Abstract: The present invention is directed to crosslinked cation exchange polymers comprising a fluoro group and an acid group and being a polymerization product of at least three monomers. Pharmaceutical compositions of these polymers are useful to bind potassium in the gastrointestinal tract.
FIELD OF THE INVENTION

[0001] The present invention is directed to processes for preparing crosslinked cation exchange polymers comprising a fluoro group and an acid group and being the product of the polymerization of at least three monomer units. Pharmaceutical compositions of these polymers are useful to bind potassium in the gastrointestinal tract.

BACKGROUND OF THE INVENTION

[0002] Potassium (K+) is one of the most abundant intracellular cations. Potassium homeostasis is maintained predominantly through the regulation of renal excretion. Various medical conditions, such as decreased renal function, genitourinary disease, cancer, severe diabetes mellitus, congestive heart failure and/or the treatment of these conditions can lead to or predispose patients to hyperkalemia. Hyperkalemia can be treated with various cation exchange polymers including polyfluoroacrylic acid (polyFAA) as disclosed in WO 2005/097081. U.S. Published Application No. 2005/0220751 discloses a method for the synthesis of polyfluoroacrylic acid crosslinked with divinylbenzene (DVB).

[0003] Removal of potassium and/or treatment of hyperkalemia have been found to raise patient compliance problems, in particular in chronic settings, which are solved by the present invention. Such problems include lack of tolerance of the therapeutically effective dose of polymeric binder (e.g., anorexia, nausea, gastric pain, vomiting and fecal impaction), dosing form (e.g., taste, mouth feel, etc.) and dose frequency (e.g., three times per day). The present invention solves these problems by providing a polymeric binder or a composition containing a polymeric binder that can be given once a day or twice a day without significant gastrointestinal side effects while retaining substantially similar efficacy. The methods of the present invention reduce the frequency and form of administration of potassium binder and increase tolerance, which will improve patient compliance, and potassium binding effectiveness.

[0004] However, it has now been found that the production of cross-linked fluoroacrylic acid polymers is improved by the addition of a second cross linker having a slower reactivity rate that DVB.
SUMMARY OF THE INVENTION

[0005] The present invention provides a crosslinked polymer, which is the product of the polymerization of at least three different monomer units, and processes for preparing these polymers. Among the various aspects of the invention are crosslinked cation exchange polymers comprising a fluoro group and an acid group and being the product of the polymerization of at least three different monomer units and processes for the preparation thereof. Typically, one monomer comprises a fluoro group and an acid group, one monomer is a difunctional arylene monomer and another monomer is a difunctional alkylene, ether- or amide-containing monomer.

[0006] Another aspect of the invention is a crosslinked polymer comprising a reaction product of a polymerization mixture comprising three or more monomers. The monomers correspond to Formula 11, Formula 22, and Formula 33; wherein (i) the monomers corresponding to Formula 11 constitute at least about 85 wt.% or from about 80 wt.% to 95 wt.% based on the total weight of monomers of Formulae 11, 22, and 33 in the polymerization mixture, and the weight ratio of the monomer corresponding to Formula 22 to the monomer corresponding to Formula 33 is from about 4:1 to about 1:4, or (ii) the mole fraction of the monomer of Formula 11 in the polymerization mixture is at least about 0.87 or from about 0.87 to about 0.94 based on the total number of moles of the monomers of Formulae 11, 22, and 33, and the mole ratio of the monomer of Formula 22 to the monomer of Formula 33 in the polymerization mixture is from about 0.2:1 to about 7:1. Formula 11, Formula 22, and Formula 33 correspond to the following structures:

[0007] Yet another aspect is a cation exchange polymer comprising structural units corresponding to Formulae 1, 2, and 3, wherein (i) the structural units corresponding to Formula 1 constitute at least about 85 wt.% or from about 80 wt.% to about 95 wt.% based on the total weight of structural units of Formulae 1, 2, and 3 in the polymer calculated from the amounts of

\[
\begin{align*}
\text{Formula 11:} & \quad R_1 \quad A_{11} \quad R_2 \\
\text{Formula 22:} & \quad X_1 \\
\text{Formula 33:} & \quad X_2
\end{align*}
\]

wherein R1 and R2 are each independently hydrogen, alkyl, cycloalkyl, or aryl; A11 is an optionally protected carboxylic, phosphonic, or phosphoric; X1 is arylene; and X2 is alkylene, an ether moiety or an amide moiety.
monomers used in the polymerization reaction, and the weight ratio of the structural unit corresponding to Formula 2 to the structural unit corresponding to Formula 3 is from about 4:1 to about 1:4, or (ii) the mole fraction of the structural unit of Formula 1 in the polymer is at least about 0.87 or from about 0.87 to about 0.94 based on the total number of moles of the structural units of Formulae 1, 2, and 3, and the mole ratio of the structural unit of Formula 2 to the structural unit of Formula 3 is from about 0.2:1 to about 7:1 (calculated from the amounts of monomers used in the polymerization reaction). Formula 1, Formula 2, and Formula 3 correspond to the following structures:

[Diagrams of Formula 1, Formula 2, and Formula 3]

wherein Ri and R2 are independently hydrogen, alkyl, cycloalkyl, or aryl; A1 is carboxylic, phosphonic, or phosphoric in its salt or acid form; X1 is arylene; and X2 is alkylene, an ether moiety or an amide moiety.

[0008] A further aspect of the invention is a crosslinked polymer comprising a reaction product of a polymerization mixture comprising three or more monomers. The monomers correspond to Formula 1IA, Formula 22A, and Formula 33A; wherein (i) the monomers corresponding to Formula 1IA constitute at least about 85 wt.% or from about 80 wt.% to about 95 wt.% based on the total weight of monomers of Formulae 1IA, 22A, and 33A in the polymerization mixture and the weight ratio of monomers corresponding to Formula 22A to monomers corresponding to Formula 33A is from about 4:1 to about 1:4, or (ii) the mole fraction of the monomer of Formula 1IA in the polymerization mixture is at least about 0.87 or from about 0.87 to about 0.94 based on the total number of moles of the monomers of Formulae 1IA, 22A, and 33A and the mole ratio of the monomer of Formula 22A to the monomer of Formula 33A in the polymerization mixture is from about 0.2:1 to about 7:1. Formula 1IA, Formula 22A, and Formula 33A correspond to the following structures:
Another aspect is a cation exchange polymer comprising structural units corresponding to Formulae IA, 2A, and 3A, wherein (i) the structural units corresponding to Formula IA constitute at least about 85 wt.% or from about 80 wt.% to about 95 wt.% based on the total weight of structural units of Formulae IA, 2A, and 3A in the polymer, and the weight ratio of the structural unit corresponding to Formula 2A to the structural unit corresponding to Formula 3A is from about 4:1 to about 1:4 (calculated from the amounts of monomers used in the polymerization reaction), or (ii) the mole fraction of the structural unit of Formula IA in the polymer is at least about 0.87 or from about 0.87 to about 0.94 based on the total number of moles of the structural units of Formulae IA, 2A, and 3A, and the mole ratio of the structural unit of Formula 2A to the structural unit of Formula 3A is from about 0.2:1 to about 7:1 (calculated from the amounts of monomers used in the polymerization reaction). Formula IA, Formula 2A and Formula 3A correspond to the following structures:

A further aspect is a pharmaceutical composition comprising any of the crosslinked cation exchange polymers described herein and a pharmaceutically acceptable excipient.
Yet another aspect of the invention is a method for removing potassium from the gastrointestinal tract of an animal subject, the method comprising administering a pharmaceutical composition described above to the subject, whereby the pharmaceutical composition passes through the gastrointestinal tract of the subject and removes a therapeutically effective amount of potassium ion from the gastrointestinal tract of the subject. In some instances, the animal subject is a mammal or a human.

Another aspect is a method of making a crosslinked cation exchange polymer comprising contacting a mixture comprising three or more monomers with a polymerization initiator to form a crosslinked polymer. The monomers correspond to Formula 11, Formula 22, and Formula 33; wherein (i) the monomers corresponding to Formula 11 constitute at least about 85 wt.% or from about 80 wt.% to about 95 wt.% based on the total weight of monomers of Formulae 11, 22, and 33 in the polymerization mixture, and the weight ratio of the monomer corresponding to Formula 22 to the monomer corresponding to Formula 33 is from about 4:1 to about 1:4, or (ii) the mole fraction of the monomer of Formula 11 in the polymerization mixture is at least about 0.87 or from about 0.87 to about 0.94 based on the total number of moles of the monomers of Formulae 11, 22, and 33, and the mole ratio of the monomer of Formula 22 to the monomer of Formula 33 in the polymerization mixture is from about 0.2:1 to about 7:1.

Formula 11, Formula 22, and Formula 33 correspond to the following structures:

[Diagram]

wherein \( R_i \) and \( R_2 \) are each independently hydrogen, alkyl, cycloalkyl, or aryl; \( A_n \) is protected carboxylic, phosphonic, or phosphoric; \( X_i \) is arylenes; and \( X_2 \) is alkylenes, an ether moiety or an amide moiety.

A further aspect is a method of making a crosslinked cation exchange polymer comprising contacting a mixture comprising three or more monomers with a polymerization initiator to form a crosslinked polymer. The monomers correspond to Formula 11A, Formula 22A, and Formula 33A; wherein (i) the monomers corresponding to Formula 11A constitute at least about 85 wt.% or from about 80 wt.% to about 95 wt.% based on the total weight of monomers of Formulae 11A, 22A, and 33A in the polymerization mixture, and the weight ratio of the monomer corresponding to Formula 22 to the monomer corresponding to Formula 33A is...
from about 4:1 to about 1:4, or (ii) the mole fraction of the monomer of Formula 1IA in the polymerization mixture is at least about 0.87 or from about 0.87 to about 0.94 based on the total number of moles of the monomers of Formulae 1IA, 22A, and 33A, and the mole ratio of the monomer of Formula 22A to the monomer of Formula 33A in the polymerization mixture is from about 0.2:1 to about 7:1. Formulae 1IA, 22A, and 33A correspond to the following structures:

![Diagram of structures](attachment:formula.png)

The methods of making the crosslinked cation exchange polymers described above can further comprise hydrolyzing the crosslinked polymer with a hydrolysis agent.

**DETAILED DESCRIPTION**

[0014] The present invention is directed to crosslinked cation exchange polymers comprising a fluoro group and an acid group that is the polymerization product of at least three monomers and processes for the preparation thereof. The polymers or pharmaceutical compositions of these polymers are useful to bind potassium in the gastrointestinal tract.

[0015] In general, two of the three monomers should be difunctional cross-linking monomers having different rates of reaction with the methyl fluoroacrylate (MeFA) monomer. Without wishing to be bound by any particular theory, it is believed that during polymerization, the use of two different cross-linking monomers having different rates of reaction of the monomer of Formula 11 (e.g., MeFA) allows for the faster rate cross-linking monomer to be consumed before the other monomers, creating an intermediate that is rich in the faster rate monomer. This in turn allows the remaining monomers to be consumed so that a second, slower reactivity rate cross linker provides additional crosslinking. Demonstration, for example, may come from analysis of the polymer product that reveals a distribution of crosslinking units within the structure such that the higher reactive rate monomer is more richly present in those portion(s) of the polymer produced earlier in time in the polymerization reaction, while the lower reactivity
rate monomer structure is more richly present in portion(s) of the final product produced later in time.

[0016] In a particular embodiment, the crosslinked cation exchange polymer comprises units having Formulae 1, 2, and 3 as represented by the following structures:

![Formulas 1, 2, and 3](attachment:image)

wherein $R_i$ and $R_2$ are independently selected from hydrogen, alkyl, cycloalkyl, or aryl; $A_i$ is carboxylic, phosphonic, or phosphoric in its salt or acid form; $X_i$ is arylene; and $X_2$ is alkylenne, an ether moiety or an amide moiety.

