



(51) International Patent Classification:  
C07F 5/02 (2006.01) A61K 31/69 (2006.01)

(21) International Application Number:  
PCT/US2020/051499

(22) International Filing Date:  
18 September 2020 (18.09.2020)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
62/903,332 20 September 2019 (20.09.2019) US

(71) Applicant: GLYSCEND, INC. [US/US]; 1812 Ashland Avenue, 1st Floor-Suite 100, Baltimore, Maryland 21205 (US).

(72) Inventors: JOZEFIAK, Thomas Henry; 27 Clover Avenue, Belmont, Massachusetts 02478 (US). NIM-GAONKAR, Ashish; 2945 Excelsior Springs Ct, Ellicott City, Maryland 21042 (US). POLOMOSCANIK, Steven C.; 49 Ponderosa Avenue, Methuen, Massachusetts 01844 (US).

(74) Agent: UNDERWOOD, Robert H.; HOGAN LOVELLS US LLP, 125 High Street, Suite 2010, Boston, MA 02110 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW,

SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

Published:

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

(54) Title: BENZOXABOROLE POLYMERS AND METHODS OF USE

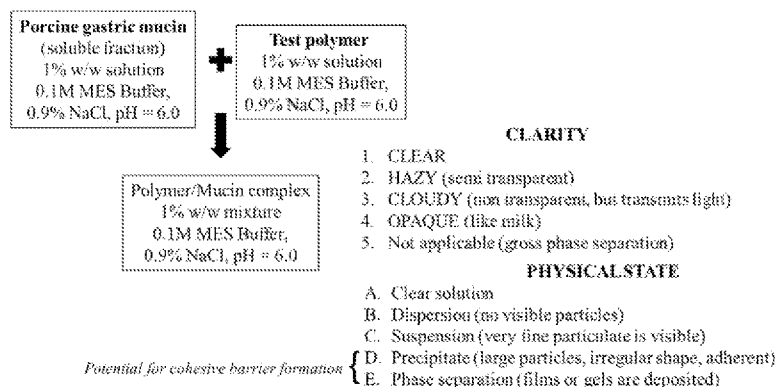


FIG. 1

(57) Abstract: The disclosure relates to benzoxaborole containing polymers and to methods of using the same to treat metabolic and gastrointestinal disorders.



## BENZOXABOROLE POLYMERS AND METHODS OF USE

### RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 62/903,332 filed on September 20, 2019, the entire disclosure of which is incorporated herein by reference.

### BACKGROUND OF THE INVENTION

[0002] Type-2 diabetes mellitus (T2DM) affects about 11.3% of the U.S. adult population, with 35% of the U.S. adults having pre-diabetic symptoms. U.S. healthcare costs due to diabetes are approaching \$200 billion annually. The incidence of T2DM continues to increase in parallel with the obesity epidemic, and a major portion of present treatment for T2DM consists of a regimen of oral medications that may be suboptimal for many subjects, in part because of side effects associated with systemic absorption of their medication. Bariatric surgery to bypass or exclude the duodenum from the digestive tract has been shown to improve T2DM. The Diabetes Surgery Summit recommends bariatric surgery to treat T2DM in some obese patients (grade III obesity), and that bariatric surgery should be considered for treatment of other patients. (See, e.g., Koliaki, C. et al., *BMC Endocr Disord.* (2017) 17:50 DOI 10.1186/s12902-017-0202-6.)

[0003] Analysis of the typical diabetic patient's path from first line drugs to insulin and on to surgery and other highly invasive treatments reveals striking gaps, not limited to ineffective treatments and clinical inertia. Surgery and other solutions also have failed to achieve widespread adoption. The addition of specialist clinicians in the care pathway has contributed to those failures. Accordingly, an effective treatment in the hands of the primary care physician would likely reach a much larger segment of the subject population than those which require a specialist, such as an endocrinologist, a gastroenterologist, or a surgeon, and would therefore have much greater impact.

[0004] WO 2017/024237 discloses certain cationic polymers and use of the polymers for complexing mucus to form an occlusive barrier in the duodenum.

[0005] A need therefore exists for new medications and non-invasive methods for treating subjects with T2MD and related metabolic disorders.

### SUMMARY OF THE INVENTION

[0006] The invention provides polymer compositions for forming a physical barrier in the gastrointestinal (GI) tract of a subject between the intestinal lining and the luminal contents. The polymers of the invention are mucin-interacting agents which form a physical barrier in-situ by interaction with resident mucin in the GI tract.

[0007] The inventors have discovered that the incorporation of pendant benzoxaborole groups into certain cationic polymers can dramatically improve the mucin-complexing activity of the polymers.

[0008] As shown in the examples, the polymers described herein have improved mucin and mucus complexing activity in comparison to comparable cationic polymers, and can effectively condense mucin and mucus at the pH of the duodenum. The polymers bind tightly to mucus at the pH of the duodenum and once bound to mucus are resistant to removal by high concentrations of salts (e.g., 1M NaCl). The resulting polymer-mucus complexes have dramatically different properties in comparison to free mucus. Without wishing to be bound by any particular theory or mechanism, these data demonstrate that the polymers are capable of complexing mucus in the duodenum to form an occlusive, non-absorbed luminal barrier when orally administered. The formation of the duodenal occlusive barrier is functionally similar or equivalent to bypassing, excluding, or ablating the duodenum by surgical or endoscopic procedures, and results in improved glucose homeostasis. (See, e.g., Koliaki, C. et al., BMC Endocr Disord. (2017) 17:50 DOI 10.1186/s12902-017-0202-6.)

[0009] This disclosure relates to cationic polymers that contain pendant benzoxaborole groups, which are bonded directly or indirectly to the polymer backbone through a covalent bond, and to a method of treating metabolic diseases that include administering a therapeutically effective amount of such a polymer to a subject in need thereof.

[0010] Another aspect of the invention is a pharmaceutical composition comprising the polymers of the present invention, along with a carrier or diluent. The pharmaceutical composition can be used for therapy, such as in the treatment of a disorder described herein. Similarly, the invention provides for the use of a polymer disclosed herein as a medicament and for the use of a polymer disclosed herein in the manufacture of a medicament for the treatment of a disorder described herein.

#### **BRIEF DESCRIPTION OF THE DRAWINGS**

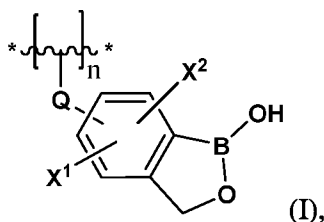
[0011] FIG. 1 illustrates the mucin complexing assay.

#### **DETAILED DESCRIPTION OF THE INVENTION**

[0012] This disclosure relates to cationic polymers that contain pendant benzoxaborole groups, which are bonded directly or indirectly to the polymer backbone through a covalent bond. The cationic polymers are preferably polycations that include amine- or ammonium containing repeat units, and if desired may contain other cationic groups such as imidazolyl, pyridinyl, and guanidino. The cationic polymers preferably contain both cationic repeat units and benzoxaborole repeat units. The pendant benzoxaborole group is substituted with one or more suitable substituents, which include electron withdrawing groups, electron donating groups, as described herein. In some embodiments the polymers may contain a repeat unit that contains a cationic group and a benzoxaborole group. The cationic polymers can be co-polymers that also contain any desired neutral or anionic repeat units, as further described herein, provided that the polymer retains a net cationic charge.

[0013] Pharmaceutical compositions comprising these polymers and methods of treatment using these polymers to treat metabolic disorders, such as Type-2 diabetes mellitus (T2DM), Type-1 diabetes mellitus (T1DM), prediabetes, hyperlipidemia, obesity, overweight, metabolic syndrome, non-alcoholic steatohepatitis, non-alcoholic fatty liver and polycystic ovary syndrome (PCOS) are also disclosed.

[0014] Exemplary polymers comprise a pendant benzoxaborole containing repeat unit of Formula (I)



[0015]

[0016] wherein

[0017] \*~~~~\* is a polymer repeat unit;

[0018] Q is a direct bond or a linker;

[0019]  $X^1$  and  $X^2$  are independently selected from a group consisting of hydrogen, halo,  $-CN$ ,  $-NO_2$ ,  $-CF_3$ ,  $-SO_2CF_3$ ,  $-SO_3(R^1)$ ,  $-SO_2(R^1)$ ,  $-N^+(R^1)(R^2)(R^3)$ ,  $-CON(R^1)(R^2)$ ,  $-COO(R^1)$ , substituted or unsubstituted alkyl,  $-NHCO(R^1)$ ,  $-(CH_2)_m-N(R^1)(R^2)$ ,  $-OCO(R^1)$  and  $-O(R^1)$ ;

[0020]  $R^1$ ,  $R^2$  and  $R^3$  in each occurrence are independently hydrogen or substituted or unsubstituted alkyl (preferably a substituted or unsubstituted  $C_1$ - $C_6$  alkyl);

[0021] n is an integer from 1 to 100,000 and

[0022] m is an integer from 0 to 4.

[0023] In some embodiments of Formula (I),  $X^1$  is halo,  $-CN$ ,  $-NO_2$ ,  $-CF_3$ ,  $-SO_2CF_3$ ,  $-SO_3(R^1)$ ,  $-SO_2(R^1)$ ,  $-N^+(R^1)(R^2)(R^3)$ ,  $-CON(R^1)(R^2)$  or  $-COO(R^1)$ , and  $X^2$  is hydrogen.

[0024] In some embodiments of Formula (I),  $X^1$  is substituted or unsubstituted alkyl,  $-NHCO(R^1)$ ,  $-(CH_2)_m-N(R^1)(R^2)$ ,  $-OCO(R^1)$  or  $-O(R^1)$ , and  $X^2$  is hydrogen.

[0025] In some embodiments of Formula (I),  $X^1$  is halo, preferably fluoro and  $X^2$  is hydrogen.

[0026] In some embodiments of Formula (I),  $X^1$  is halo, preferably fluoro and

$X^2$  is halo, preferably fluoro.

[0027] In some embodiments of Formula (I),  $X^1$  is  $-CF_3$ , and  $X^2$  is hydrogen.

[0028] In some embodiments of Formula (I),  $X^1$  is hydrogen, and  $X^2$  is hydrogen.

[0029] It is advantageous to have substituents such as  $-F$ ,  $-Cl$ ,  $-CN$ ,  $-NO_2$ ,  $-CF_3$ ,  $-SO_2CF_3$ ,  $-SO_3(R^1)$ ,  $-SO_2(R^1)$ ,  $-N^+(R^1)(R^2)(R^3)$ ,  $-CON(R^1)(R^2)$  and  $-COO(R^1)$  on the benzoxaborole as these groups are electron withdrawing by nature and can lower the pKa of the benzoxaborole.

