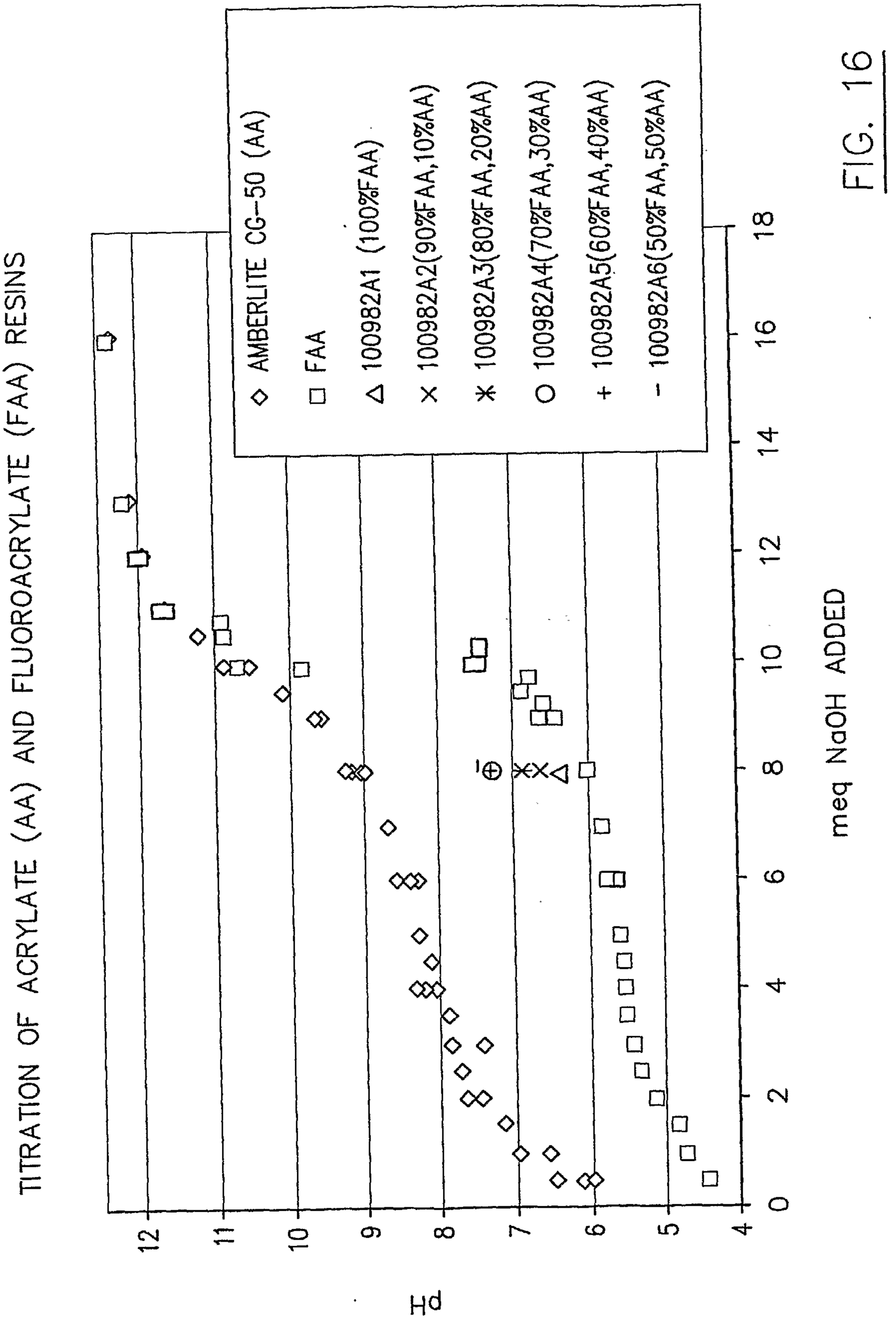

TITRATION OF ACRYLATE (AA) AND FLUOROACRYLATE (FAA) RESINS
◇ AMBERLITE CG-50 (AA)
□ FAA
△ 100982A1 (100%FAA)
× 100982A2(90%FAA,10%AA)
✳ 100982A3(80%FAA,20%AA)
○ 100982A4(70%FAA,30%AA)
+ 100982A5(60%FAA,40%AA)
– 100982A6(50%FAA,50%AA)
meq NaOH ADDED
pH