[0017] When $X_2$ is an ether moiety, the ether moiety can be $-(\text{CH}_2)_d\text{-O-(CH}_2)_e\text{-}$ or $-(\text{CH}_2)_d\text{-O-(CH}_2)_e\text{-O-(CH}_2)_d\text{-}$, wherein $d$ and $e$ are independently an integer of 1 through 5. In some instances, $d$ is an integer from 1 to 2 and $e$ is an integer from 1 to 3. When $X_2$ is an amide moiety, the amide moiety can be $-\text{C(O)}\text{-NH-(CH}_2)_p\text{-NH-C(O)}\text{-}$ wherein $p$ is an integer of 1 through 8. In some instances, $p$ is an integer of 4 to 6.

[0018] The unit corresponding to Formula 2 can be derived from a difunctional crosslinking monomer having the formula $\text{CH}_2=\text{CH}-X_i=\text{CH}=\text{CH}_2$ wherein $X_i$ is as defined in connection with Formula 2. Further, the unit corresponding to Formula 3 can be derived from a difunctional crosslinking monomer having the formula $\text{CH}_2=\text{CH}-X_2=\text{CH}=\text{CH}_2$ wherein $X_2$ is as defined in connection with Formula 3.

[0019] In connection with Formula 1, in one embodiment, $R_i$ and $R_2$ are hydrogen and $A_i$ is carboxylic. In connection with Formula 2, in one embodiment, $X_i$ is an optionally substituted phenylene, and preferably phenylene. In connection with Formula 3, in one embodiment, $X_2$ is optionally substituted ethylene, propylene, butylene, pentylene, or hexylene; more specifically, $X_2$ is ethylene, propylene, butylene, pentylene, or hexylene; and preferably $X_2$ is butylene. In one specific embodiment, $R_i$ and $R_2$ are hydrogen, $A_i$ is carboxylic acid, $X_i$ is phenylene and $X_2$ is butylene.

[0020] Generally, the Formulae 1, 2 and 3 structural units of the terpolymer have specific ratios, for example, wherein the structural units corresponding to Formula 1 constitute at least about 80 wt.%, particularly at least about 85 wt.%, and more particularly at least about 90
wt.% or from about 80 wt.% to about 95 wt.%, from about 85 wt.% to about 95 wt.%, from about 85 wt.% to about 93 wt.% or from about 88 wt.% to about 92 wt.% based on the total weight of structural units of Formulae 1, 2, and 3 in the polymer, calculated based on the monomers of Formulae 11, 22, and 33 used in the polymerization reaction, and the weight ratio of the structural unit corresponding to Formula 2 to the structural unit corresponding to Formula 3 is from about 4:1 to about 1:4, or about 1:1. Further, the ratio of structural units when expressed as the mole fraction of the structural unit of Formula 1 in the polymer is at least about 0.87 or from about 0.87 to about 0.94, or from about 0.9 to about 0.92 based on the total number of moles of the structural units of Formulae 1, 2, and 3, and the mole ratio of the structural unit of Formula 2 to the structural unit of Formula 3 is from about 0.2:1 to about 7:1, from about 0.2:1 to about 3.5:1; from about 0.5:1 to about 1.3:1, from about 0.8 to about 0.9, or about 0.85:1; again these calculations are performed using the amounts of monomers of Formulae 11, 22, and 33 used in the polymerization reaction. It is not necessary to calculate conversion.

[0021] In some aspects, the crosslinked cation exchange polymer comprises units corresponding to Formulae IA, 2A, and 3A, wherein Formula IA, Formula 2A and Formula 3A correspond to the following structures.

![Formulae](image)

[0022] In Formula 1 or IA, the carboxylic acid can be in the acid form (i.e., balanced with hydrogen), in salt form (i.e., balanced with a counter-ion such as Ca²⁺, Mg²⁺, Na⁺, NH₄⁺, and the like) or in an ester form (i.e., balanced with an alkyl, such as methyl). Preferably, the carboxylic acid is in the salt form and balanced with a Ca²⁺ counterion. When the carboxylic acid of the crosslinked cation exchange form is balanced with a divalent counterion, two carboxylic acid groups can be associated with the one divalent cation.

[0023] The polymers described herein are generally random polymers wherein the exact order of the structural units of Formulae 1, 2, or 3 (derived from monomers of Formulae 11, 22, or 33), or IA, 2A, or 3A (derived from monomers of Formulae 1IA, 22A, or 33A) is not predetermined.
A cation exchange polymer derived from monomers of Formulae 11, 22, and 33, followed by hydrolysis, can have the structure as follows:

\[
\text{Formula 40}
\]

\[
\begin{align*}
R_1 & \quad A_1 \quad R_2 \\
F & \quad m
\end{align*}
\]

\[
\begin{align*}
X_1 & \quad n \\
\end{align*}
\]

\[
\begin{align*}
X_2 & \quad p
\end{align*}
\]

wherein \( R_1, R_2, A_1, X_1, \) and \( X_2 \) are as defined in connection with Formulae 1, 2, and 3 and \( m \) is in the range of from about 85 to about 93 mol\%, \( n \) is in the range of from about 1 to about 10 mol\% and \( p \) is in the range of from about 1 to about 10 mol\% calculated based on the ratio of monomers and crosslinkers added to the polymerization mixture. The wavy bonds in the polymer structures of Formula 40 are included to represent the random attachment of structural units to one another wherein the structural unit of Formula 1 can be attached to another structural unit of Formula 1, a structural unit of Formula 2, or a structural unit of Formula 3; the structural units of Formulae 2 and 3 have the same range of attachment possibilities.

Using the polymerization process described herein, with monomers of Formulae 11A, 22A and 33A, followed by hydrolysis and calcium ion exchange, a polymer having the general structure shown below is obtained:

\[
\text{Formula 40A}
\]
wherein m is in the range of from about 85 to about 93 mol%, n is in the range of from about 1 to about 10 mol% and p is in the range of from about 1 to about 10 mol%, calculated based on the ratios of monomers and crosslinkers added to the polymerization mixture. The wavy bonds in the polymer structures of Formula 4OA are included to represent the random attachment of structural units to one another wherein the structural unit of Formula 1A can be attached to another structural unit of Formula 1A, a structural unit of Formula 2A, or a structural unit of Formula 3A; the structural units of Formulae 2A and 3A have the same range of attachment possibilities.

[0026] The crosslinked cation exchange polymer is generally a reaction product of a polymerization mixture that is subjected to polymerization conditions. The polymerization mixture may also contain components that are not chemically incorporated into the polymer. The crosslinked cation exchange polymer typically comprises a fluoro group and an acid group that is the product of the polymerization of three different monomer units where one monomer comprises a fluoro group and an acid group, another monomer is a difunctional arylene monomer and a third monomer is a difunctional alkylene, ether- or amide-containing monomer. More specifically, the crosslinked cation exchange polymer can be a reaction product of a polymerization mixture comprising monomers of Formulae 11, 22, 33. The monomer of Formula 11, the monomer of Formula 22, and the monomer of Formula 33 have the general formulas:

\[ \text{Formula 11} \]

\[ \text{Formula 22} \]

\[ \text{Formula 33} \]

wherein Ri and R2 are as defined in connection with Formula 1, Xi is as defined in connection with Formula 2, X2 is as defined in connection with Formula 3, and An is an optionally protected carboxylic, phosphonic, or phosphoric. In a preferred embodiment, An is a protected carboxylic, phosphonic, or phosphoric. The polymerization mixture typically further comprises a polymerization initiator.

[0027] The reaction product of the polymerization mixture comprising Formulae 11, 22, 33 comprises a polymer having protected acid groups and comprising units corresponding to Formula 10 and units corresponding to Formulae 2 and 3. Polymer products having protected
acid groups can be hydrolyzed to form a polymer having unprotected acid groups and comprising units corresponding to Formulae 1, 2, and 3. The structural units corresponding to Formula 10 have the structure

![Formula 10](image)

wherein $R_1$, $R_2$, and $A_n$ are as defined in connection with Formula 11.

[0028] In preferred embodiments of any of the methods of the invention wherein the crosslinked cation exchange polymer is a reaction product of a polymerization mixture of monomers, A11 is a protected carboxylic, phosphonic, or phosphoric. The polymer formed in the polymerization reaction contains protected carboxylic, phosphonic, or phosphoric groups. A hydrolysis agent can be added to the polymer formed in the polymerization reaction to hydrolyze these protected groups, converting them to carboxylic, phosphonic, or phosphoric groups, or other methods of deprotection well known in the art can be used. The hydrolyzed polymer is preferably subjected to ion exchange to obtain a preferred polymer salt for therapeutic use.

[0029] Generally, the reaction mixture comprises at least about 85 wt.% or from about 80 wt.% to about 95 wt.% of monomers corresponding to Formula 11 based on the total weight of the monomers corresponding to Formulae 11, 22, and 33; and the mixture having a weight ratio of the monomer corresponding to Formula 22 to the monomer corresponding to Formula 33 from about 4:1 to about 1:4, from about 2:1 to 1:2, or about 1:1. Additionally, the reaction mixture can comprise a unit corresponding to Formula 11 having a mole fraction of at least about 0.87 or from about 0.87 to about 0.94 based on the total number of moles of the monomers corresponding to Formulae 11, 22, and 33 and the mixture having a mole ratio of the monomer corresponding to Formula 22 to the monomer corresponding to Formula 33 of from about 0.2:1 to about 7:1, from about 0.2:1 to about 3.5:1; from about 0.5:1 to about 1.3:1, from about 0.8 to about 0.9, or about 0.85:1.

[0030] Particular crosslinked cation exchange polymers are the reaction product of a monomer corresponding to Formula 11A, a monomer corresponding to Formula 22A, a monomer corresponding to Formula 33A, and a polymerization initiator. The monomers corresponding to Formulae 11A, 22A, and 33A have the structure:
wherein alkyl is preferably selected from methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl, sec-butyl, tert-butyl, pentyl, iso-pentyl, sec-pentyl, or tert-pentyl. Most preferably, the alkyl group is methyl or tert-butyl. The -O-alkyl moiety protects the carboxyl moiety from reacting with other reactive moieties during the polymerization reaction and can be removed by hydrolysis or other deprotection methods as described in more detail below.

[0031] Further, the reaction mixture contains at least about 80 wt.%, particularly at least about 85 wt.%, and more particularly at least about 90 wt.% or from about 80 wt.% to about 95 wt.%, from about 85 wt.% to about 95 wt.%, from about 85 wt.% to about 93 wt.% or from about 88 wt.% to about 92 wt.% of monomers corresponding to Formula 1IA based on the total weight of monomers of Formulae 1IA, 22A, and 33A and has a weight ratio of the monomer corresponding to Formula 22A to the monomer corresponding to Formula 33A of from about 4:1 to about 1.4 or about 1:1. Additionally, the reaction mixture can have a mole fraction of at least about 0.87 or from about 0.87 to about 0.94 of the monomer of Formula 1IA based on the total number of moles of the monomers of Formulae 1IA, 22A, and 33A and the mixture has a mole ratio of the monomer of Formula 22A to the monomer of Formula 33A of from about 0.2:1 to about 7:1, from about 0.2:1 to about 3.5:1; from about 0.5:1 to about 1.3:1, from about 0.8 to about 0.9, or about 0.85:1.

[0032] Generally, the reaction mixture contains from about 80 wt.% to about 95 wt.% of monomers corresponding to Formula 1IA based on the total weight of monomers corresponding to Formulae 1IA, 22A, and 33A. Additionally, the weight ratio of the monomer corresponding to Formula 22A to the monomer corresponding to Formula 33A of from about 4:1 to about 1.4 or about 1:1. Further, the reaction mixture can have a mole fraction of from about 0.9 to about 0.92 of the monomer of Formula 1IA based on the total number of moles of the monomers of Formulae 1IA, 22A, and 33A. Also, the mixture has a mole ratio of the monomer
of Formula 22A to the monomer of Formula 33A of from about 0.2:1 to about 7:1, from about 0.2:1 to about 3.5:1; from about 0.5:1 to about 1.3:1, from about 0.8 to about 0.9, or about 0.85:1.