[0030] Without wishing to be bound by any particular theory, it is believed that certain substituted benzoxaborole polymers have a lower pKa than unsubstituted benzoxaborole polymers which lead to greater sensitivity to the pH increase between the stomach and duodenum, enhancing the mucin-complexing activity of the polymers at the desired site of barrier formation.

[0031] In some aspects, the polymer contains a repeat unit of Formula (I) and Q is a direct bond and  $X^1$ ,  $X^2$  and n are as described above.

[0032] In other aspects, the polymer contains a repeat unit of Formula (I) and Q is a linker selected from a group consisting of  $-N(R^1)-(CH_2)_m-$ ,  $-(CH_2)_m-N(R^1)-C(O)-$ ,  $-C(O)-N(R^1)-$ ,  $-C(O)-(CH_2)_m-$ ,  $-C(O)-N(R^1)-(CH_2)_m-N(R^1)-$ ,  $-(CH_2)_m-$ ,  $-O-(CH_2)_m-$ ,  $-S-(CH_2)_m-$ , and  $-OC(O)-(CH_2)_m-$  and  $X^1$ ,  $X^2$ , m and n are as described above.

[0033] In some aspects, the polymer contains a repeat unit of Formula (I),  $X^1$ ,  $X^2$  and n are as described above and Q is  $-N(R^1)-(CH_2)_m-$ , wherein m is 0 or 1 and  $R^1$  is preferably hydrogen.

[0034] In some aspects, the polymer contains a repeat unit of Formula (I),  $X^1$ ,  $X^2$  and n are as described above and Q is  $-NH-$ .

[0035] In some aspects, the polymer contains a repeat unit of Formula (I),  $X^1$ ,  $X^2$  and n are as described above and Q is  $-NH-CH_2-$ .

[0036] In some aspects, the polymer contains a repeat unit of Formula (I),  $X^1$ ,  $X^2$  and  $n$  are as described above and  $Q$  is  $-(CH_2)_m-N(R^1)-C(O)-$ , wherein  $m$  is 0 or 1 and  $R^1$  is preferably hydrogen.

[0037] In some aspects, the polymer contains a repeat unit of Formula (I),  $X^1$ ,  $X^2$  and  $n$  are as described above and  $Q$  is  $-NH-C(O)-$ .

[0038] In some aspects, the polymer contains a repeat unit of Formula (I),  $X^1$ ,  $X^2$  and  $n$  are as described above and  $Q$  is  $-CH_2-NH-C(O)-$ .

[0039] In some aspects, the polymer contains a repeat unit of Formula (I),  $X^1$ ,  $X^2$  and  $n$  are as described above and  $Q$  is  $-C(O)-N(R^1)-$ , wherein  $R^1$  is preferably hydrogen.

[0040] In some aspects, the polymer contains a repeat unit of Formula (I),  $X^1$ ,  $X^2$  and  $n$  are as described above and  $Q$  is  $-C(O)-NH-$ .

[0041] In some aspects, the polymer contains a repeat unit of Formula (I),  $X^1$ ,  $X^2$  and  $n$  are as described above and  $Q$  is  $-C(O)-(CH_2)_m-$ , wherein  $m$  is 0 or 1.

[0042] In some aspects, the polymer contains a repeat unit of Formula (I),  $X^1$ ,  $X^2$  and  $n$  are as described above and  $Q$  is  $-C(O)-CH_2-$ .

[0043] In some aspects, the polymer contains a repeat unit of Formula (I),  $X^1$ ,  $X^2$  and  $n$  are as described above and  $Q$  is  $-C(O)-N(R^1)-(CH_2)_m-N(R^1)-$ , wherein  $m$  is 0 or 1 and  $R^1$  is preferably hydrogen.

[0044] In some aspects, the polymer contains a repeat unit of Formula (I),  $X^1$ ,  $X^2$  and  $n$  are as described above and  $Q$  is  $-C(O)-NH-CH_2-NH-$ .

[0045] In some aspects, the polymer contains a repeat unit of Formula (I),  $X^1$ ,  $X^2$  and  $n$  are as described above and  $Q$  is  $-(CH_2)_m-$ ,  $-O-(CH_2)_m-$ ,  $-S-(CH_2)_m-$ , and  $-OC(O)-(CH_2)_m-$  and  $m$  is an integer from 0 to 4.

[0046] In some aspects, the polymer repeat unit comprises of cationic repeat units, amine-functionalized repeat units and repeat units that contain nitrogen.

[0047] In some aspects, the polymer repeat unit comprises of cationic repeat units.

[0048] In some aspects, the polymer repeat unit comprises of amine-functionalized repeat units.

[0049] In some aspects, the polymer repeat unit comprises of repeat units that contain nitrogen.

[0050] Suitable cationic polymers that can be modified to include pendant benzoxaborole groups include: vinylic polyamines, polyethyleneimines, acrylamido-based polyamines, chitosan, chemically modified chitosan derivatives such as thiolated chitosan, polyamidoamine (PANAM) dendrimers, poly(vinylpyridine), poly(vinylimidazole), and poly(vinyl aniline).

[0051] Vinylic polyamines that can be modified to include pendant benzoxaborole groups include: poly(allylamine) (PAA), poly(diallylamine) (PDA), and poly(vinylamine).

[0052] Acrylamide-based polyamines that can be modified to include pendant benzoxaborole groups include: poly(acrylamidopropylamine), poly(methacrylamidopropylamine), and related poly(acrylamidoalkylamines).

[0053] Suitable repeat units that contain nitrogen for inclusion in the polymers are well-known in the art, and include for example, polyvinylamine, poly-N-alkylvinylamine, polyacrylamide, polyalkylacrylamides (e.g. polymethacrylamides), poly-N-alkylacrylamides, polyalkyl-N-alkylacrylamides, polyallylamine, poly-N-alkylallylamine, polydiallylamine, poly-N-alkyldiallylamine, polyethylenimine, polyaminostyrene, polyvinylimidazole, polyvinylpyridine, and the like.

[0054] Amine-containing repeat units are cationic when the amino nitrogen is protonated. If desired the cationic character can be altered using known methods, such as, by converting amines into guanidino, biguanide, quaternary ammoniums, or by introducing additional amino groups e.g., by alkylating an amine with an alkylamino or

alkylammonium group.

**[0055]** The cationic polymers are preferably polycations that include amine- or ammonium containing repeat units, and if desired may contain other cationic groups such as imidazolyl and pyridinyl.

**[0056]** Polyamines typically are highly charged at duodenal pH (about pH 5-6), however, due to a high density of protonated amine sites in close proximity, they deprotonate to a small extent as they pass from the stomach (pH ~2) to the duodenum (pH ~ 5) following ingestion. Even a small amount of neutralization effectively lowers the polymer charge density and causes these polymer chains become more coiled, compact, and less well hydrated as pH is increased. Without wishing to be bound by theory, this pH responsiveness is believed to contribute to preferential complexing of the mucus in the duodenum over the stomach. Other polymers of this invention which are capable of responding to the pH increase of the duodenum contain cationic repeat units (e.g., repeat units with protonated amines) that have inductive or structural features resulting in a lower pKa value than that of a standard protonated aliphatic amine. The lower pKa of these protonated polymers results in a greater sensitivity to the pH increase coincident with transit from the stomach to the duodenum. These types of polymers can therefore be targeted to interact with the loose mucus of the proximal duodenum, and include polyamines substituted with polar groups, such as hydroxyl groups less than three carbon atoms away from the protonated amine. In some embodiments, the polymers include amines that are modified to have a lower pKa than the unmodified amines. For example, the cationic polymers can have pKa values less than 9.0, more preferably a pKa less than 8.0, and most preferably a pKa less than or equal to 7.0.

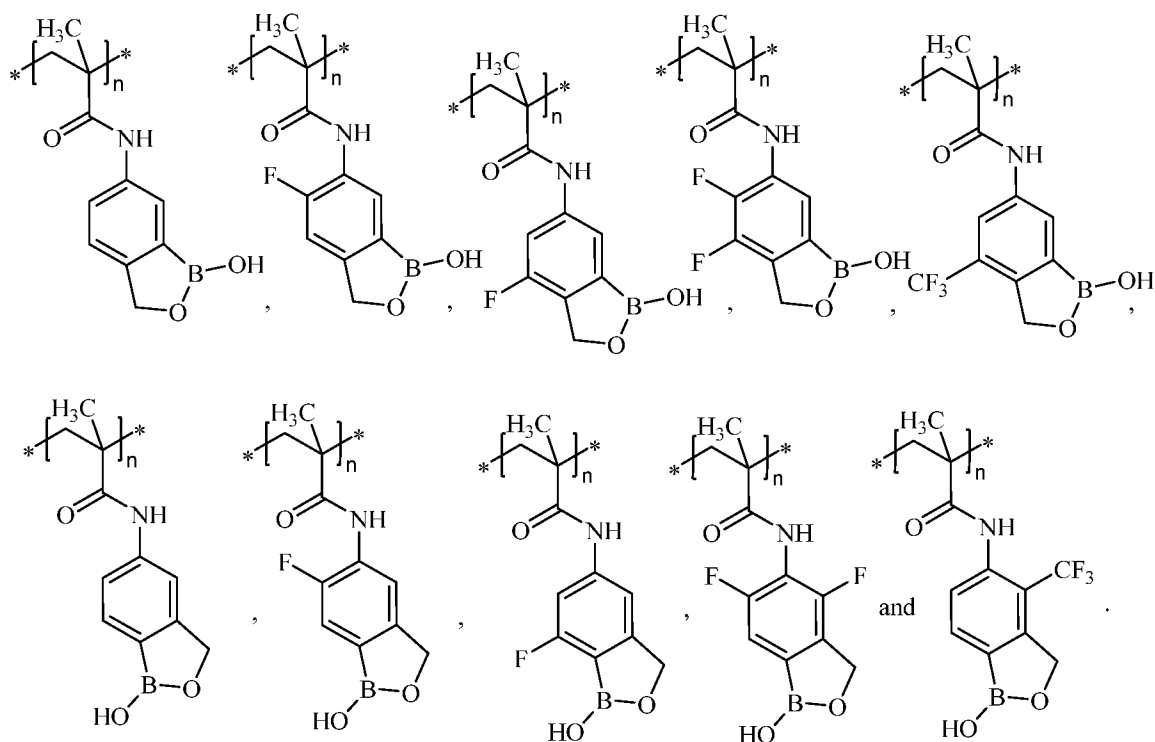
**[0057]** The polymers can be homopolymers. When homopolymers, the polymers may contain a nitrogen-containing repeat unit (e.g. is a polyamine or polyamide) with pendant benzoxaborole groups bonded to the polymer backbone directly or indirectly through the nitrogen atom of the repeat unit.