FIG. 16

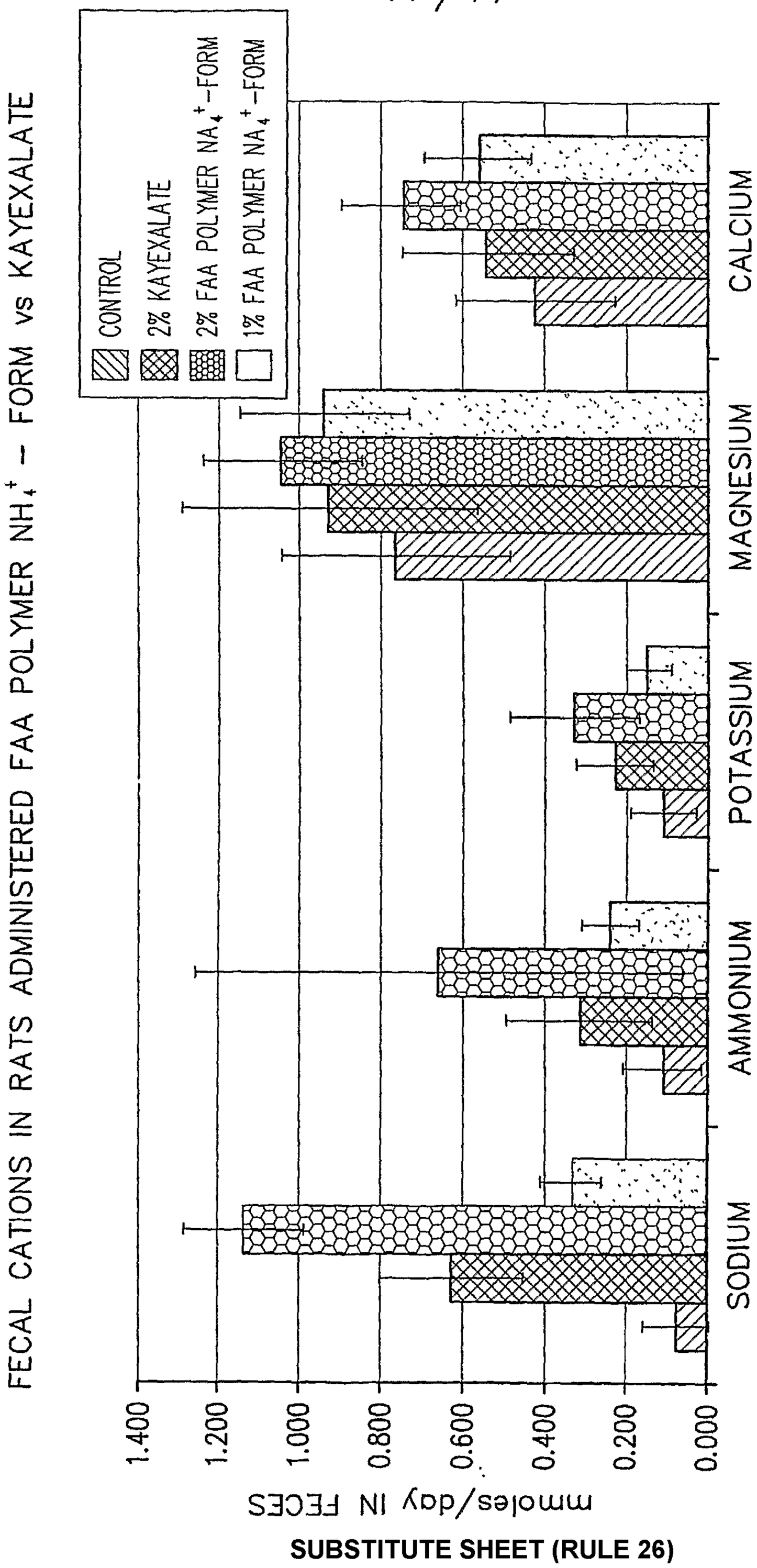
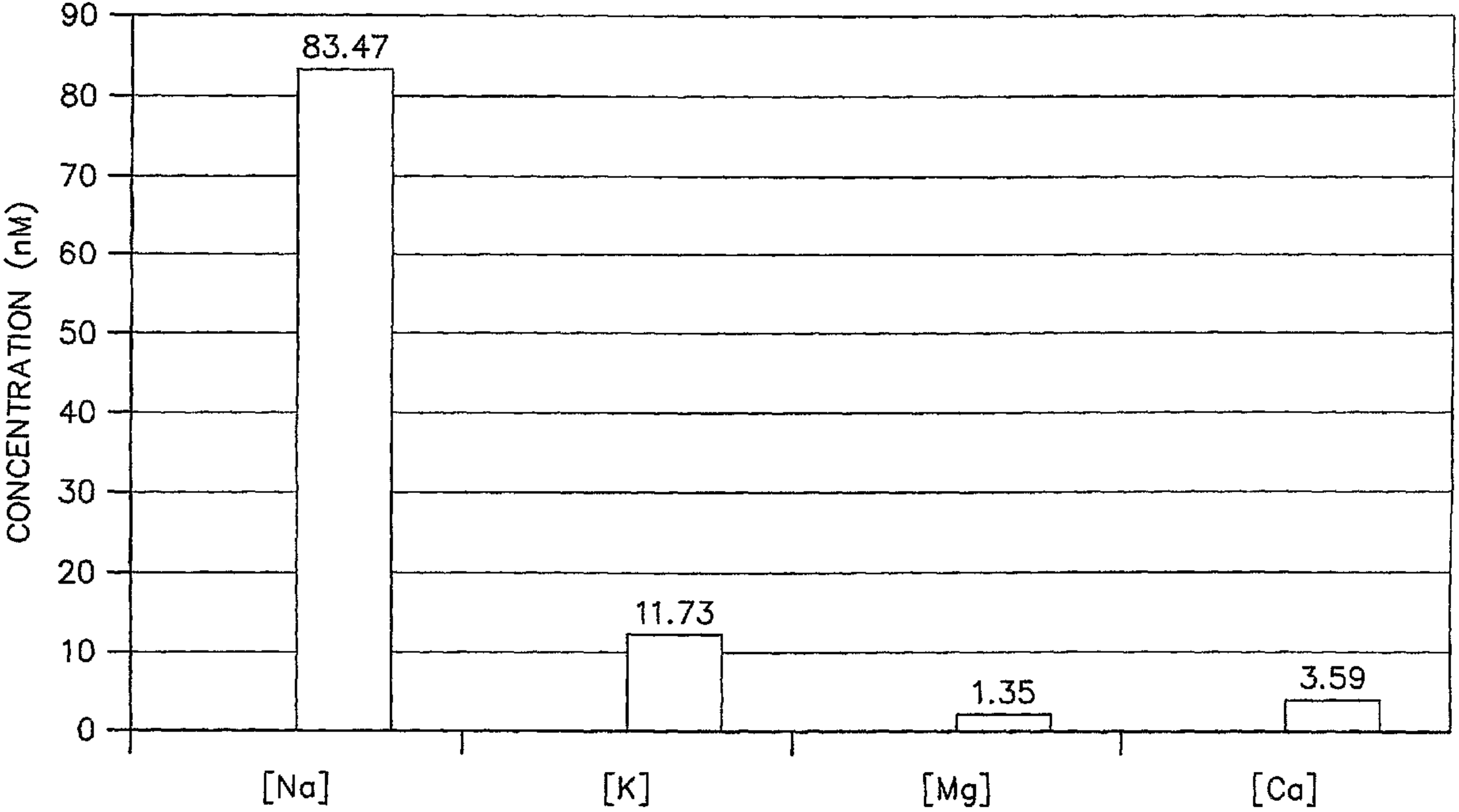

FECAL CATIONS IN RATS ADMINISTERED FAA POLYMER NH_4^+ – FORM vs KAYEXALATE
CONTROL
2% KAYEXALATE
2% FAA POLYMER NA_4^+–FORM
1% FAA POLYMER NA_4^+–FORM
CALCIUM
MAGNESIUM
POTASSIUM
AMMONIUM
SODIUM
1.400
1.200
1.000
0.800
0.600
0.400
0.200
0.000
mmoles/day IN FECES

FIG. 17

STARTING CATION CONCENTRATIONS IN MEAL MIMIC