[0033] In a preferred embodiment, an initiated polymerization reaction is employed where a polymerization initiator is used in the polymerization reaction mixture to aid initiation of the polymerization reaction. When preparing poly(methylfluoro acrylate) or (polyMeFA) or any other crosslinked cation exchange polymer of the invention in a suspension polymerization reaction, the nature of the free radical initiator plays a role in the quality of the suspension in terms of polymer particle stability, yield of polymer particles, and the polymer particle shape. Use of water-insoluble free radical initiators, such as lauroyl peroxide, can produce polymer particles in a high yield. Without being bound by any particular theory, it is believed that a water-insoluble free radical initiator initiates polymerization primarily within the dispersed phase containing the monomers of Formulae 11, 22, and 33. Such a reaction scheme provides polymer particles rather than a bulk polymer gel. Thus, the process uses free radical initiators with water solubility lower than 0.1 g/L, particularly lower than 0.01 g/L. In particular embodiments, polymethylfluoroacrylate particles are produced with a combination of a low water solubility free radical initiator and the presence of a salt in the aqueous phase, such as sodium chloride.

[0034] The polymerization initiator can be chosen from a variety of classes of initiators. For instance, initiators that generate polymer initiating radicals upon exposure to heat include peroxides, persulfates or azo type initiators (e.g., 2,2'-azobis(2-methylpropionitrile), lauroyl peroxide (LPO), tert-butyl hydro peroxide, dimethyl-2,2'-azobis(2-methylpropionate), 2,2'-azobis[2-methyl-N-(2-hydroxyethyl)propionamide], 2,2'-azobis[2-(2-imidazolin-2-yl)propane], (2,2''-azo bis(2,4-dimethylvaleronitrile), azobisisobutyronitrile (AIBN) or a combination thereof. Another class of polymer initiating radicals is radicals generated from redox reactions, such as persulfates and amines. Radicals can also be generated by exposing certain initiators to UV light or exposure to air.

[0035] For those polymerization reactions that contain additional components in the polymerization mixture that are not intended to be incorporated into the polymer, such additional components typically comprise surfactants, solvents, salts, buffers, aqueous phase polymerization inhibitors and/or other components known to those of skill in the art. When the polymerization is carried out in a suspension mode, the additional components may be contained in an aqueous phase while the monomers and initiator may be contained in an organic phase. When an aqueous phase is present, the aqueous phase may be comprised of water, surfactants,
stabilizers, buffers, salts, and polymerization inhibitors. A surfactant may be selected from the group consisting of anionic, cationic, nonionic, amphoteric, zwitterionic, or a combination thereof. Anionic surfactants are typically based on sulfate, sulfonate or carboxylate anions. These surfactants include, sodium dodecyl sulfate (SDS), ammonium lauryl sulfate, other alkyl sulfate salts, sodium laureth sulfate (or sodium lauryl ether sulfate (SLES)), N-lauroylsarcosine sodium salt, lauryldimethylamine-oxide (LDAO), ethyltrimethylammoniumbromide (CTAB), bis(2-ethylhexyl)sulfosuccinate sodium salt, alkyl benzene sulfonate, soaps, fatty acid salts, or a combination thereof. Cationic surfactants, for example, contain quaternary ammonium cations. These surfactants are cetyl trimethylammonium bromide (CTAB or hexadecyl trimethyl ammonium bromide), cetylpyridinium chloride (CPC), polyethoxylated tallow amine (POEA), benzalkonium chloride (BAC), benzethonium chloride (BZT), or a combination thereof. Zwitterionic or amphoteric surfactants include dodecyl betaine, dodecyl dimethylamine oxide, cocamidopropyl betaine, coco ampho glycinate, or a combination thereof. Nonionic surfactants include alkyl poly(ethylene oxide) copolymers of poly(ethylene oxide) and poly(propylene oxide) (commercially called Poloxamers or Poloxamines), alkyl polyglucosides (including octyl glucoside, decyl maltoside) fatty alcohols, cetyl alcohol, oleyl alcohol, cocamide MEA, cocamide DEA, or a combination thereof. Other pharmaceutically acceptable surfactants are well known in the art and are described in McCutcheon's Emulsifiers and Detergents, N. American Edition (2007).

[0036] Polymerization reaction stabilizers may be selected from the group consisting of organic polymers and inorganic particulate stabilizers. Examples include polyvinyl alcohol-co-vinylacetate and its range of hydrolyzed products, polyvinylacetate, polyvinylpyrrolidinone, salts of polyacrylic acid, cellulose ethers, natural gums, or a combination thereof.

[0037] Buffers may be selected from the group consisting of, for example, 4-2-hydroxyethyl-1-piperazineethanesulfonic acid, 2-[[tris(hydroxymethyl)methyl]amino]ethanesulfonic acid, 3-(N-morpholino)propanesulfonic acid, piperazine-N,N'-bis(2-ethanesulfonic acid), sodium phosphate dibasic heptahydrate, sodium phosphate monobasic monohydrate or a combination thereof.

[0038] Polymerization reaction salts may be selected from the group consisting of potassium chloride, calcium chloride, potassium bromide, sodium bromide, sodium bicarbonate, ammonium peroxodisulfate, or a combination thereof.

[0039] Polymerization inhibitors may be used as known in the art and selected from the group consisting of 1,1,3-tris(2-methyl-4-hydroxy-5-tert-butylphenyl)butane, 1,3,5-trimethyl-
2,4,6-tris(3,5-di-tert-butyl-4-hydroxybenzyl)benzene, 1-aza-3,7-dioxabicyclo[3.3.0]octane-5-methanol, 2,2'-ethyldiene-bis(4,6-di-tert-butylphenol), 2,2'-ethyldenebis(4,6-di-tert-butylphenyl) fluorophosphite, 2,2'-methylenebis(6-tert-butyl-4-ethylphenol), 2,2'-methylenebis(6-tert-butyl-4-methylphenol), 2,5-di-tert-butyl-4-methoxyphenol, 2,6-di-tert-butyl-4-(dimethylaminomethyl)phenol, 2-heptanone oxime, 3,3\&5,5'-tetramethylbiphenyl-4,4'-dil, 3,9-bis(2,4-dicumylphenoxy)-2,4,8,10-tetraoxa-3,9-diphosphaspiro[5.5]undecane, 4,4-dimethylloxazolidine, 4-methyl-2-pentanone oxime, 5-ethyl-l-aza-3,7-dioxabicyclo[3.3.0]octane, 6,6'-dihydroxy-5,5'-dimethoxy-[1,1'-biphenyl]-3,3'-dicarboxaldehyde, diestearyl-3,3'-thiodipropionate, ditetradecyl-3,3'-thiodipropionate, ditiadecyl-3,3'-thiodipropionate, octadecyl-3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate, pentadecyl tetrakis(3,5-di-tert-butyl-4-hydroxyhydrocinnamate), poly(1,2-dihydro-2,2,4-trimethylquinoline), sodium D-isoascorbate monohydrate, tetrakis(2,4-di-tert-butylphenyl)-4,4'-biphenyldiphenosphonite, tris(3,5-di-tert-butyl-4-hydroxybenzyl) isocyanurate, tris(4-tert-butyl-3-hydroxy-2,6-dimethylbenzyl) isocyanurate, sodium nitrite or a combination thereof.

[0040] Generally, the polymerization mixture is subjected to polymerization conditions. While suspension polymerization is preferred, as already discussed herein, the polymers of this invention may also be prepared in bulk, solution or emulsion polymerization processes. The details of such processes are within the skill of one of ordinary skill in the art based on the disclosure of this invention. The polymerization conditions typically include polymerization reaction temperatures, pressures, mixing and reactor geometry, sequence and rate of addition of polymerization mixtures and the like. Polymerization temperatures are typically in the range of from about 50 to 100°C. Polymerization pressures are typically run at atmospheric pressure, but can be run at higher pressures (for example 130 PSI of nitrogen). Polymerization depends on the scale of the polymerization and the equipment used, and is within the skill of one of ordinary skill in the art. Various alpha-fluoroacrylate polymers and the synthesis of these polymers are described in U.S. Patent Application Publication No. 2005/0220752, herein incorporated by reference.

[0041] As described in more detail in connection with the examples herein, in various particular embodiments, the crosslinked cation exchange polymer can be synthesized in a polymerization suspension polymerization reaction by preparing an organic phase and an aqueous phase. The organic phase typically contains a monomer of Formula 11, a monomer of Formula 22, a monomer of Formula 33, and a polymerization initiator. The aqueous phase contains a suspension stabilizer, a water soluble salt, water, and optionally a buffer. The organic
phase and the aqueous phase are then combined and stirred under nitrogen. The mixture is generally heated to about 60°C to about 80°C for about 2.5 to about 3.5 hours, allowed to rise up to 95°C after polymerization is initiated, and then cooled to room temperature. After cooling, the aqueous phase is removed. Water is added to the mixture, the mixture is stirred, and the resulting solid is filtered. The solid is washed with water, alcohol or alcohol/water mixtures.

[0042] As described above, polymerization suspension stabilizers, such as polyvinyl alcohol, are used to prevent coalescence of particles during the polymerization process. Further, it has been observed that the addition of sodium chloride in the aqueous phase decreased coalescence and particle aggregation. Other suitable salts for this purpose include salts that are soluble in the aqueous phase. In this embodiment, water soluble salts are added at a concentration of from about 0.1 wt.% to about 10 wt.%, particularly from about 2 wt.% to about 5 wt.% and even more particularly from about 3 wt.% to about 4 wt.%.

[0043] Preferably, an organic phase of methyl 2-fluoroacrylate (90 wt.%), 1,7-octadiene (5 wt.%) and divinylbenzene (5 wt.%) is prepared and 0.5 wt.% of lauroyl peroxide is added to initiate the polymerization reaction. Additionally, an aqueous phase of water, polyvinyl alcohol, phosphates, sodium chloride, and sodium nitrite is prepared. Under nitrogen and while keeping the temperature below about 30°C, the aqueous and organic phases are mixed together. Once mixed completely, the reaction mixture is gradually heated with continuous stirring. After the polymerization reaction is initiated, the temperature of the reaction mixture is allowed to rise up to about 95°C. Once the polymerization reaction is complete, the reaction mixture is cooled to room temperature and the aqueous phase is removed. The solid can be isolated by filtration after water is added to the mixture. The resulting product is a crosslinked (methyl 2-fluoroacrylate)-divinylbenzene-1,7-octadiene terpolymer.

[0044] As discussed herein, after polymerization, the product may be hydrolyzed or otherwise deprotected by methods known in the art. For hydrolysis of the polymer having ester groups to form a polymer having carboxylic acid groups, preferably, the polymer is hydrolyzed with a strong base (e.g., NaOH, KOH, Mg(OH)₂, or Ca(OH)₂) to remove the alkyl (e.g., methyl) group and form the carboxylate salt. Alternatively, the polymer can be hydrolyzed with a strong acid (e.g., HCl) to form the carboxylate salt. Preferably, the (methyl 2-fluoroacrylate)-divinylbenzene-1,7-octadiene terpolymer is hydrolyzed with an excess of aqueous sodium hydroxide solution at a temperature from about 30°C to about 100°C to yield (sodium 2-fluoroacrylate)-divinylbenzene-1,7-octadiene terpolymer. Typically, the hydrolysis reaction is
carried out for about 15 to 25 hours. After hydrolysis, the solid is filtered and washed with water and/or an alcohol.