**[0058]** Preferably, the polymers are copolymers that contain a repeat unit of

Formula (I) and other repeat units. The other repeat units are preferably cationic (e.g., a nitrogen-containing repeat unit), but can be neutral or anionic, provided that the polymer retains an overall cationic charge.

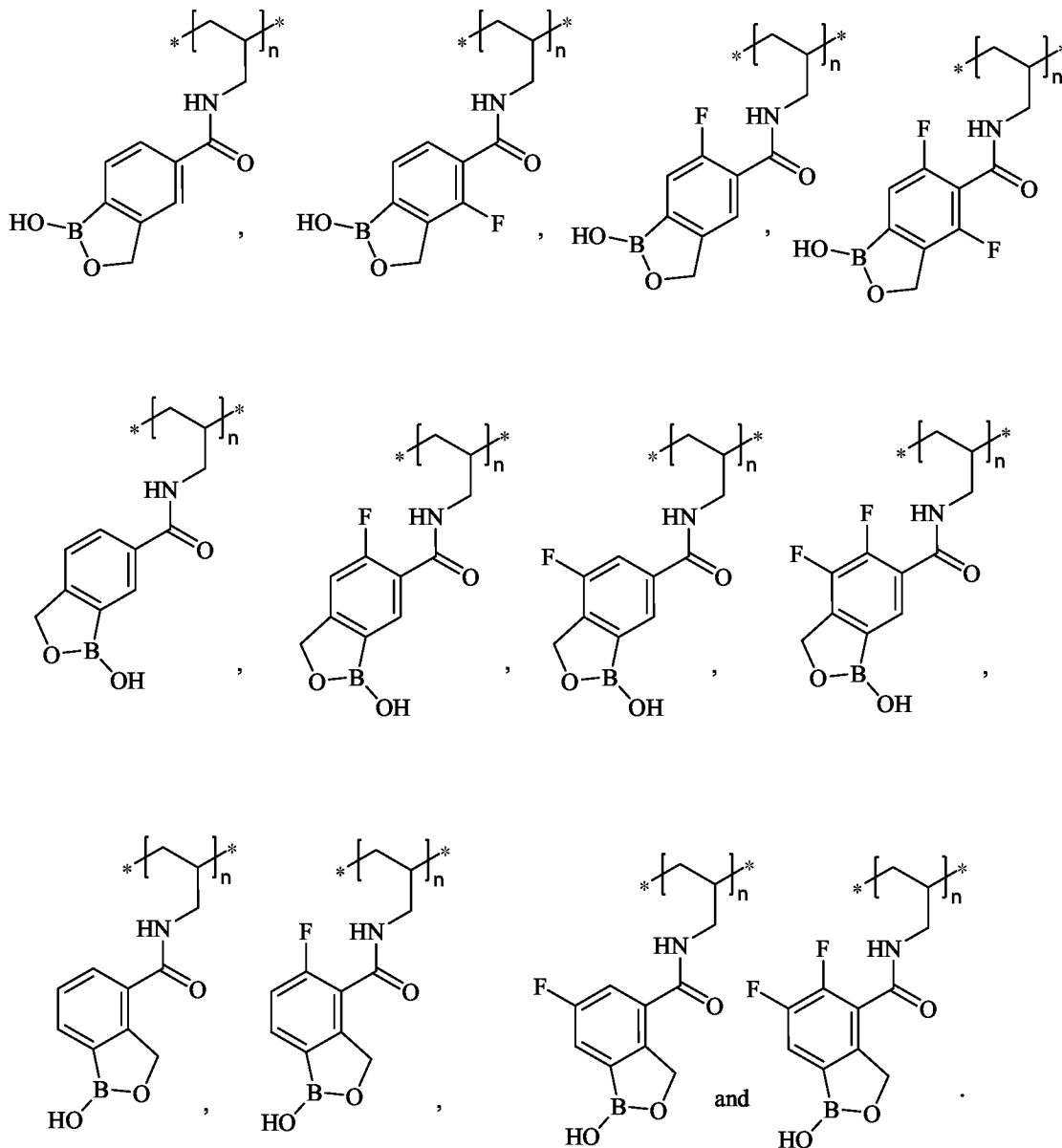
**[0059]** In the polymers disclosed herein, at least about 5% of the repeating chemical units contain a pendant benzoxaborole group. In some instances, substantially all of the chemical repeat units in the polymer contain a pendant benzoxaborole group. Preferably, about 5% to about 50%, about 5% to about 40%, about 5% to about 30%, about 5% to about 20%, or about 5% to about 15% of the repeating chemical units contain a pendant benzoxaborole group.

**[0060]** Suitable benzoxaborole containing repeat units for inclusion in the polymers described herein include the following:

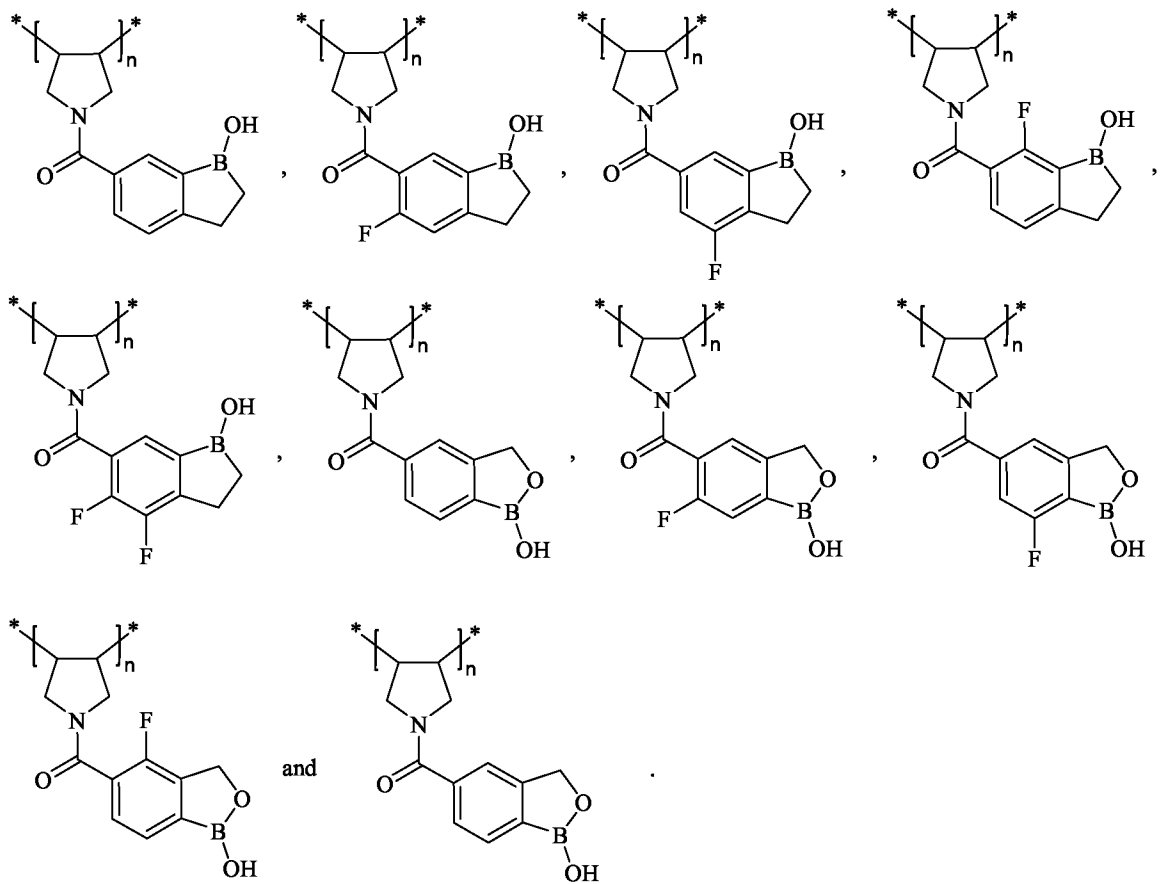


**[0061]** Suitable benzoxaborole containing repeat units for inclusion in the polymers described herein include the following:

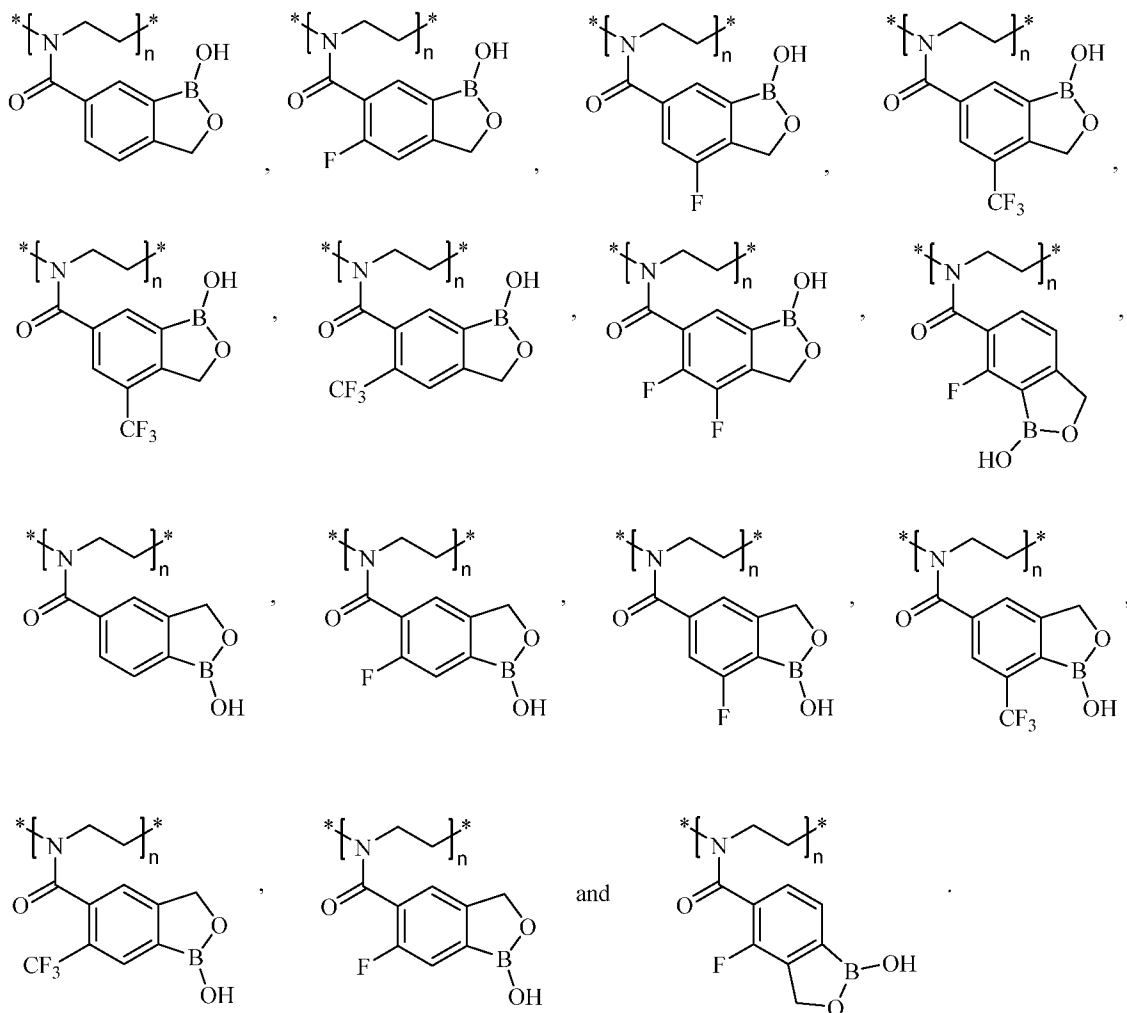
10



[0062] Suitable benzoxaborole containing repeat units for inclusion in the polymers described herein include the following:

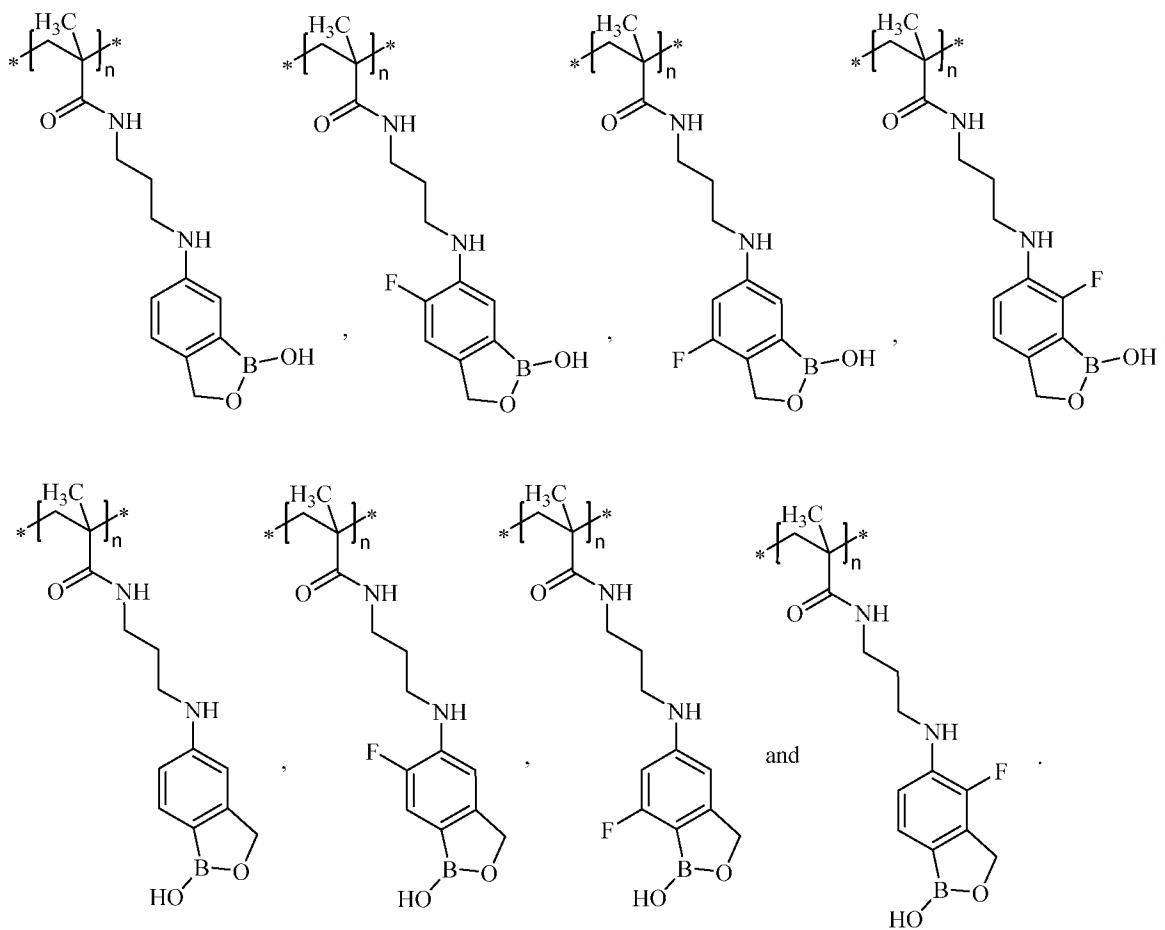


[0063] Suitable benzoxaborole containing repeat units for inclusion in the polymers described herein include the following:



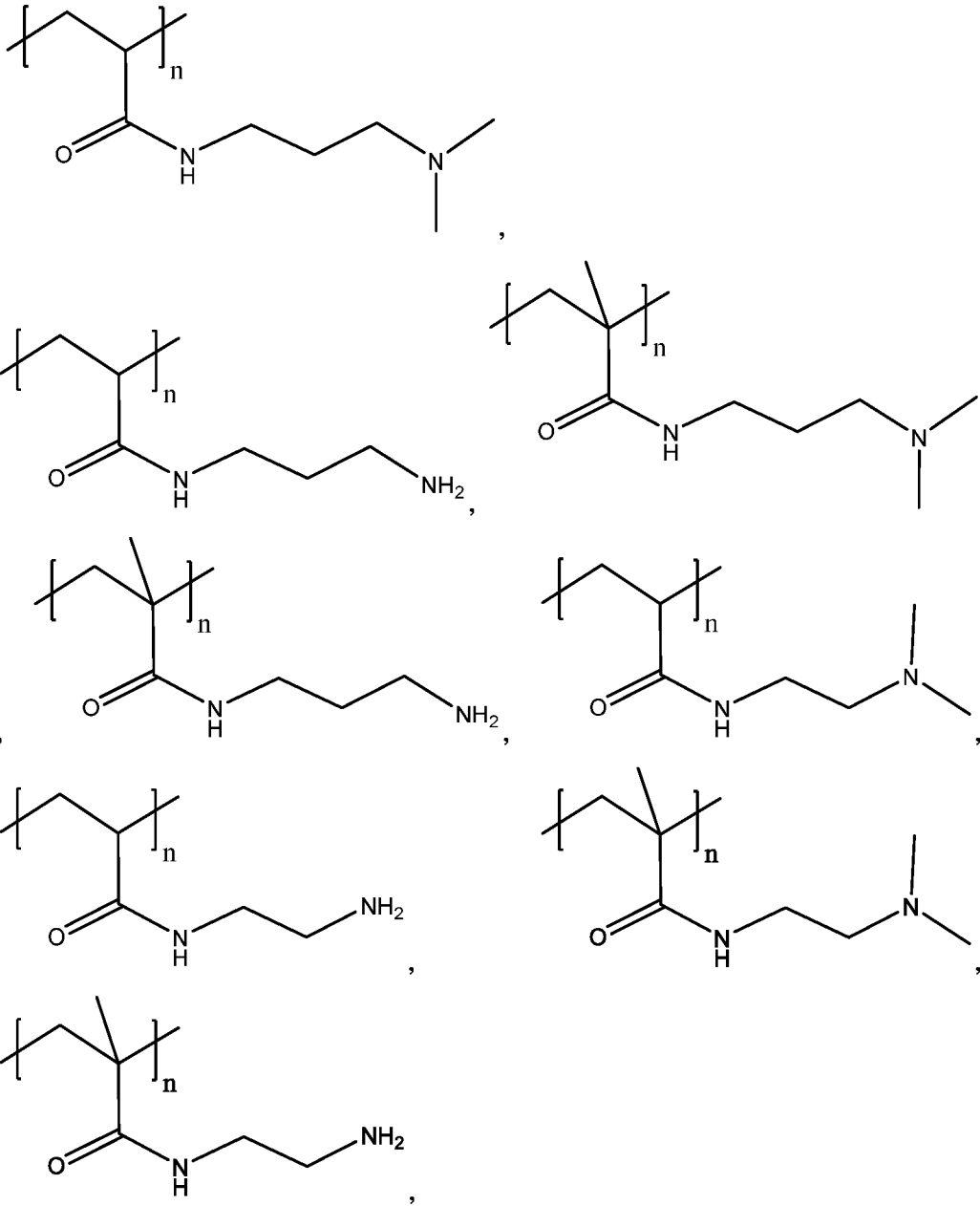
[0064] Suitable benzoxaborole containing repeat units for inclusion in the polymers described herein include the following:

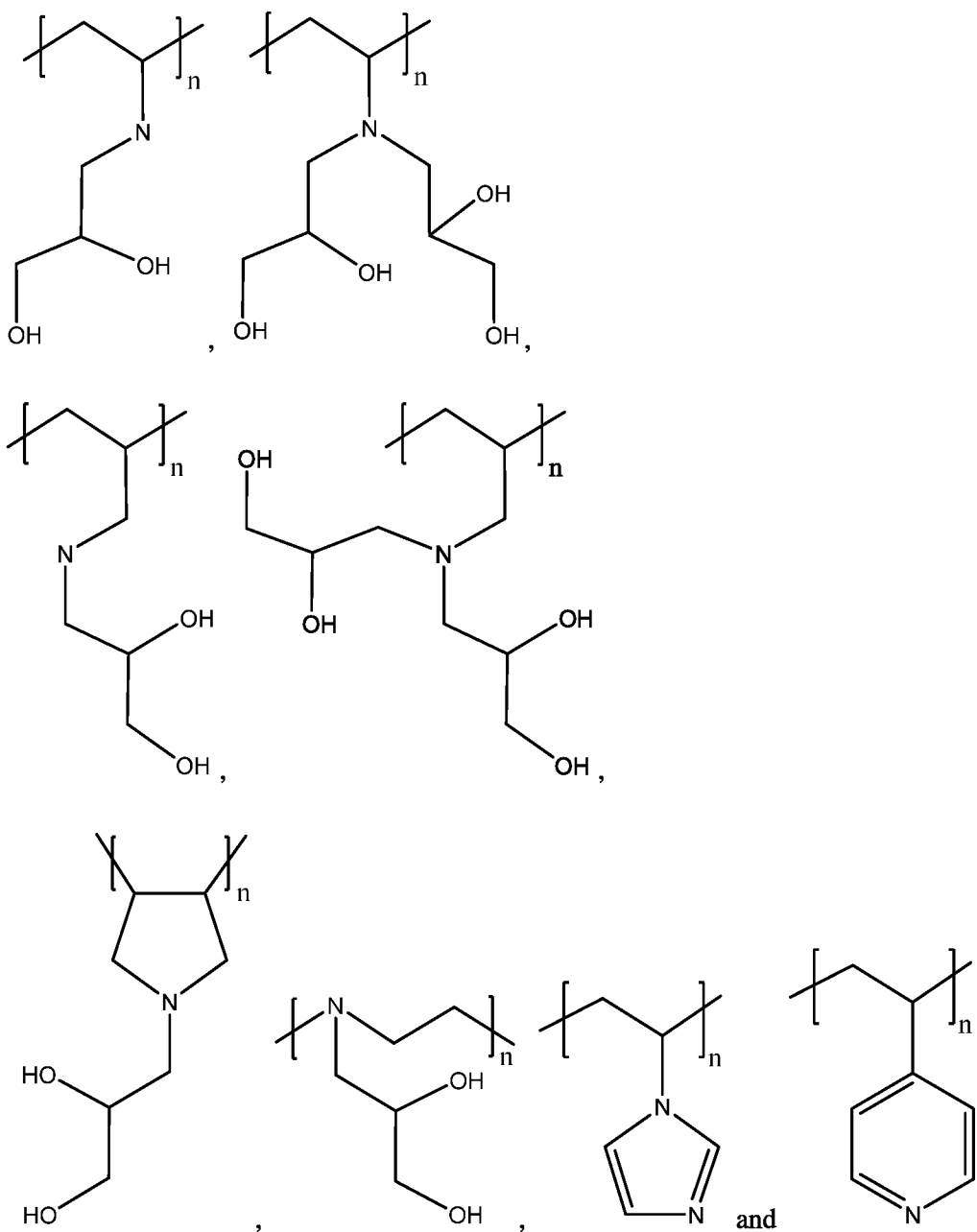
13



[0065] Suitable benzoxaborole containing repeat units for inclusion in the polymers described herein include the following:







where “n” represents an integer from 1 to 100,000.

[0067] If desired, the cationic polymers that contain pendant benzoxaborole groups can also include a hydrophobic group, e.g., a pendant hydrophobic group. As used herein hydrophobic groups are moieties that are more soluble in octanol than water (as a separate chemical entity). For example, an octyl substituent is a

hydrophobic group because octane is more soluble in octanol than in water. Suitable hydrophobic groups are C6 or greater linear, branched or cyclic hydrocarbons that can be substituted, for example with one or more hydroxy, halo, and/or aryl (e.g., benzyl) groups.

**[0068]** Additional repeat units that can be included in the polymers described herein, when desired, include neutral and acid repeat units, such as, polyacrylates, polyalkylene glycols, polystyrene, polyvinyl alcohols, polyvinylphosphates, polyvinylsulfates, and the like.

**[0069]** Copolymers of the present invention can exist in a variety of forms. Suitable forms include block copolymers, graft copolymers, comb copolymers, star copolymers, dendrimers, hyperbranched copolymers, random copolymers, gradient block copolymers, and alternate copolymers.

**[0070]** This disclosure also relates to cationic polymers that contain pendant hydrophobic groups, and to the use of such polymers for treating metabolic disease as disclosed herein.

**[0071]** Preferably, the polymers disclosed herein are of sufficient size so that the polymers are substantially not absorbed when administered orally to a subject, such as a human. The threshold molecular weight above which polymers are not absorbed from the GI tract into the systemic circulation is dependent on the specific polymer and conditions in the GI tract and other factors, but it is generally recognized that polymers of greater than 1,000 Da are not substantially absorbed from the GI tract into the systemic circulation. Accordingly, the compositions of this invention that are substantially not absorbed from the GI tract are substantially free of polymer chains smaller than 1,000 Da, and preferably 5,000 Da or more preferably 10,000 Da and have average molecular weights ( $M_w$ ) of at least about 10,000 Da and preferably in the range of 20,000 to 250,000 Da or greater. The polymers of the invention can contain a distribution of polymer chain lengths, and may have a polydispersity index (PDI) in the 1.5 - 4.0 range, but they contain substantially no material under 1,000 Da, preferably they contain no material under 5,000 Da or more preferably under 10,000 Da.

[0072] The inventive polymers are soluble and are preferably not cross-linked. In some embodiments the polymers may be lightly cross-linked but remain soluble and do not form an extended network or gel.

[0073] Also included in the present invention are pharmaceutically acceptable salts of the disclosed polymers. For example, polymers which have acid functional groups can also be present in the anionic, or conjugate base, form, in combination with a cation. Suitable cations include alkaline earth metal ions, such as sodium and potassium ions, alkaline earth ions, such as calcium and magnesium ions, and unsubstituted and substituted (primary, secondary, tertiary and quaternary) ammonium ions. Polymers which have basic groups such as amines can also be protonated and have a pharmaceutically acceptable counter anion, such as halides ( $\text{Cl}^-$  and  $\text{Br}^-$ ),  $\text{CH}_3\text{OSO}_3^-$ ,  $\text{HSO}_4^-$ ,  $\text{SO}_4^{2-}$ ,  $\text{HCO}_3^-$ ,  $\text{CO}_3^{2-}$ , nitrate, hydroxide, persulfate, sulfite, acetate, formate, sulfate, phosphate, lactate, succinate, propionate, oxalate, butyrate, ascorbate, citrate, dihydrogen citrate, tartrate, taurocholate, glycocholate, cholate, hydrogen citrate, maleate, benzoate, folate, an amino acid derivative, a nucleotide, a lipid, or a phospholipid. Similarly, ammonium groups comprise a pharmaceutically acceptable counteranion.

[0074] The polymers disclosed herein are typically provided as a mixture of polymer chains with some variability in chain length. This distribution of polymer chain lengths can be measured using size exclusion chromatography (SEC) and a detector capable of measuring polymer molar mass such as a multi-angle laser light scattering (MALLS). This method can also confirm the absence of short, low molecular weight polymer chains. It can also provide a polydispersity index (PDI), which is typically considered to be the ratio  $M_w/M_n$ , where  $M_w$  is the weight fraction-average molecular weight and  $M_n$  is the number average molecular weight.

$$\text{PDI} = M_w/M_n$$

[0075] Values of  $M_w$ ,  $M_n$  and PDI can be obtained by SEC, preferable with a MALLS detector. For synthetic polymer materials made from standard free-radical

processes, it is common to find PDI values greater than 2, and even greater than 3. In contrast, living free radical polymerization processes such as atom transfer radical polymerization (ATRP) or reversible addition fragmentation chain transfer (RAFT) are capable of producing materials with PDI less than 2, or even less than 1.5.

**[0076]** The polymers disclosed herein can be prepared using any suitable methods, such as by direct polymerization of one, two or more monomers or by polymer modification.

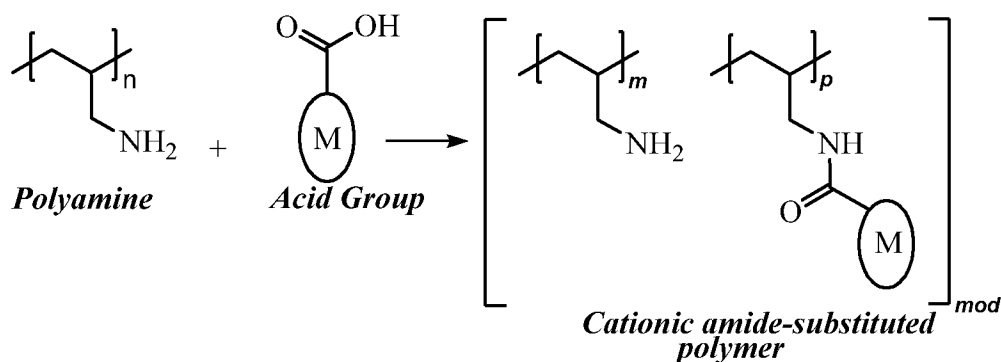
**[0077]** Polymerization can be accomplished using techniques known in the art of polymer synthesis (See, for example, Shalaby et al, ed., Water-Soluble Polymers, American Chemical Society, Washington, D.C. [1991]). Several cationic monomers are available as hydrochloride salts and can be polymerized by methods known in the art, for example, via a free radical addition process. In this case, the polymerization mixture includes a free-radical initiator. Suitable free-radical initiators include azobis(isobutyronitrile), azobis(4-cyanovaleric acid), 2,2'-azobis(2-amidinopropane)dihydrochloride, potassium persulfate, ammonium persulfate, and potassium hydrogen persulfate. Other suitable initiators include ionizing radiation and ultraviolet light. The free radical initiator is preferably present in the reaction mixture in an amount ranging from about 0.01 mole percent to about 5 mole percent relative to the monomer.

**[0078]** Polymer modification approach employs polyamines and copolymer approach employs acrylamide derivatives. In reaction Schemes 1, 2, 3 and 4, the "M" group represents a substituted or unsubstituted benzoxaborole group.

**[0079]** Polyamines can serve as mucus-interacting agents as well as starting materials for chemical modification with benzoxaborole groups. Exemplary polyamines include polyethyleneimine, hydroxyethylated polyethyleneimine, polyamidoamine (PAMAM) dendrimers, poly(allylamine) (PAA<sub>n</sub>) and its copolymers, poly(diallylamine) (PDA<sub>n</sub>) and its copolymers, poly(vinylamine) and its copolymers, poly(vinylimidazole) and its copolymers, poly(vinylpyridine) and its copolymers, poly(vinylaniline) and its copolymers, amine containing acrylamide and

methacrylamide copolymers, and the like. Preferred polyamines include poly(allylamine) (PAA<sub>n</sub>), poly(diallylamine) (PDAAn), poly(ethyleneimine) (PEI) and poly(methacrylamidopropylamine) (PMAAn).