[0045] The cation of the polymer salt formed in the hydrolysis reaction reaction or other deprotection step depends on the base used in that step. For example, when sodium hydroxide is used as the base, the sodium salt of the polymer is formed. This sodium ion can be exchanged for another cation by contacting the sodium salt with an excess of an aqueous metal salt to yield an insoluble solid of the desired polymer salt. After the desired ion exchange, the product is washed with an alcohol and/or water and dried directly or dried after a dewatering treatment with denatured alcohol; preferably, the product is washed with water and dried directly. For example, the sodium salt of the cation exchange polymer is converted to the calcium salt by washing with a solution that substitutes calcium for sodium, for example, by using calcium chloride, calcium acetate, calcium lactate gluconate, or a combination thereof. And, more specifically, to exchange sodium ions for calcium ions, the (sodium 2-fluoroacrylate)-divinylbenzene-1,7-octadiene terpolymer is contacted with an excess of aqueous calcium chloride to yield an insoluble solid of crosslinked (calcium 2-fluoroacrylate)-divinylbenzene-1,7-octadiene terpolymer.

[0046] Using this suspension polymerization process, a cross-linked polyMeFA polymer is isolated in good yield, generally above about 85%, more specifically above about 90%, and even more specifically above about 93%. The yield of the second step (i.e., hydrolysis) preferably occurs in 100%, providing an overall yield after hydrolysis of above about 85%, more specifically above about 90%, and even more specifically above about 93%.

[0047] The polymers or compositions of the invention can be tested for their characteristics and properties using a variety of established testing procedures. For example, the percent calcium in the polymer or the composition is tested after extraction with an appropriate acid (e.g., 3M hydrochloric acid) using inductively coupled plasma optical emission spectroscopy (ICP-OES) analysis in a manner known to those of skill in the art, for example, using a Thermo IRIS Intrepid II XSP (Thermo Scientific, Waltham, MA). In general, the amount of calcium in the polymer is in the range of from about 8 wt.% to about 25 wt.%, and preferably about 10 wt.% to about 20 wt.%, based on the total weight of the polymer.

[0048] Also for example, the potassium binding capacity can be used for polymer or composition characterization. In this example, the potassium binding capacity is performed in vitro by weighing and transferring approximately 300 mg of a dried sample of polymer or composition into a 40 mL screw-top vial, and then adding a calculated volume of 200 mM KCl
solution to achieve a concentration of 20 mg/mL of test substance. The vial is shaken vigorously for two hours, and the supernatant is filtered through a 0.45 μm filter followed by dilution to 1:20 in water. The supernatant is analyzed for potassium concentration via ICP-OES, and the potassium binding is calculated using the following formula.

\[
\text{Potassium binding} = \frac{20 \times (\text{dilution factor})}{20 \text{ mg/mL (sample cone)}}\times (\frac{[K]_{\text{blank}} - [K]_{\text{sample}}}{\text{g polymer}}) \text{ mmol K}
\]

[0049] One aspect of the invention is a method of removing potassium ions from the gastrointestinal tract of an animal subject in need thereof with a crosslinked cation exchange polymer or a pharmaceutical composition of the invention. The crosslinked cation exchange polymer generally has a high overall exchange capacity. The overall exchange capacity is the maximum amount of cations bound by the cation exchange polymer measured in mEq/g. A higher exchange capacity is desired as it is a measure of the density of acid groups in the polymer and the more acid groups per unit weight, the greater the overall exchange capacity of the polymer.

[0050] The crosslinked cation exchange polymers also generally have a high binding capacity for potassium. In particular, the in vivo binding capacity is relevant to therapeutic benefit in a patient. Generally, a higher in vivo binding capacity results in a more pronounced therapeutic effect. However, since patients can have a wide range of responses to the administration of cation exchange polymers, one measure of the in vivo binding capacity for potassium is the average in vivo binding capacity calculated over a sample group. The term "high capacity" as used herein encompasses an average in vivo binding of about 1.0 mEq or more of potassium per gram of polymer.

[0051] One measure of the in vivo potassium binding capacity is the use of \( \propto \) vivo human aspirates. For this method, healthy patients are given a meal as a digestion mimic and aliquots of chyme are then sampled using a tube placed in the lumen of the small intestine and other portions of the intestines. For example, normal subjects are intubated with a double lumen polyvinyl tube, with a mercury weighted bag attached to the end of the tube to facilitate movement of the tube into the small intestine. One aspiration aperture of the double lumen tube is located in the stomach and the other aperture is at the Ligament of Treitz (in the upper jejunum). Placement takes place with the use of fluoroscopy. After the tube is placed, 550 mL of a liquid standard test meal (supplemented with a marker, polyethylene glycol (PEG) - 2 g/550mL) is infused into the stomach through the gastric aperture at a rate of 22 mL per minute.
It requires approximately 25 minutes for the entire meal to reach the stomach. This rate of ingestion simulates the duration of time required to eat normal meals. Jejunal chyme is aspirated from the tube whose lumen is located at the Ligament of Treitz. This fluid is collected continuously during 30-minute intervals for a two and a half hour period. This process results in five specimens that are mixed, measured for volume, and lyophilized.

[0052] The potassium binding procedure is identical to the one described below with the non-interfering buffer experiment, except that the ex vivo aspirate liquid is used (after reconstitution of the freeze-dried material in the proper amount of de-ionized water). The binding capacity in the ex vivo aspirate (VA) is calculated from the concentration of potassium in the aspirate with and without polymer. In some embodiments, the average ex vivo potassium binding capacity of a human gastrointestinal aspirate can be equal to or more than about 0.7 mEq per gram of polymer. More specifically, the ex vivo potassium binding capacity of a human gastrointestinal aspirate is about 0.8 mEq or more per gram, more particularly is about 1.0 mEq or more per gram, even more particularly is about 1.2 mEq or more per gram, and most particularly is about 1.5 mEq or more per gram.

[0053] Another measure of the in vivo binding capacity for potassium is the in vitro binding capacity for potassium in non-interfering environment or an interfering environment at a particular pH. In a non-interfering environment, the crosslinked cation exchange polymer is placed in a solution having potassium ions as the only cation. This solution is preferably at an appropriate GI physiological pH (e.g., about 6.5). The in vitro binding capacity for potassium in a non-interfering environment is a measure of the total binding capacity for cations.

[0054] Further, in an interfering environment, the environment contains cations in concentrations relevant to the typical concentrations in the gastrointestinal tract and is at physiological pH (e.g., about 6.5). In the interfering environment, it is preferred that the polymer or the pharmaceutical composition exhibits selective binding for potassium ions.

[0055] 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 mEq per gram of polymer. A particular range of in vitro potassium binding capacity in a pH of about 5.5 or more is about 6 mEq to about 12 mEq per gram of polymer. Preferably the in vitro potassium binding capacity in a pH of about 5.5 or more is equal to about 6 mEq or more per gram, more particularly is about 7 mEq or more per gram, and even more particularly is about 8 mEq or more per gram.
The higher capacity of the polymeric composition may enable the administration of a lower dose of the polymer or the composition. Typically the dose of the polymeric composition used to obtain the desired therapeutic and/or prophylactic benefits is about 0.5 gram/day to about 60 gram/day. A particular dose range is about 5 grams/day to about 60 grams/day, and more particularly is about 5 grams/day to about 30 grams/day. In various administration protocols, the dose is administered about three times a day, for example, with meals. In other protocols, the dose is administered once a day or twice a day. These doses can be for chronic or acute administration.

Polymers of the invention are crosslinked materials, meaning that they do not generally dissolve in solvents, and, at most, swell in solvents. As used herein, "swelling ratio" refers to the number of grams of solvent taken up by one gram of otherwise non-solvated crosslinked polymer when equilibrated in an aqueous environment. When more than one measurement of swelling is taken for a given polymer, the mean of the measurements is taken to be the swelling ratio.

The swelling ratio in physiological isotonic buffer, representative of the gastrointestinal tract, is typically in the range of about 1 to about 7, specifically about 1 to 5; more particularly about 1 to 2. In some embodiments, crosslinked cation exchange polymers of the invention have a swelling ratio of less than 5, or less than about 4, or less than about 3, or less than about 2.5, or less than about 2.

Generally, the polymers and pharmaceutical compositions described herein retain a significant amount of the bound potassium, and specifically, the potassium bound by the polymer is 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 prior to excretion. A sufficient amount of the bound potassium is retained, such that a therapeutic and/or prophylactic benefit is obtained. Particular amounts of bound potassium that can be retained range from about 5% to about 100%. The polymer or pharmaceutical composition should retain about 25% of the bound potassium, more particularly is about 50%, even more particularly is about 75% and most particularly is retention of about 100% of the bound potassium. The period of retention is generally during the time that the composition is being used therapeutically. 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 gastrointestinal tract and more particularly the average residence time in the colon.
Generally, the cation exchange polymers are not significantly absorbed from the gastro-intestinal tract. Depending upon the size distribution of the cation exchange polymer particles, clinically insignificant amounts of the polymers may be absorbed. More specifically, about 90% or more of the polymer is not absorbed, about 95% or more is not absorbed, even more specifically about 97% or more is not absorbed, and most specifically about 98% or more of the polymer is not absorbed.

The methods, polymers and compositions described herein are suitable for removal of potassium from a patient wherein a patient is in need of such potassium removal. For example, patients experiencing hyperkalemia caused by disease and/or use of certain drugs benefit from such potassium removal. Further, patients at risk for developing high serum potassium concentrations through use of agents that cause potassium retention could be in need of potassium removal. The methods described herein are applicable to these patients regardless of the underlying condition that is causing the high serum potassium levels.

If necessary, the crosslinked cation exchange polymers or pharmaceutical 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.

Further, patients suffering from chronic kidney disease and/or congestive heart failure can be particularly in need of potassium removal because agents used to treat these conditions may cause potassium retention in a significant population of these patients. For these patients, decreased renal potassium excretion results from 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 (ACEs), angiotensin receptor blockers (ARBs), beta blockers, renin inhibitors, aldosterone synthase inhibitors, non-steroidal anti-inflammatory drugs, heparin, or trimethoprim. For example, patients suffering from chronic kidney disease can be prescribed various agents that will slow the progression of the disease; for this purpose, angiotensin-converting enzyme inhibitors (ACEs), angiotensin receptor blockers (ARBs), and aldosterone antagonists are commonly prescribed. In these treatment regimens the angiotensin-converting enzyme inhibitor is captopril, zofenopril, enalapril, ramipril, quinapril, perindopril, lisinopril, benazipril, fosinopril, or combinations thereof and the angiotensin receptor blocker is candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan, or combinations thereof and the renin inhibitor is aliskiren. The aldosterone antagonists can also cause potassium retention.
Thus, it can be advantageous for patients in need of these treatments to also be treated with an agent that removes potassium from the body. The aldosterone antagonists typically prescribed are spironolactone, eplerenone, and the like.

[0064] In certain particular embodiments, the crosslinked cation exchange polymers described herein can be administered on a periodic basis to treat a chronic condition. Typically, such treatments will enable patients to continue using drugs that may cause hyperkalemia, such as potassium-sparing diuretics, ACEs, ARBs, aldosterone antagonists, β-blockers, renin inhibitors, non-steroidal anti-inflammatory drugs, heparin, trimethoprim, or combinations thereof. Also, use of the polymeric compositions described herein will enable certain patient populations, who were unable to use certain above-described drugs, to use such drugs.

[0065] In certain use situations, the crosslinked cation exchange polymers used are those that are capable of removing less than about 5 mEq of potassium per day or in the range of about 5 mEq to about 60 mEq of potassium per day.

[0066] In certain other embodiments, the compositions and methods described herein are used in the treatment of hyperkalemia in patients in need thereof, for example, when caused by excessive intake of potassium. Excessive potassium intake alone is an uncommon cause of hyperkalemia. More often, hyperkalemia is caused by indiscriminate potassium consumption in a patient with impaired mechanisms for the intracellular shift of potassium or renal potassium excretion.