[0080] Polyamine derivatives can be obtained from the chemical modification of polyamines by amide-forming chemistry using EDC coupling (Scheme 1).

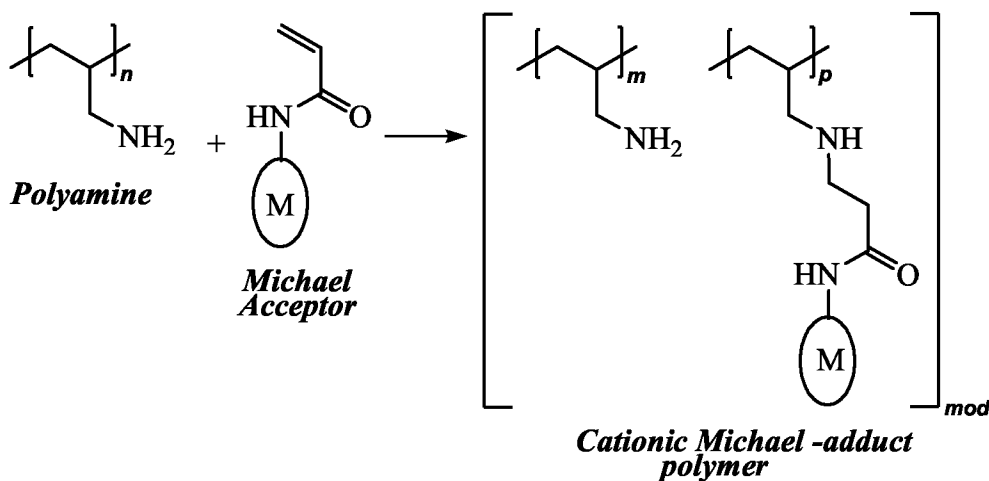


**Scheme 1:** Amide-forming reaction of a polyamine with a carboxylic acid using EDC as a coupling reagent.

[0081] A 1% wt/vol of desired polyamine is prepared in deionized water the pH is adjusted to 5.0. Ethanol or other suitable organic is added to the polymer solution at 50% of initial polymer solution volume. The M-carboxylic acid to be coupled is placed into water at 25% of initial polymer solution volume to form a solution or slurry. The EDC coupling agent is dissolved in ethanol or other suitable solvent at 25% of initial polymer solution volume. The EDC solution is then mixed with the M-carboxylic acid solution or slurry. The combined EDC/M-carboxylic acid solution is added to the polymer solution dropwise by pipette or pressure equalizing addition funnel, over approximately 10 minutes. The reaction solutions contains polymer at about 0.5% wt/vol with about 62% vol water and about 38% vol ethanol or other suitable organic solvent. The reaction is stirred and pH is maintained at 5.0. With pH stabilized at 5.0, the reaction is allowed to stir at room temperature for about 18 hours. The polymer is precipitated with excess (3X volume) acetone.

[0082] The polyamine derivatives can be obtained from the chemical modification of polyamines by Michael addition reaction. The polyamine is the nucleophile and the acrylamides are the Michael acceptor (Scheme 2).

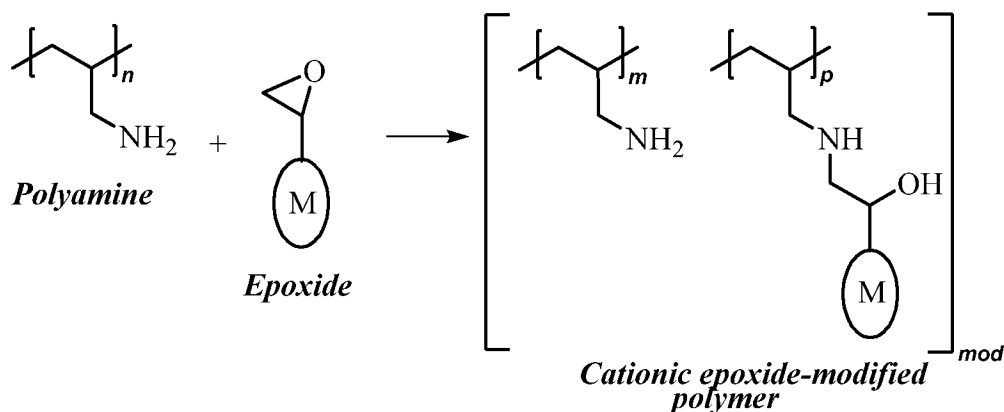
21



**Scheme 2:** Michael addition reaction of a polyamine nucleophile with an acrylamides Michael acceptor.

[0083] A 1% wt/vol of desired polyamine is prepared in deionized water and the pH was adjusted to 8.5. This pH can be increased or lowered depending on level of modification desired. The desired M-acrylamide is dissolved in ethanol or other suitable solvent at 20% of initial polymer solution volume. The acrylamide solution is then added to the polymer solution to form a reaction mixture with the polymer at about 0.83% wt/vol with about 83% vol water and about 17% vol ethanol or other suitable solvent. The reaction mixture is heated to 70 °C and stirred for 48 hours. The polymer is precipitated with excess (3X volume) acetone.

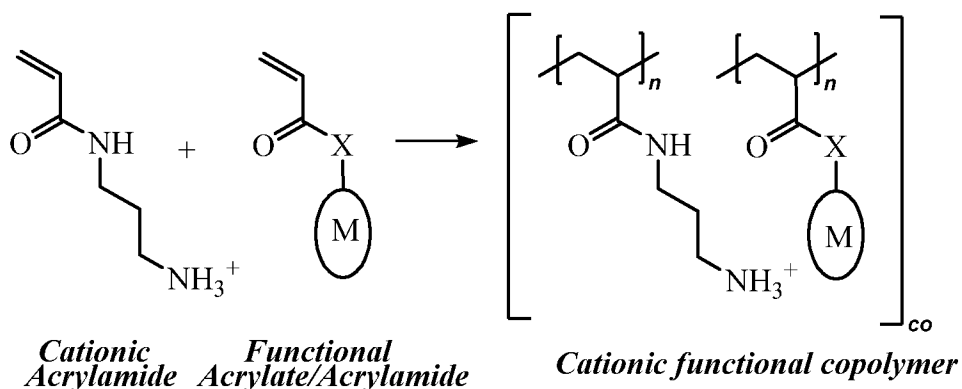
[0084] The polyamine derivatives can be obtained from the chemical modification of polyamines by hydroxyalkylation using epoxide-opening chemistry (Scheme 3).



**Scheme 3: Reaction of a polyamine with an epoxide.**

[0085] A 2% wt/vol of desired polyamine is prepared in deionized water and the pH is adjusted to 6.0. This pH can be increased or lowered depending on level of modification desired. The desired M-epoxide is dissolved in water/ethanol (25%/75%) at 100% of initial polymer solution volume. This solution is then added to the polymer solution to prepare a reaction solution in which the polymer was about 1% wt/vol with about 62% vol water and about 38% vol ethanol. The reaction mixture was heated at 60 °C for 48 hr. If the epoxide is not fully in solution at 60 °C, a small portion of additional ethanol may be added to aid in solubility. The polymer is precipitated with excess (3X volume) acetone.

[0086] Polyacrylamide derivatives can be obtained, for example, by the polymerization of 3-acrylamidopropylamine with a desired M-acrylate or M-acrylamide (Scheme 4).

**Scheme 4: Reaction of an acrylamide with an acrylate.**

[0087] A desired amount of the desired M-acrylate or M-acrylamide monomer is placed into a 30 ml glass vial equipped with magnetic stirring and an N<sub>2</sub> (g) inlet. The desired M-acrylate or M-acrylamide monomer is dissolved in dimethylformamide or other suitable water-miscible organic solvent. The desired amount of cationic, neutral or anionic co-monomer is then added. A small amount of water will likely be needed to fully dissolve the charged co-monomer in a binary solvent system. An appropriate amount of AIBN initiator is added. The co-monomer solution is N<sub>2</sub> (g)

purged for at least ~15 minutes. The reaction is then heated at 65°C while under a blanket of N<sub>2</sub> (g). After several hours of heating, the copolymer solution or suspension is isolated by precipitation from acetone. The addition of some water and adjustment to lower pH will be needed for some of the polymers to facilitate precipitation in acetone. Finally, the product may be dissolved in deionized water, IPA/dry ice frozen and lyophilized.

**[0088]** Accordingly, in some aspects, the invention provides a method for applying a physical barrier to the gastrointestinal (GI) tract of a subject between the intestinal lining and the luminal contents. The method includes administering to the GI tract of the subject a therapeutic effective amount of a polymer described herein.

**[0089]** As used herein, the term “physical barrier” or “luminal barrier” refers to a complex of polymer and mucus that prevents or reduces chyme from contacting the mucosal epithelium located under the polymer-mucus complex in the intestinal tract. The physical barrier is created when the polymer combines in-situ with the anionic mucins contained within the mucus lining the wall of the intestines. The physical barrier can be substantially complete or partial. A substantially complete physical barrier extends to substantially cover an entire target area, such as the epithelial lining of the proximal duodenum. A partial physical barrier extends to cover a portion of a target area, such as a portion of the epithelial lining of the duodenum. For example, a partial barrier can cover at least about 1%, 5%, 10%, 20%, 25%, 30%, 40%, 50% or more of the epithelium at the target site.

**[0090]** The partial physical barrier can be discontinuous and spatially distributed, and may have varying degrees of permeability. For instance, physical barrier can be a semi-permeable complex of polymer and mucus or mucins on the luminal surface of the intestines, preferably in the duodenum.

**[0091]** In embodiments, the physical barrier or a formulation thereof is passed by natural digestive processes of the subject. In yet other embodiments, the physical barrier is removable or reversible by the ingestion of a liquid or solvent.

**[0092]** The polymers described herein bind tightly to the mucus and mucins to form a polymer-mucus complex that is resistant to disassociation (e.g., by high salt and low pH). Accordingly, once formed, the physical barrier will typically be present for a “retention period” or “residence time,” and is removed by the natural actions of the digestive system. Typical retention periods can range from about half an hour to about 7 days, including time period ranging from about 1 hour to about 3 hours, about 1 hour to about 5 hours, about 1 hour to about 24 hours, about 1 to about 3 days, and others.