[0067] In the present invention, the crosslinked cation exchange polymers or 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 crosslinked cation exchange polymer or composition of the invention can be co-administered with drugs that cause the hyperkalemia, such as potassium-sparing diuretics, angiotensin-converting enzyme inhibitors (ACEs), angiotensin receptor blockers (ARBs), beta blockers, renin inhibitors, non-steroidal anti-inflammatory drugs, heparin, or trimethoprim. In particular, the crosslinked cation exchange polymer or composition can be co-administered with ACEs (e.g., captopril, zofenopril, enalapril, ramipril, quinapril, perindopril, lisinopril, benazipril, and fosinopril), ARBs (e.g., candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, and valsartan) and renin inhibitors (e.g. aliskiren). In particular embodiments, the agents are simultaneously administered, wherein both
the agents are present in separate compositions. In other embodiments, the agents are administered separately in time (i.e., sequentially).

[0068] The term "treating" as used herein includes achieving a therapeutic 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 experiencing 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 hyperkalemia, like renal failure. In some treatment regimens, the crosslinked cation exchange polymer or composition of the invention may be administered to a patient at risk of developing hyperkalemia or to a patient reporting one or more of the physiological symptoms of hyperkalemia, even though a diagnosis of hyperkalemia may not have been made.

[0069] The pharmaceutical compositions of the present invention include compositions wherein the crosslinked cation exchange 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. 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.

[0070] The polymers and 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. The polymers and compositions can also be used in fodder for animals to lower potassium levels, which is desirable in fodders for pigs and poultry to lower the water secretion.

[0071] The crosslinked cation exchange polymers or pharmaceutically acceptable salts thereof, or compositions described herein, 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. Rectal routes of administration are known to those of skill in the art.
Intestinal routes of administration generally refer to administration directly into a segment of the gastrointestinal tract, e.g., through a gastrointestinal tube or through a stoma. The most preferred route for administration is oral.

[0072] 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 excipient. Pharmaceutical compositions for use in accordance with the present invention may be formulated in conventional manner using one or more pharmaceutically acceptable excipients comprising carriers, diluents, and auxiliaries which facilitate processing of the active compounds into preparations which can be used physiologically. Proper composition is dependent upon the route of administration chosen.

[0073] For oral administration, the polymers or compositions of the invention can be formulated readily by combining the polymer or composition with pharmaceutically acceptable excipients well known in the art. Such excipients enable the compositions 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 composition 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 or sucrose; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinyl pyrrolidone (PVP); and various flavoring agents known in the art. 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.

[0074] In various embodiments, the active ingredient (e.g., polymer) constitutes over about 20%, more particularly over about 40%, even more particularly over about 50%, and most particularly more than about 60% by weight of the oral dosage form, the remainder comprising suitable excipient(s).

[0075] In some embodiments, the polymers of the invention are provided as pharmaceutical compositions in the form of liquid compositions. In various embodiments, the pharmaceutical composition contains a crosslinked cation exchange polymer dispersed in a
suitable liquid excipient. Suitable liquid excipients are known in the art; see, e.g., Remington's Pharmaceutical Sciences.

Unless otherwise indicated, an alkyl group as described herein alone or as part of another group is an optionally substituted linear saturated monovalent hydrocarbon radical containing from one to twenty carbon atoms and preferably one to eight carbon atoms, or an optionally substituted branched saturated monovalent hydrocarbon radical containing three to twenty carbon atoms, and preferably three to eight carbon atoms. Examples of unsubstituted alkyl groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, i-pentyl, s-pentyl, t-pentyl, and the like.

The term "amide moiety" as used herein represents a bivalent (i.e., difunctional) group including at least one amido linkage (i.e., \( \text{O} \quad \text{C} - \text{N} \)), such as -C(O)-NR\(_A\)-R\(_C\)-NR\(_B\)-C(O)- wherein R\(_A\) and R\(_B\) are independently hydrogen or alkyl and R\(_C\) is alkylene. For example, an amide moiety can be -C(O)-NH-(CH\(_2\))\(_p\)-NH-C(O)- wherein \( p \) is an integer of 1 to 8.

The term "aryl" as used herein alone or as part of another group denotes an optionally substituted monovalent aromatic hydrocarbon radical, preferably a monovalent monocyclic or bicyclic group containing from 6 to 12 carbons in the ring portion, such as phenyl, biphenyl, naphthyl, substituted phenyl, substituted biphenyl or substituted naphthyl. Phenyl and substituted phenyl are the more preferred aryl groups. The term "aryl" also includes heteroaryl.

The terms "carboxylic acid group", "carboxylic" or "carboxyl" denote the monovalent radical -C(O)OH. Depending upon the pH conditions, the monovalent radical can be in the form -C(O)O\(^-\) Q\(^+\) whereby Q\(^+\) is a cation (e.g., sodium), or two of the monovalent radicals in close proximity can bond with a divalent cation Q\(^{2+}\) (e.g., calcium, magnesium), or a combination of these monovalent radicals and -C(O)OH are present.

The term "cycloalkyl" as used herein denotes optionally an optionally substituted cyclic saturated monovalent bridged or non-bridged hydrocarbon radical containing from three to eight carbon atoms in one ring and up to 20 carbon atoms in a multiple ring group. Exemplary unsubstituted cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, adamantyl, norbornyl, and the like.

The term ";-ene" as used as a suffix as part of another group denotes a bivalent radical in which a hydrogen atom is removed from each of two terminal carbons of the group, or if the group is cyclic, from each of two different carbon atoms in the ring. For example, alkylene
denotes a bivalent alkyl group such as methylene (-CH₂) or ethylene (-CH₂CH₂), and arylene
denotes a bivalent aryl group such as o-phenylene, m-phenylene, or p-phenylene.

[0082] The term "ether moiety" as used herein represents a bivalent (i.e., difunctional) group including at least one ether linkage (i.e., -O-). For example, in Formulae 3 or 33 as defined herein, the ether moiety can be -RAORB- or -RAOR_CORB- wherein RA, RB and Rc are independently alkylene.

[0083] The term "heteroaryl," as used herein alone or as part of another group, denotes an optionally substituted monovalent monocyclic or bicyclic aromatic radical of 5 to 10 ring atoms, where one or more, preferably one, two, or three, ring atoms are heteroatoms independently selected from N, O, and S, and the remaining ring atoms are carbon. Exemplary heteroaryl moieties include benzofuranyl, benzo[d]thiazolyl, isoquinolinyl, quinolinyl, thiophenyl, imidazolyl, oxazolyl, quinolinyl, furanyl, thiazolyl, pyridinyl, furyl, thienyl, pyridyl, oxazolyl, pyrrolyl, indolyl, quinolinyl, isoquinolinyl, and the like.

[0084] The term "heterocyclo," as used herein alone or as part of another group, denotes a saturated or unsaturated monovalent monocyclic group of 4 to 8 ring atoms, in which one or two ring atoms are heteroatom(s), independently selected from N, O, and S, and the remaining ring atoms are carbon atoms. Additionally, the heterocyclic ring may be fused to a phenyl or heteroaryl ring, provided that the entire heterocyclic ring is not completely aromatic. Exemplary heterocyclo groups include the heteroaryl groups described above, pyrrolidino, piperidino, morpholino, piperazino, and the like.

[0085] The term "hydrocarbon" as used herein describes a compound or radical consisting exclusively of the elements carbon and hydrogen.

[0086] The term "phosphonic" or "phosphonyl" denotes the monovalent radical

[0087] The term "phosphoric" or "phosphoryl" denotes the monovalent radical

[0088] The term "protected" as used herein as part of another group denotes a group that blocks reaction at the protected portion of a compound while being easily removed under conditions that are sufficiently mild so as not to disturb other substituents of the compound. For
example, a protected carboxylic acid group-C(O)OP_g or a protected phosphoric acid group -OP(O)(OH)OP_g or a protected phosphonic acid group -P(O)(OH)Op_g each have a protecting group P_g associated with the oxygen of the acid group wherein P_g can be alkyl (e.g., methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl, t-butyl, n-pentyl, i-pentyl, s-pentyl, t-pentyl, and the like), benzyl, silyl (e.g., trimethylsilyl (TMS), triethylsilyl (TES), triisopropylsilyle (TIPS), triphenylsilyl (TPS), t-butyldimethylsilyl (TBDMS), t-butyldiphenylsilyl (TBDPS) and the like. A variety of protecting groups and the synthesis thereof may be found in "Protective Groups in Organic Synthesis" by T.W. Greene and P.G.M. Wuts, John Wiley & Sons, 1999. When the term "protected" introduces a list of possible protected groups, it is intended that the term apply to every member of that group. That is, the phrase "protected carboxylic, phosphonic or phosphoric" is to be interpreted as "protected carboxylic, protected phosphonic or protected phosphoric." Likewise, the phrase "optionally protected carboxylic, phosphoric or phosphonic" is to be interpreted as "optionally protected carboxylic, optionally protected phosphonic or optionally protected phosphoric."

[0089] The term "substituted" as in "substituted aryl," "substituted alkyl," and the like, means that in the group in question (i.e., the alkyl, aryl or other group that follows the term), at least one hydrogen atom bound to a carbon atom is replaced with one or more substituent groups such as hydroxy (-OH), alkylthio, phosphino, amido (-CON(RA)(RB)), wherein R_A and R_B are independently hydrogen, alkyl, or aryl), amino(-N(RA)(RB)), wherein R_A and R_B are independently hydrogen, alkyl, or aryl), halo (fluoro, chloro, bromo, or iodo), silyl, nitro (-NO_2), an ether (-OR_A wherein R_A is alkyl or aryl), an ester (-OC(O)R_A wherein R_A is alkyl or aryl), keto (-C(O)R_A wherein R_A is alkyl or aryl), heterocyclo, and the like. When the term "substituted" introduces a list of possible substituted groups, it is intended that the term apply to every member of that group. That is, the phrase "optionally substituted alkyl or aryl" is to be interpreted as "optionally substituted alkyl or optionally substituted aryl."

[0090] Having described the invention in detail, it will be apparent that modifications and variations are possible without departing from the scope of the invention defined in the appended claims.

EXAMPLES

[0091] The following non-limiting examples are provided to further illustrate the present invention.
Materials for Examples 1-5. Methyl 2-fluoroacrylate (MeFA; SynQuest Labs) contained 0.2 wt% hydroquinone and was vacuum distilled before use. Divinylbenzene (DVB; Aldrich) was technical grade, 80%, mixture of isomers. 1,7-octadiene (ODE 98%; Aldrich), lauroyl peroxide (LPO 99%; ACROS Organics), polyvinyl alcohol (PVA typical molecular weight 85,000-146,000, 87-89% hydrolyzed; Aldrich), sodium chloride (NaCl; Aldrich), sodium phosphate dibasic heptahydrate (Na2HPO4·7H2O; Aldrich), and sodium phosphate monobasic monohydrate (NaH2PO4·H2O; Aldrich) were used as received.

Example 1: DVB as crosslinking monomer

The polymerization was carried out in a 1 L three-neck Morton-type round bottom flask, and it was equipped with an overhead mechanical stirrer with a Teflon paddle and a water condenser. An organic phase was prepared by mixing MeFA (54g), DVB (6g) and LPO (0.6g), and an aqueous phase was prepared by dissolving PVA (3g) and NaCl (11.25g) in water (285.75g). The organic and aqueous phases were then mixed in the flask and stirred at 300 rpm under nitrogen. The flask was immersed in a 76°C oil bath for 3 hours, and cooled to room temperature. The internal temperature during the reaction was about 65°C. The solid product was washed with water and collected by decanting off supernatant solution. The white solid was freeze-dried, affording dry solid polyMeFA particles (or beads) (56.15g, 94%).

Hydrolysis was carried out in the same setup as for the polymerization. PolyMeFA particles (48.93g) from above were suspended in KOH solution (500g, 10wt%) and stirred at 300 rpm. The mixture was heated in a 95°C oil bath for 20 hours and cooled to room temperature. The solid product was washed with water and collected by decanting off the supernatant solution. After freeze-drying, poly fluoroacrylic acid (polyFAA) particles (48.54g, 82%) were obtained. These particles were in the form of beads.