**[0093]** The desired residence time can vary depending on the clinical application and can be adjusted based on the amount of polymer that is administered, and the frequency and interval between administrations. For instance, up to 50% of subjects with T2DM have gastroparesis, or delayed gastric emptying, that may require the mucoadhesive lining to remain in place for a longer time than a pre-diabetic or non-diabetic obese subject. Blood glucose levels spike often within the first two hours of eating a meal, most often within the first 60 minutes; thus, the lining should adhere for a minimum of 60 minutes in one embodiment. In another embodiment, in the case of pre-diabetic subjects who may not take medication prior to every meal, and thus may not comply with a treatment that would require to change their behavior, a longer lasting mucoadhesive lining may be required. In this application, the lining may adhere for a minimum of 6-8 hours with a maximum of 24 hours could be required. Residence time will also be influenced by the mucus layer at which the polymer develops the most affinity to. For instance, the superficial, loosely adherent layer sloughs off on the order of minutes to hours, whereas affinity to the deeper firmly adherent layer would lead to a longer lasting mucoadhesive coating. Overall, residence time can be tuned to various clinical and technical considerations in the embodiments outlined in this disclosure.

**[0094]** Polymers of the invention can form an occlusive barrier layer in the proximal intestine, specifically the duodenum. Preferably, the occlusive barrier is formed in the proximal duodenum or duodenal bulb. The polymers are therefore fully capable of forming a barrier layer immediately upon release from the stomach and entry into the proximal duodenum.

**[0095]** The polymers are administered orally in any suitable dosage form. A

variety of dosage forms that are suitable for oral administration are well-known in the art and include, liquid formulations (e.g., solutions, suspensions, slurries, syrups), gels, ointments, powder, tablets, caplets, capsules and the like.

**[0096]** In one example, the polymers can be administered in a liquid form and are typically sufficiently stable and soluble in the stomach allowing immediate delivery to the duodenum in an active state without requiring further swelling, solubilization, or equilibration with the surrounding milieu. The polymers described herein are typically polyamines, which undergo some degree of deprotonation as they transition from the highly acidic stomach (pH~2) to the duodenum (pH ~5) which targets the complexing activity of the polymers to the duodenum. However, the polymers may also form a barrier layer in the stomach.

**[0097]** In other examples, the polymer is administered in a solid form capable of being hydrated in the stomach. The solid form can be formulated to provide slow dissolution, which can protect the polymers from gastric acidity, but resulting in the polymers entering the proximal duodenum in a fully active state. In other examples, the polymers are administered in the form of an enteric-coated tablet, caplet, capsule or other enteric-coated dosage form to protect the polymers from gastric acidity. In such examples, the enteric coating is formulated to dissolve or degrade as soon as possible after or during passage through the pyloric valve (when the pH increases from pH~2) permitting the immediate release of the polymers. Such dosage forms can include a superdisintegrant to facilitate immediate release of the polymers at the desired site in the intestinal tract, such as the proximal duodenum. Suitable superdisintegrant excipients are well-known in the art. (See, e.g., Mohanachandran, P.S. et al, Superdisintegrants: An Overview, *Int. J. Pharma. Sci. Review and Research*, (2011) 6:1 pp 105-109.) For example, enteric capsules have been described in the literature that are capable of targeting delivery to the duodenum. (See, e.g., Reix N. et al. *Intl J Pharm* (2012) 422:1-2 pp. 338-340.)

**[0098]** The polymers of the invention can quickly dissolve after oral administration in the stomach, in the duodenum or on other mucosal surfaces.

**[0099]** In some aspects, the pharmaceutical formulations of the polymers of this invention may optionally include a calcium salt, such as calcium chloride or calcium citrate. It is believed that the physical barrier formation can be accelerated in the presence of a calcium salt.

**[00100]** If desired, the polymers can be administered to the gastrointestinal tract of the subject via an endoscope, a nasal feeding tube, an oral feeding tube, or similar device. The polymer can also be sprayed onto the mucosa at the desired site of action, for example, the spraying can be done endoscopically.

**[00101]** For therapeutic purposes, a “therapeutically effective amount” of the polymer is administered. A therapeutically effective amount, as used herein is an amount sufficient to affect the desired response under the conditions of administration, including clinical response. The therapeutically effective amount may be sufficient, for example, to improve glucose homeostasis, to reduce insulin resistance, to cause weight loss, and/or to improve other signs and/or symptoms of T1DM, T2DM or other metabolic disorders such as hyperlipidemia, non-alcoholic steatohepatitis, non-alcoholic fatty liver and other conditions such as obesity and overweight. For example, a therapeutically effective amount can be an amount sufficient to lower blood glucose levels and/or reduce HbA1C.

**[00102]** The precise amount that is administered will depend on a number of well-known considerations, including the age, weight, gender, particular condition to be treated and its severity, sensitivity to drugs, and overall health of the subject. A skilled clinician can determine appropriate amounts to administer based on these and other considerations. Typically, 1 to 5 tablets/capsules are administered per dose, each of size 0 or 0E or 00 or 00E or 000. A dose can be administered one, two, three or four times per day. The dose timing will be based on the underlying indication. Preferably, a dose is administered at least 5, 10, 15, 30 or 60 min and not more than 12 hrs before a meal for the treatment of metabolic conditions. For other indications, dosing right before or along with food may be preferred.

**[00103]** As used herein and as well understood in the art, “treatment” is an

approach for obtaining beneficial or desired results, including clinical results. Beneficial or desired clinical results may include, but are not limited to, alleviation or amelioration of one or more symptoms or conditions, diminution of extent of disease or affliction, a stabilized (*i.e.*, not worsening) state of disease or affliction, preventing spread of disease or affliction, delay or slowing of disease or affliction progression, amelioration or palliation of the disease or affliction state and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment.

**[00104]** This disclosure relates to methods of treating metabolic disease by administering a therapeutically effective amount of a polymer disclosed herein to a subject in need thereof. Metabolic diseases that can be treated using the method include, for example, glucose intolerance, T1DM, T2DM, prediabetes, hyperlipidemia, obesity, overweight, obesity, dyslipidemia, hypertension, hyperglycemia, impaired glucose tolerance, insulin resistance, metabolic syndrome, non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD) and polycystic ovary syndrome (PCOS).

**[00105]** This disclosure also relates to methods of treating gastrointestinal disorders by administering a therapeutically effective amount of a polymer disclosed herein to a subject in need thereof. Gastrointestinal disorders that can be treated using the method include, for example, celiac disease, irritable bowel syndrome, inflammatory bowel disease, colitis, clostridium difficile, endotoxemia, diarrhea and constipation.

**[00106]** The methods of the invention are also useful in addressing leaky gut syndrome and associated conditions. Leaky gut syndrome is a term of art that describes a condition in which there is increased intestinal permeability due to alteration/damage to the tight epithelial junctions which results in a compromised epithelial barrier function. This impaired barrier acts as a conduit for intraluminal macromolecules and antigens to permeate through the gut wall triggering inflammatory, immunological reactions that result in various health conditions. For example, leaky gut syndrome has been implicated in IBS (irritable bowel syndrome). Certain proteins in foods can

behave as antigens eliciting an immune response. For example, in Celiac disease, preventing gluten from coming into contact with the epithelium can reduce the immunological response. Leaky gut has also been implicated in other immunological conditions like Inflammatory Bowel Disease (Crohn's disease, Ulcerative Colitis). An enhanced intestinal barrier can reduce the absorption of endotoxins in the gastrointestinal tract. Some of these endotoxins are a result of normal bacterial metabolism/breakdown or due to bacterial overgrowth. This is particularly relevant in patients with impaired liver function, e.g., in liver cirrhosis, in whom the endotoxins are not metabolized (detoxified) by the liver resulting in impaired brain function (called hepatic encephalopathy). Thus the methods described herein can be used to enhance the barrier properties of the intestine and can treat or reduce the incidence of hepatic encephalopathy. Uremia is another condition associated with an impairment of intestinal barrier function that can be treated or reduced using the methods described herein. Similarly, the methods described herein can be used to treat or reduce the incidence of Chronic Kidney Disease (CKD), as clinical evidence has documented greater intestinal permeability in patients with advanced CKD.

**[00107]** The therapeutic methods can also provide benefit by reducing the clinical biomarkers associated with a variety of disorders, such as reducing systemic inflammation, oxidative stress and hyperuricaemia.

**[00108]** The disclosed polymers can be administered to the subjects in the form of a pharmaceutical composition that includes a pharmaceutically acceptable carrier, excipient, buffer or diluent.

**[00109]** For oral administration, the pharmaceutical compositions of the invention may be presented in dosage forms such as capsules, tablets, caplets, powders, granules, gels, suspensions, solutions or other suitable dosage form. Capsule may be gelatin, soft-gel or solid. Tablet, caplet and capsule formulations may further contain one or more adjuvants, binders, diluents, disintegrants, excipients, fillers, or lubricants, each of which are known in the art. Examples of such include carbohydrates such as lactose or sucrose, dibasic calcium phosphate anhydrous, corn starch, mannitol, xylitol, cellulose or derivatives thereof, microcrystalline cellulose, gelatin, stearates, silicon

dioxide, talc, sodium starch glycolate, acacia, flavoring agents, preservatives, buffering agents, disintegrants, and colorants.

[00110] Orally administered compositions may contain one or more optional agents such as, for example, sweetening agents such as fructose, aspartame or saccharin; flavoring agents such as peppermint, oil of wintergreen, or cherry; coloring agents; and preservative agents, to provide a pharmaceutically palatable preparation. Suitable pharmaceutical formulations for oral administration and methods for preparing them are well-known in the art. See, e.g., Remington: The Science and Practice of Pharmacy, twentieth edition, 2000.

[00111] Pharmaceutical preparations that can be used orally include push-fit capsules made of a suitable material, such as gelatin, as well as soft, sealed capsules made of a suitable material, for example, gelatin, and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds can be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers can be added. All formulations for oral administration should be in dosages suitable for such administration. Methods for encapsulating compositions (such as in a coating of hard gelatin or cyclodextran) are known in the art (Baker, et al., "Controlled Release of Biological Active Agents", John Wiley and Sons, 1986).