Example 2: Polymer synthesis using two crosslinking monomers

Multiple suspension polymerizations were carried out in a manner substantially similar to Example 1. The synthesis conditions and results are summarized in Table 1. Compared to Example 1, the addition of ODE as a second crosslinker in all ratios tested increased the yield after the hydrolysis step. Therefore the overall yield for polyFAA bead synthesis was improved to a level of greater than 90%
Table 1. Synthesis conditions and selected properties

<table>
<thead>
<tr>
<th>Exp #</th>
<th>Aqueous Phase</th>
<th>Organic Phase</th>
<th>Yield</th>
<th>Swelling Ratio</th>
<th>BC mmol/g</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Buffer</td>
<td>NaCl</td>
<td>pH before polymz</td>
<td>pH after polymz</td>
<td>MeFA wt.%</td>
</tr>
<tr>
<td>Comp 1</td>
<td>no</td>
<td>3.75%</td>
<td>nm</td>
<td>4.00</td>
<td>95</td>
</tr>
<tr>
<td>Comp 2</td>
<td>no</td>
<td>3.75%</td>
<td>nm</td>
<td>3.90</td>
<td>90</td>
</tr>
<tr>
<td>Comp 3</td>
<td>no</td>
<td>3.75%</td>
<td>nm</td>
<td>3.50</td>
<td>80</td>
</tr>
<tr>
<td>Ex 789</td>
<td>no</td>
<td>3.75%</td>
<td>5.10</td>
<td>3.50</td>
<td>90</td>
</tr>
<tr>
<td>Ex 792</td>
<td>0.25%</td>
<td>3.50%</td>
<td>8.30</td>
<td>3.95</td>
<td>nm</td>
</tr>
<tr>
<td>Ex 793</td>
<td>0.50%</td>
<td>3.25%</td>
<td>8.45</td>
<td>5.28</td>
<td>nm</td>
</tr>
<tr>
<td>Ex 808</td>
<td>0.50%</td>
<td>3.25%</td>
<td>nm</td>
<td>nm</td>
<td>nm</td>
</tr>
<tr>
<td>Ex 811</td>
<td>0.50%</td>
<td>3.25%</td>
<td>7.25</td>
<td>5.05</td>
<td>nm</td>
</tr>
<tr>
<td>Ex 815</td>
<td>0.75%</td>
<td>2.50%</td>
<td>7.24</td>
<td>5.26</td>
<td>nm</td>
</tr>
<tr>
<td>Ex 816</td>
<td>1.00%</td>
<td>2.00%</td>
<td>7.66</td>
<td>5.51</td>
<td>nm</td>
</tr>
<tr>
<td>Ex 814</td>
<td>0.75%</td>
<td>2.50%</td>
<td>7.16</td>
<td>4.62</td>
<td>87%</td>
</tr>
</tbody>
</table>

Note: (1) buffer, Na₂HPO₄/NaH₂PO₄; (2) swelling ratio, measured using salt form; (3) BC, binding capacity, measured using H form in 100mM KOH solution; (4) In Ex 816, 200ppm NaNO₂ was added in aqueous phase; (5) nm, means not measured; (6) polymz means polymerization; (7) Susp. means suspension; (8) Hydro, means hydrolysis.
Examples 3-5: Synthesis of FAA beads with DVB/ODE

[0096] The polymers of examples 3-5 were prepared as follows. A polymerization was carried out in a 1 L three-neck Morton-type round bottom flask equipped with an overhead mechanical stirrer with a Teflon paddle and a water condenser. An organic phase was prepared by mixing MeFA, DVB, ODE and LPO (0.6g), and an aqueous phase was prepared by dissolving PVA (3g) and NaCl (11.25g) in water (285.75g). The organic and aqueous phases were then mixed in the flask, and stirred at 300 rpm under nitrogen. The flask was immersed in a 70°C oil bath for 5 hours, and cooled to room temperature. The internal temperature during reaction was about 65°C. The solid product was washed with water and collected by filtration. The white solid was freeze-dried, affording dry solid polyMeFA beads.

[0097] Hydrolysis was carried out in the same setup as for the polymerization. PolyMeFA beads from the polymerization reaction were suspended in a NaOH solution (400g, 10wt%) and stirred at 200 rpm. The mixture was heated in a 95°C oil bath for 20 hours and cooled to room temperature. The solid product was washed with water and collected by filtration. After freeze-drying, polyFAA beads were obtained. The synthesis conditions and selected properties are summarized below:

<table>
<thead>
<tr>
<th>Ex</th>
<th>Organic Phase</th>
<th>Hydrolysis</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>p</td>
<td>MeFA (g)</td>
<td>DVB (g)</td>
<td>ODE (g)</td>
</tr>
<tr>
<td>3</td>
<td>54</td>
<td>4.8</td>
<td>1.2</td>
</tr>
<tr>
<td>4</td>
<td>54</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>54</td>
<td>1.2</td>
<td>4.8</td>
</tr>
</tbody>
</table>

[0098] The calcium form of the polyFAA beads of Example 4 was prepared by exposing the (sodium 2-fluoroacrylate)-divinylbenzene-1,7-octadiene copolymer to an excess of aqueous calcium chloride solution to yield insoluble cross-linked (calcium 2-fluoroacrylate)-divinylbenzene-1,7-octadiene copolymer. After the calcium ion exchange, the Ca(polyFAA) final product was washed with ethanol and water.

Example 6: Preparation of Sample A

[0099] In a 2L reactor with appropriate stirring and other equipment, a 180:10:10 weight ratio mixture of organic phase of monomers was prepared by mixing methyl 2-fluoroacrylate (-0.24 kg), 1,7-octadiene (-0.0124 kg), and divinylbenzene (-0.0124 kg). One
part of lauroyl peroxide (-0.0012 kg) was added as an initiator of the polymerization reaction. A stabilizing aqueous phase was prepared from water, polyvinyl alcohol, phosphates, sodium chloride, and sodium nitrite. The aqueous and monomer phases were mixed together under nitrogen at atmospheric pressure, while maintaining the temperature below 30°C. The reaction mixture was gradually heated while stirring continuously. Once the polymerization reaction has started, the temperature of the reaction mixture was allowed to rise to a maximum of 95°C. After completion of the polymerization reaction, the reaction mixture was cooled and the aqueous phase was removed. Water was added, the mixture was stirred, and the solid material was isolated by filtration, and then washed with water.

[00100] The polymerization reaction was repeated 5 more times, the polymer from the batches were combined together to yield about 1.7 kg of a crosslinked (methyl 2-fluoroacrylate)-divinylbenzene-1,7-octadiene polymer. The (methyl 2-fluoroacrylate)-divinylbenzene-1,7-octadiene polymer was hydrolyzed with an excess of aqueous sodium hydroxide and isopropanol solution at 65°C for 24 hours to yield (sodium 2-fluoroacrylate)-divinylbenzene-1,7-octadiene polymer. After hydrolysis, the solid was filtered and washed with water. The (sodium 2-fluoroacrylate)-divinylbenzene-1,7-octadiene polymer was exposed at room temperature to an excess of aqueous calcium chloride solution to yield insoluble cross-linked (calcium 2-fluoroacrylate)-divinylbenzene-1,7-octadiene polymer. After the calcium ion exchange, the Sample A-Ca product was washed with water and dried.

[00101] To prepare the sodium form of the polymer, ten grams of resin from above was placed in a 250 mL bottle, 200 ml of IN hydrochloric acid (HCl) was added, and the mixture was agitated by swirling for approximately 10 minutes. The beads were allowed to sediment, the supernatant was decanted, and the procedure was repeated. After decanting the acid, the beads were washed once with approximately 200 mL of water, then twice with 200 mL of 1M sodium hydroxide (NaOH) for approximately 10 minutes. The beads were then washed again with 200 mL of water and finally were transferred to a fritted funnel and washed (with suction) with 1 L of deionized water. The resulting cake was dried overnight at 60°C, resulting in Sample A-Na.

Example 7: Ex vivo potassium binding studies

[00102] Potassium binding by Sample A-Na and Sample A-Ca, from Example 6, was evaluated in ex vivo human fecal and colonic extracts. Two fecal samples, and one colonic sample obtained through use of a colostomy bag, were provided by three human volunteers. The
samples were centrifuged, and the resulting supernatant was isolated for use as a test medium in the binding study. Sample A in both sodium and calcium form was added to the extract samples at 20 mg/mL, and incubated for 24 hours at 37°C. Binding of potassium, as well as other cations present in the extracts was determined per gram of Sample A.

Both test agents were dried by lyophilization before use. The sodium form (Sample A-Na) bound and removed an average of 1.54 milliequivalents (mEq) of potassium per gram, while the calcium form (Sample A-Ca) bound an average of 0.85 mEq potassium per gram from the three extracts.

Fecal samples were supplied by two healthy male volunteers (subjects #1 and #2), ages 36 and 33, of Caucasian and Asian descent, respectively. Fecal samples were collected in one-gallon Ziploc bags and immediately mixed and transferred into centrifuge tubes. The colonic sample was provided by an 81-year-old Caucasian female donor (subject #3) through use of a colostomy bag. The colostomy bag contents were shipped on dry ice, thawed, mixed and transferred into centrifuge tubes. The fecal and colonic samples were centrifuged at 21,000 rpm for 20 hours at 4°C (Beckman JS-25.50 rotor in Beckman-Coulter Avanti J-E centrifuge). The resulting supernatant was pooled per subject, and filtered using a Nalgene 0.2 µm disposable filter unit. The fecal and colonic extracts were then either used fresh, or were frozen at -20°C until needed.

**Method to determine cation binding of Sample A in fecal and colonic extracts.**

Fecal and colonic extracts were thawed in a room temperature water bath and stirred on a magnetic stir plate. Penicillin G / Streptomycin (Gibco, 15140-122) (1/100 volume of 100x stock solution) and sodium azide (1/1000 volume of 10% stock solution) were added to each extract sample to discourage bacterial or fungal growth during the assay. Sample A-Na and Sample A-Ca were added to 16x100 mm glass tubes in duplicate, with each tube receiving 140 to 170 mg of dried, accurately weighed sample. While stirring, fecal or colonic extract was dispensed into the tubes to create a final concentration of 20 mg of test sample per mL of extract. Each extract was additionally dispensed into duplicate tubes containing no test sample. All tubes were sealed and incubated for 24 hours at 37°C, rotating on a rotisserie mixer. Following incubation, 25 µL of each sample was diluted into 475 µL of Milli-Q purified water (1:20 dilution). The diluted samples were then filtered by centrifugation at 13,200 rpm through Microcon YM-3 filter units (3000 MWCO) for 1 hour. Filtrates were transferred to a 1 mL 96-well plate and submitted for analysis of cation concentrations by ion chromatography.
[00106] Ion chromatography method for measurement of cation concentrations in fecal and colonic extracts. Cation concentrations in the fecal and colonic extract samples were analyzed using a strong cation exchange column set (Dionex CG16 50x5mm ID and CS16 250x5mm ID), on a Dionex ICS2000 system equipped with a Dionex WPS3000 auto sampler, DS3 conductivity flow cell and CSRS-Ultra II 4mm Suppressor. The ion chromatography detection method included an isocratic elution using 30 mM of methanesulfonic acid at a flow rate of 1 mL/minute, and the total run time was 30 minutes per sample.

[00107] Data Analysis. Cation binding was calculated as \((C_{\text{start}} - C_{\text{eq}}) / 20 \times \text{valency of the ion}\), where \(C_{\text{start}}\) is the starting concentration of cation in the fecal or colonic extract (in mM), \(C_{\text{eq}}\) is the concentration of cation remaining in the sample at equilibrium after exposure to the test agent (in mM), and 20 corresponds to the concentration of the test agent (in mg/mL). Multiplying by the valency of the ion (1 for potassium, ammonium and sodium; 2 for calcium and magnesium) gives a binding value expressed in milliequivalents (mEq) of ion bound per gram of test agent. All samples were tested in duplicate with values reported as an average (Avg), +/- standard deviation (SD).

Table 2.

<table>
<thead>
<tr>
<th>No.</th>
<th>Extract Sample</th>
<th>(C_{\text{start}}) (mM)</th>
<th>(C_{\text{eq}}) (mM)</th>
<th>(K^+) Binding (mEq/g)</th>
<th>(K^+) Binding in Individual Extracts</th>
<th>All Extract Samples Avg ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Avg</td>
<td>SD</td>
</tr>
<tr>
<td>Sample A-Na</td>
<td>Fecal, subject #1</td>
<td>92.7</td>
<td>65.3</td>
<td>1.37</td>
<td>1.33</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>Fecal, subject #2</td>
<td>106.6</td>
<td>73.9</td>
<td>1.64</td>
<td>1.63</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>Colonic, subject #3</td>
<td>128.8</td>
<td>93.9</td>
<td>1.74</td>
<td>1.67</td>
<td>0.10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>96.6</td>
<td>1.61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample A-Ca</td>
<td>Fecal, subject #1</td>
<td>92.7</td>
<td>77.8</td>
<td>0.75</td>
<td>0.77</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>Fecal, subject #2</td>
<td>106.6</td>
<td>90.2</td>
<td>0.82</td>
<td>0.82</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>Colonic, subject #3</td>
<td>128.8</td>
<td>109.0</td>
<td>0.99</td>
<td>0.97</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>109.7</td>
<td>0.96</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[00108] Potassium binding in mEq/g was determined for calcium- and sodium-loaded Sample A following a 24-hour incubation in two human fecal extracts and one colonic extract. Initial potassium levels in the three extract samples ranged from 92.7 mM to 128.8 mM. With
the addition of 20 mg/ml of sodium-loaded Sample A-Na, the potassium concentration in the extracts was reduced by approximately 28%. The potassium bound per gram of polymer averaged 1.54 mEq/g. Calcium-loaded Sample A-Ca bound an average of 0.85 mEq/g.

Example 8: Pig model cation binding studies

[00109] Pigs with normal renal function were used as a model to assess the pharmacological effects of Ca(polyFAA) in binding and removing potassium from the gastrointestinal tract. A pig model is used based on the well known similarities between the pig and human gastrointestinal tracts. The pigs were fed a diet supplemented with Ca(polyFAA) at a concentration of 1 gram per kilogram of body weight per day. As a control, pigs were fed the diet without Ca(polyFAA).

[00110] Materials. Ca(polyFAA) was synthesized using a method similar to that described in Example 6 and used in its calcium form. Ferric oxide (purchased from Fisher Scientific), lot number 046168, was added as an indigestible marker. The ferric oxide was used as a daily visible marker to determine the passage rate of the digesta through the gastrointestinal tract of each animal.

[00111] Animals. Fourteen approximately nine-week old grower barrows (Camborough 15 or 22 dams x Terminal Sire boars; PIC Canada Inc.) weighing approximately 25 kg were used in this study. At the start of the experiment, fourteen pigs were weighed and randomized by weight into control and treatment groups. The experiment was divided into two feeding periods. The first period was the acclimation period, days (D(-7) to D(-1)), and the second was the test period, (D(I) to D(9)).

[00112] Before the acclimation period, the pigs were fed a standard production diet. During the acclimation period, pigs were progressively offered increasing amounts of the control diet as a ratio to a standard production grower diet.

[00113] On the same day the pigs were fed the ferric oxide, the seven test pigs were switched to the test diet. The control pigs remained on the control (acclimation) diet. The test diet was fed for ten days (D(I) to D(IO)). Throughout the entire study, daily feed allowance for individual pigs was divided in two equal sizes and offered at approximately 08:30 and 15:30. The pigs were trained to clean up their daily feed allowance once it was provided; any feed that was not eaten was weighed and removed before the next feeding.

[00114] Urine Collection. Urine collection began with the offering of the ferric oxide bolus on D(I). Each day's sample was kept separate for each pig. Following the completion of
urine collection, the daily samples for each pig were thawed, mixed well and sub-sampled. The sub-sample of at least 10 mL of each pig’s 24-hour sample was analyzed for electrolyte concentrations as described below.

[F00115] Fecal Collections. Fecal collection began with the offering of the ferric oxide bolus on D(I). Each day’s sample was kept separate for each pig.

[F00116] Urine electrolytes. Urine samples were thawed, diluted 30 fold in 50 mM hydrochloric acid and then filtered (Whatman 0.45 micron PP filter plate, 1000xg for 10 minutes). The cation concentrations in these urine samples were analyzed using a strong cation exchange column set (Dionex CG16 50x5mm ID and CS16 250x5mm ID), on a Dionex ICS2000 system equipped with a Dionex AS50 auto sampler, DS3 conductivity flow cell and CSRS-Ultra II 4mm Suppressor. The ion chromatography detection method included an isocratic elution using 31 mM methanesulfonic acid at a flow rate of 1mL/minute, and the total run time was 33 minutes per sample.

[F00117] Fecal electrolytes. To a 15mL conical tube, 200mg of feces and 10mL of 1M hydrochloric acid was added. The fecal mixture was incubated for approximately 40 hours on a rotisserie mixer at room temperature. A sample of fecal supernatant was isolated after centrifugation (2000xg, 15 minutes) and then filtered (Whatman 0.45 micron PP filter plate, 1000xg for 10 minutes). The filtrate was diluted 2 fold with Milli-Q water.

[F00118] Diluted filtrate cation content was measured by inductively coupled plasma optical emission spectrometry (ICP-OES) using a Thermo Intrepid II XSP Radial View. Samples were infused into the spray chamber using a peristaltic pump and CETAC ASX-510 autosampler. An internal standard, yttrium (10ppm in 1M hydrochloric acid), was employed for correcting variation in sample flow as well as plasma conditions. The emission line that was used for quantifying potassium was 7664nm (internal standard 437.4nm).

[F00119] Data Analysis. Fecal electrolytes were calculated in milliequivalents per day (mEq/day) using the following equation:

\[
\text{mEq/day} = \left(\frac{\text{mEq/L electrolyte x assay volume}}{\text{grams feces in assay}}\right) \times \left(\frac{\text{Total feces ferams}}{\text{Day}}\right)
\]

In the above equation, mEq/L electrolyte was the concentration of an electrolyte reported by ICP spectrometry after adjusting for dilution factor and valence, and total feces per day was the amount, in grams, of feces collected in a 24 hour period after lyophilization.
Urinary electrolytes were calculated in mEq electrolyte excreted per day (mEq/day) using the following equation: (mEq electrolyte per L) * (24 hour urine volume). Data was presented using means ± standard deviation, and/or by scatter plot. Statistical analysis was performed in GraphPad Prism, version 4.03. For urine and fecal analyses, probability (p) values were calculated using a two-tailed t-test to compare the Ca(polyFAA) treated group to the non-treatment control group. Statistical significance is indicated if the calculated p value is less than 0.05.

For fecal analysis, the mean result from each group was determined by averaging the combined mEq/day electrolyte values from treatment days three through day eight for each animal and then averaging this result for each treatment group. This methodology was also employed for urinary electrolytes, but the average for each animal was from treatment (1) through day (8).

**GI Transit Time.** The transit times of the ferric oxide marker dosed on day (1) of the study, based on the appearance of red in the feces is shown in Table 3. In no pig was the transit time greater than 60 hours. Therefore, feces from day 3 onward were assessed for cation content.

Table 3. Transit time of Ferric Oxide

<table>
<thead>
<tr>
<th>Transit Time of Ferric Oxide</th>
<th>Average (hours)</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>hours to first appearance</td>
<td>23.9</td>
<td>11.3</td>
</tr>
<tr>
<td>hours to last appearance</td>
<td>54.6</td>
<td>5.2</td>
</tr>
</tbody>
</table>

**Fecal Electrolytes.** On day 1, the baseline fecal cations were measured in samples collected before the presence of ferric oxide was seen in the feces. Baseline fecal potassium values are summarized in Table 4. Fecal potassium values for treatment days 3-8 are summarized in Table 5. The Ca(polyFAA) treated pigs had significantly higher levels of fecal potassium excretion than the non-treatment group (p<0.05).

Table 4. Fecal ELECTROLYTES, BASELINE (day 1)

<table>
<thead>
<tr>
<th></th>
<th>Potassium mEq/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-treatment</td>
<td>31.2 ± 5.5</td>
</tr>
<tr>
<td>Ca(polyFAA)</td>
<td>27.0 ± 7.2</td>
</tr>
<tr>
<td>p*</td>
<td>ns</td>
</tr>
</tbody>
</table>

*p values calculated using a two-tailed t-test
ns= not statistically significant

Table 5. Fecal Electrolytes, Average (days 3-8)

<table>
<thead>
<tr>
<th></th>
<th>Potassium mEq/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-treatment</td>
<td>37.4 ± 7.8</td>
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<tr>
<td>Ca(polyFAA)</td>
<td>45.3 ± 5.3</td>
</tr>
</tbody>
</table>

*p values calculated using a two-tailed t-test

Table 6. Urine Electrolytes, Average (days 1-8)

<table>
<thead>
<tr>
<th></th>
<th>Potassium mEq/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-treatment</td>
<td>88.9 ± 15.5</td>
</tr>
<tr>
<td>Ca(polyFAA)</td>
<td>71.8 ± 9.7</td>
</tr>
</tbody>
</table>

*p values calculated using a two-tailed t-test

Example 9: Synthesis of crosslinked (calcium 2-fluoroacrylate)-divinylbenzene-1,7-octadiene polymer.

Methyl 2-fluoroacrylate (MeFA) was purchased and was vacuum distilled before use. Divinylbenzene (DVB) was purchased from Aldrich, technical grade, 80%, mixture of isomers, and was used as received. 1,7-octadiene (ODE), lauroyl peroxide (LPO), polyvinyl alcohol (PVA) (typical molecular weight 85,000-146,000, 87-89% hydrolyzed), sodium chloride (NaCl), sodium phosphate dibasic heptahydrate (Na$_2$HPO$_4$·7H$_2$O) and sodium phosphate monobasic monohydrate (NaH$_2$PO$_4$·H$_2$O) were purchased from commercial sources and used as received.

In an appropriately sized reactor with appropriate stirring and other equipment, a 90:5:5 weight ratio mixture of organic phase of monomers was prepared by mixing methyl 2-fluoroacrylate, 1,7-octadiene, and divinylbenzene. One-half part of lauroyl peroxide was added as an initiator of the polymerization reaction. A stabilizing aqueous phase was prepared from water, polyvinyl alcohol, phosphates, sodium chloride, and sodium nitrite. The aqueous and monomer phases were mixed together under nitrogen at atmospheric pressure, while maintaining the temperature below 30°C. The reaction mixture was gradually heated while stirring.

Urine electrolytes. No baseline urine electrolyte measurements were taken. Urine electrolyte values for treatment days 1-8 are summarized in Table 6.
continuously. Once the polymerization reaction has started, the temperature of the reaction mixture was allowed to rise to a maximum of 95°C.

After completion of the polymerization reaction, the reaction mixture was cooled and the aqueous phase was removed. Water was added, the mixture was stirred, and the solid material was isolated by filtration. The solid was then washed with water to yield a crosslinked (methyl 2-fluoroacrylate)-divinylbenzene-l,7-octadiene polymer. The (methyl 2-fluoroacrylate)-divinylbenzene-l,7-octadiene copolymer was hydrolyzed with an excess of aqueous sodium hydroxide solution at 90°C for 24 hours to yield (sodium 2-fluoroacrylate)-divinylbenzene-l,7-octadiene polymer. After hydrolysis, the solid was filtered and washed with water. The (sodium 2-fluoroacrylate)-divinylbenzene-l,7-octadiene polymer was exposed at room temperature to an excess of aqueous calcium chloride solution to yield insoluble cross-linked (calcium 2-fluoroacrylate)-divinylbenzene-l,7-octadiene polymer.

After the calcium ion exchange, the wet polymer is slurried with 25-30 % w/w aqueous solution of sorbitol at ambient temperature to yield sorbitol-loaded polymer. Excess sorbitol is removed by filtration. The resulting polymer is dried at 20-30°C until the desired moisture content (10-25 w/w%) is reached. This provides a sorbitol loaded, cross-linked (calcium 2-fluoroacrylate)-divinylbenzene-l,7-octadiene polymer.

When introducing elements of the present invention or the embodiments(s) thereof, the articles "a", "an", "the" and "said" are intended to mean that there are one or more of the elements. The terms "comprising", "including" and "having" are intended to be inclusive and mean that there may be additional elements other than the listed elements.

In view of the above, it will be seen that the several objects of the invention are achieved and other advantageous results attained.

As various changes could be made in the above compositions and methods without departing from the scope of the invention, it is intended that all matter contained in the above description shall be interpreted as illustrative and not in a limiting sense.
WHAT IS CLAIMED IS:

1. A crosslinked cation exchange polymer comprising a reaction product of a polymerization mixture comprising three or more monomers, the monomers corresponding to Formula 11, Formula 22, and Formula 33;

   wherein
   
   (i) the monomers corresponding to Formula 11 constitute at least about 85 wt.% based on the total weight of monomers of Formulae 11, 22, and 33 in the polymerization mixture, and the weight ratio of the monomer corresponding to Formula 22 to the monomer corresponding to Formula 33 is from about 4:1 to about 1:4, or
   
   (ii) the mole fraction of the monomer of Formula 11 in the polymerization mixture is at least about 0.87 based on the total number of moles of the monomers of Formulae 11, 22, and 33, and the mole ratio of the monomer of Formula 22 to the monomer of Formula 33 in the polymerization mixture is from about 0.2:1 to about 7:1, and

   Formula 11, Formula 22, and Formula 33 correspond to the following structures:

   \[
   \text{Formula 11:} \quad R_1, R_2, A_{11}, F \\
   \text{Formula 22:} \quad X_1 \\
   \text{Formula 33:} \quad X_2
   \]

   wherein
   
   R_i and R_2 are each independently hydrogen, alkyl, cycloalkyl, or aryl;
   
   A_n is an optionally protected carboxylic, phosphonic, or phosphoric;
   
   X_i is arylene; and
   
   X_2 is alkylene, an ether moiety or an amide moiety.

2. The polymer of claim 1 wherein Formula 11, Formula 22, and Formula 33 correspond to the following structures:
3. The polymer of claim 1 wherein Aₙ is protected carboxylic, phosphonic, or phosphoric.

4. The polymer of any one of claims 1 to 3 wherein the polymerization mixture further comprises a polymerization initiator.

5. A crosslinked cation exchange polymer in an acid or salt form, the cation exchange polymer comprising a reaction product of the crosslinked polymer of any one of claims 1 to 4 and a hydrolysis agent.

6. The polymer of any one of claims 1 to 5 wherein Aₙ is carboxylic, phosphonic, or phosphoric.

7. The polymer of any one of claims 1 to 6 wherein the polymerization mixture does not comprise a polymerization initiator.

8. A crosslinked cation exchange polymer comprising structural units corresponding to Formulae 1, 2, and 3, wherein

   (i) the structural units corresponding to Formula 1 constitute at least about 85 wt.% based on the total weight of structural units of Formulae 1, 2, and 3 in the polymer, calculated from the amounts of monomers used in the polymerization reaction, and the weight ratio of the structural unit corresponding to Formula 2 to the structural unit corresponding to Formula 3 is from about 4:1 to about 1:4, or

   (ii) the mole fraction of the structural unit of Formula 1 in the polymer is at least about 0.87 based on the total number of moles of the structural units of Formulae 1, 2, and 3, calculated from the amounts of monomers used in the polymerization reaction, and the mole
ratio of the structural unit of Formula 2 to the structural unit of Formula 3 is from about 0.2:1 to about 7:1, and

Formula 1, Formula 2, and Formula 3 correspond to the following structures:

![Chemical Structures](image)

wherein

- $R_1$ and $R_2$ are independently hydrogen, alkyl, cycloalkyl, or aryl;
- $A_1$ is carboxylic, phosphonic, or phosphoric, in its salt or acid form;
- $X_1$ is arylene;
- $X_2$ is alkylene, an ether moiety or an amide moiety.

9. The polymer of claim 3 wherein Formula 1, Formula 2 and Formula 3 correspond to the following structures:

![Chemical Structures](image)

10. The polymer of any one of claims 1 and 3 to 8 wherein $X_2$ of Formulae 3 or 33 is either (a) an ether moiety selected from either $-(CH_2)_d-O-(CH_2)_e$ or $-(CH_2)_d-O-(CH_2)_e-O-(CH_2)_d$- wherein $d$ and $e$ are independently an integer of 1 through 5, or (b) an amide moiety of the formula $-C(O)-NH-(CH_2)_p-NH-C(O)$- wherein $p$ is an integer of 1 through 8, or (c) Formulae 3 or 33 is a mixture of structural units having the ether moiety and the amide moiety.

11. The polymer of claim 10 wherein $X_2$ is the ether moiety, $d$ is an integer from 1 to 2, and $e$ is an integer from 1 to 3.
12. The polymer of claim 10 wherein $X_2$ is the amide moiety and $p$ is an integer of 4 to 6.

13. The polymer of any one of claims 1 and 3 to 8 wherein $X_2$ is alkylene.

14. The polymer of claim 13 wherein $X_2$ is ethylene, propylene, butylene, pentylene, or hexylene.

15. The polymer of claim 13 wherein $X_2$ is butylene.

16. The polymer of any one of claims 1, 3 to 8 and 10 to 15 wherein $X_i$ is phenylene.

17. The polymer of any one of claims 1, 3 to 8 and 10 to 16 wherein $R_1$ and $R_2$ are hydrogen.

18. The polymer of any one of claims 1, 3 to 8 and 10 to 17 wherein $A_n$ is protected carboxylic.

19. The polymer of claim 18 wherein protected carboxylic is -C(O)O-alkyl.

20. The polymer of any one of claims 5 and 10 to 19 wherein the hydrolysis agent is a strong base.

21. The polymer of claim 20 wherein the strong base is sodium hydroxide, potassium hydroxide, magnesium hydroxide, calcium hydroxide, or a combination thereof.

22. The polymer of any one of claims 1 to 5 and 10 to 21 wherein the weight ratio of the monomer of Formula 22 to the monomer of Formula 33 in the crosslinked cation exchange polymer is from about 2:1 to 1:2.

23. The polymer of any one of claims 1 to 5 and 10 to 21 wherein the weight ratio of the monomer of Formula 22 to the monomer of Formula 33 in the crosslinked cation exchange polymer is about 1:1.

24. The polymer of any one of claims 1 to 5 and 10 to 21 wherein the mole ratio of the monomer of Formula 22 to the monomer of Formula 33 in the crosslinked cation exchange polymer is from 0.2:1 to 3.5:1.
25. The polymer of any one of claims 1 to 5 and 10 to 21 wherein the mole ratio of the monomer of Formula 22 to the monomer of Formula 33 in the crosslinked cation exchange polymer is from about 0.5:1 to about 1.3:1.

26. The polymer of any one of claims 8 to 21 wherein the mole ratio of the structural unit of Formula 2 to the structural unit of Formula 3 in the crosslinked cation exchange polymer is from 0.2:1 to 3.5:1.

27. The polymer of any one of claims 8 to 21 wherein the mole ratio of the structural unit of Formula 2 to the structural unit of Formula 3 in the crosslinked cation exchange polymer is from about 0.5:1 to about 1.3:1.

28. The polymer of any one of claims 1 to 27 wherein the cation of the salt is calcium, sodium, or a combination thereof.

29. The polymer of claim 28, wherein the cation of the salt is calcium.

30. A pharmaceutical composition comprising a crosslinked cation exchange polymer of any one of claims 1 to 29 and a pharmaceutically acceptable excipient.

31. A method of making a crosslinked cation exchange polymer comprising contacting a mixture comprising three or more monomers to form the crosslinked cation exchange polymer, the monomers corresponding to Formula 11, Formula 22, and Formula 33; wherein

(i) the monomers corresponding to Formula 11 constitute at least about 85 wt.% based on the total weight of monomers of Formulae 11, 22, and 33 in the polymerization mixture, and the weight ratio of the monomer corresponding to Formula 22 to the monomer corresponding to Formula 33 is from about 4:1 to about 1:4, or

(ii) the mole fraction of the monomer of Formula 11 in the polymerization mixture is at least about 0.87 based on the total number of moles of the monomers of Formulae 11, 22, and 33, and the mole ratio of the monomer of Formula 22 to the monomer of Formula 33 in the polymerization mixture is from about 0.2:1 to about 7:1, and

Formula 11, Formula 22, and Formula 33 correspond to the following structures:
wherein

$R_i$ and $R_2$ are each independently hydrogen, alkyl, cycloalkyl, or aryl;

$A_n$ is an optionally protected carboxylic, phosphonic, or phosphoric;

$X_i$ is arylene; and

$X_2$ is alkylene, an ether moiety or an amide moiety.

32. The method of claim 31 wherein Formulae 11, 22, and 33 correspond to the following structures:
33. The method of claim 31 or 32 further comprising hydrolyzing the crosslinked cation exchange polymer with a hydrolysis agent.

34. The method of claim 31 or 32 wherein the polymerization yield is at least about 85%.

35. The method of claim 33 wherein the yield after a hydrolysis step is at least about 85%.

36. The method of any one of claims 31 to 35 wherein An is carboxylic, phosphonic, or phosphoric.

37. The method of any one of claims 31 to 36 wherein the polymerization mixture does not comprise a polymerization initiator.

38. A crosslinked cation exchange polymer or a pharmaceutical composition for removing potassium from the gastrointestinal tract wherein the therapy comprises administering a pharmaceutical composition of claim 30 or a polymer of any one of claims 1 to 29 to an animal subject in need thereof, whereby the pharmaceutical composition or the polymer passes through the gastrointestinal tract of the subject, and removes a therapeutically effective amount of potassium ion from the gastrointestinal tract of the subject.

39. The polymer or composition of claim 38 wherein the animal subject is a mammal and the polymer of any one of claims 1 to 29 is administered to the subject.

40. The polymer or composition of claim 38 or 39 wherein the subject suffers from chronic kidney disease.

41. The polymer or composition of claim 38 or 39 wherein the subject suffers from congestive heart failure.

42. The polymer or composition of claim 40 or 41 wherein the subject is undergoing dialysis.

43. The polymer or composition of any one of claims 38 to 42 wherein the subject is experiencing hyperkalemia.
44. The polymer or composition of any one of claims 38 to 43 wherein the subject is a human.

45. The polymer or composition of any one of claims 38 to 44 wherein the potassium-binding polymer is administered in a dose of about 10 grams/day to about 30 grams/day.

46. The polymer or composition of claim 44 or 45 wherein the human is being treated with an agent that causes potassium retention.

47. The polymer or composition of claim 46 wherein the potassium-binding polymer and the agent that causes potassium retention are administered simultaneously.

48. The polymer or composition of claim 46 or 47 wherein the agent that causes potassium retention is an angiotensin-converting enzyme inhibitor.

49. The polymer or composition of claim 48 wherein the angiotensin-converting enzyme inhibitor is captopril, zofenopril, enalapril, ramipril, quinapril, perindopril, lisinopril, benazipril, fosinopril, or a combination thereof.

50. The polymer or composition of claim 46 or 47 wherein the agent that causes potassium retention is an angiotensin receptor blocker.

51. The polymer or composition of claim 49 wherein the angiotensin receptor blocker is candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan, or a combination thereof.

52. The polymer or composition of claim 46 or 47 wherein the agent that causes potassium retention is an aldosterone antagonist.

53. The polymer or composition of claim 52 wherein the aldosterone antagonist is spironolactone, eplerenone, or a combination thereof.