[00112] The methods of the invention include a co-formulation of the polymeric composition comprising with probiotics. Probiotic formulations assist in building the beneficial probiotic bacteria in the intestinal tract. It is known in the art that probiotics have significant effects on the reduction of blood sugar, HbA1c, insulin levels and insulin resistance in subjects with diabetes. Suitable probiotics include, but not limited to *Lactobacillus Bifidobacteria*, *Saccharomyces boulardii*, and *Bacillus coagulans*, *Akkermansia muciniphila*, *Bifidobacterium spp*, *Escherichia spp*. Methods to prepare formulations containing probiotics are well known in the art.

**[00113]** If desired, the therapeutic methods described herein can include co-administration of the polymeric compositions with one or more additional therapeutic agents. Therapeutic agents for co-administration in subjects with diabetes may include classes of drugs that are GLP-1 receptor agonists, DPP-4 inhibitors, SGLT-2 inhibitors, glucosidase inhibitors, insulin, metformin, sulfonylureas and thiazolidinediones.

**[00114]** In particular examples, the additional therapeutic agent is one or more agent indicated for the treatment of diabetes (type 1 and/or type 2), pre-diabetes, hyperglycemia, impaired glucose tolerance or insulin resistance. Such agents include biguanides (e.g., metformin), sulfonylureas (e.g., limepiride, gliclazide, glipizide, glimepiride, tolbutamide, glibenclamide (glyburide), gliquidone, and glycopyramide), meglinitinides (e.g., repaglinide and nateglinide); thiazolidindiones (e.g., pioglitazone and rosiglitazone), alpha-glucosidase inhibitors (e.g., acarbose and miglitol), dipeptidyl peptidase 4 (DPP4) inhibitors (e.g., vildagliptin, sitagliptin, saxagliptin, and linagliptin), GLP-1 analogues (e.g., exenatide, lixisenatide, dulaglutide, and liraglutide), sodium-glucose co-transporter 2 (SGLT2) inhibitors (e.g., dapagliflozin, ganagliflozin, and empagliflozin), amylin mimetics (e.g., pramlintide), D2-dopamine agonists (e.g., bromocriptine), bile acid sequestrants (e.g., cholestyramine, colesevelam, colestilan, and colestimide), and insulin (e.g., human insulin, insulin glulisine, insulin lispro, insulin isophane human, insulin zinc suspension mixed bovine, insulin protamine zinc bovine, insulin isophane porcine, insulin isophane human, and the like).

**[00115]** The co-therapeutic methods can provide several advantages over monotherapy. For example, administering the polymer and an additional therapeutic agent can enhance the efficacy of and/or reduce the amount of additional therapeutic agent that is needed for the desired effect. Accordingly, undesired side effects of the additional therapeutic agent can be reduced or eliminated. Additionally, the polymers of the invention and the additional therapeutic can provide superior therapy in comparison to each agent as a monotherapy, and co-therapy can provide additive or synergistic effects.

**[00116]** The subject to be treated by the presently disclosed methods is typically a mammal and preferably a human subject. Suitable subjects include mammals

including, but not limited to, primates, e.g., humans, monkeys, apes, and the like; bovines, e.g., cattle, oxen, and the like; ovines, e.g., sheep and the like; caprines, e.g., goats and the like; porcines, e.g., pigs, hogs, and the like; equines, e.g., horses, donkeys, zebras, and the like; felines, including wild and domestic cats; canines, including dogs; lagomorphs, including rabbits, hares, and the like; and rodents, including mice, rats, and the like. Preferably, the subject is a human including, but not limited to, fetal, neonatal, infant, juvenile, and adult humans.

**[00117]** The terms “a,” “an,” and “the” refer to “one or more” when used in this application, including the claims. Thus, for example, reference to “a subject” includes a plurality of subjects, unless the context clearly is to the contrary (e.g., a plurality of subjects), and so forth.

**[00118]** Throughout this specification and the claims, the terms “comprise,” “comprises,” and “comprising” are used in a non-exclusive sense, except where the context requires otherwise. Likewise, the term “include” and its grammatical variants are intended to be non-limiting, such that recitation of items in a list is not to the exclusion of other like items that can be substituted or added to the listed items.

**[00119]** Although specific terms are employed herein, they are used in a generic and descriptive sense only and not for purposes of limitation. Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this presently described subject matter belongs.

**[00120]** The term “about,” when referring to a value means  $\pm 20\%$ , or  $\pm 10$ . Further, the term “about” when used in connection with one or more numbers or numerical ranges, should be understood to refer to all such numbers, including all numbers in a range and modifies that range by extending the boundaries above and below the numerical values set forth. The recitation of numerical ranges by endpoints includes all numbers, e.g., whole integers, including fractions thereof, subsumed within that range (for example, the recitation of 1 to 5 includes 1, 2, 3, 4, and 5, as well as fractions thereof, e.g., 1.5, 2.25, 3.75, 4.1, and the like) and any range within that range.

[00121] As used herein, the term ‘alkyl’ refers to monovalent aliphatic hydrocarbon typically containing 1 to about 6 carbon atoms. An alkyl group can be straight chain, branched chain, monocyclic moiety or polycyclic moiety or combinations thereof. Suitable substituents for an alkyl group include aryl, —OH, halogen (—Br, —Cl, —I and —F), —O(R'), —O—CO—(R'), —CN, —NO<sub>2</sub>, —COOH, —NH<sub>2</sub>, —NH(R'), —N(R')<sub>2</sub>, —COO(R'), —CONH<sub>2</sub>, —CONH(R'), —CON(R')<sub>2</sub>, —S(O)R', —S(O)<sub>2</sub>R', —SH and —S(R'). Each R' is independently an alkyl group or an aryl group. A substituted alkyl group can have more than one substituent. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, norbornyl, and the like.

[00122] As used herein, the term ‘alkylene’ refers to —(CH<sub>2</sub>)<sub>x</sub>—, that may be optionally substituted, where x is an integer between 1 to 5. Preferably, x is between 1 to 3, more preferably x is 1 or 2. Suitable substituents for an alkylene group are identical to those for alkyl groups.

[00123] As used herein, the term “alkoxy” refers to a group of formula —O—alkyl. Example of alkoxy groups include methoxy, ethoxy, propoxy (e.g., *n*-propoxy and isopropoxy), *tert*-butoxy, and the like.

[00124] As used herein, the term “aryl,” refer to stable aromatic monocyclic ring system having 3-7 ring atoms, of which all the ring atoms are carbon, and which may be substituted or unsubstituted. Aryl substituents include, —OH, halogen (—Br, —Cl, —I and —F), —O(R'), —O—CO—(R'), —CN, —NO<sub>2</sub>, —COOH, —NH<sub>2</sub>, —NH(R'), —N(R')<sub>2</sub>, —COO(R'), —CONH<sub>2</sub>, —CONH(R'), —CON(R')<sub>2</sub>, —S(O)R', —S(O)<sub>2</sub>R', —SH and —S(R'). Each R' is independently an alkyl group.

[00125] As used herein, the term “aryloxy” refers to a group of formula —O—aryl. The aryl group may optionally substituted.

[00126] As used herein, the term “electron withdrawing” refers to an atom or a group that draws electron density from neighboring atoms towards itself, usually by

resonance or inductive effects. Suitable electron withdrawing groups include, but not limited to halo,  $-\text{CN}$ ,  $-\text{NO}_2$ ,  $-\text{CF}_3$ ,  $-\text{SO}_2\text{CF}_3$ ,  $-\text{SO}_3(\text{R}^1)$ ,  $-\text{SO}_2(\text{R}^1)$ ,  $-\text{N}^+(\text{R}^1)(\text{R}^2)(\text{R}^3)$ ,  $-\text{CON}(\text{R}^1)(\text{R}^2)$  and  $-\text{COO}(\text{R}^1)$ .

**[00127]** As used herein, the term “electron donating” refers to an atom or a group that donates electron density to neighboring atoms, usually by resonance or inductive effects. Suitable electron donating groups include, but not limited to alkyl, amino,  $-\text{NHCO}(\text{R}^1)$ ,  $-(\text{CH}_2)_m-\text{N}(\text{R}^1)(\text{R}^2)$ ,  $-\text{OCO}(\text{R}^1)$  and  $-\text{O}(\text{R}^1)$ .

**[00128]** As used herein, the term “hydroxy” refers to a group of formula  $-\text{OH}$ .

**[00129]** As used herein, “halo” or “halogen” refers to F, Cl, Br, or I.

**[00130]** As used herein, the phrase “optionally substituted” means unsubstituted or substituted. As used herein, the term “substituted” means that a hydrogen atom is removed and replaced by a substituent. It is to be understood that substitution at a given atom is limited by valency.

**[00131]** The following examples are provided to further illustrate the embodiments of the present invention, but are not intended to limit the scope of the invention. While they are typical of those that might be used, other procedures, methodologies, or techniques known to those skilled in the art may alternatively be used.

## **EXAMPLES**

### **I. Synthesis:**

**[00132]** **Reagents:** Poly(allylamine hydrochloride) was obtained from Nittobo Medical, Japan (PAA $\text{N}$ -HCl, Cat# PAA-HCl-3L, 50.3% solution in water) and used as received. The material was qualified by  $^1\text{H-NMR}$ , TGA, and size exclusion chromatography (SEC-MALLS). 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride was obtained from Chem-Impex International, Wood Dale, IL (EDC-HCl, Cat# 00050, 99.8%) and used as received. The material was qualified by  $^1\text{H-NMR}$ , FT-IR, and melting point. 1-Hydroxybenzotriazole hydrate was obtained from

Chem-Impex International, Wood Dale, IL (HOBt, Cat# 24755, 99.8% (odb), 21.3% water) and used as received. The material was qualified by <sup>1</sup>H-NMR, and FT-IR. 4-Carboxyphenylboronic acid was obtained from Chem-Impex International, Wood Dale, IL (CPBA, Cat# 28086, 99.7%) and used as received. The material was qualified by <sup>1</sup>H-NMR, FT-IR, and melting point. 1-Hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxylic acid was obtained from Combi-Blocks, San Diego, CA (Cat# QB-6821, 95%). The material was qualified by <sup>1</sup>H-NMR, and FT-IR. 1-Hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxylic acid and 6-Fluoro-1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-5-carboxylic acid were obtained from Jiangyin PharmaAdvance Inc., Jiangyin, Jiangsu Province, P. R. China and fully characterized by HPLC, <sup>1</sup>H-NMR, and mass spectroscopy.

**EXAMPLE 1. SYNTHESIS OF PAA<sub>n</sub> modified with 4-Carboxyphenylboronic acid:** PAA<sub>n</sub>-HCl 50.3% solution (5.964 g, 32 mmol of amine equivalents) was placed in a 250 ml beaker with a magnetic stir bar and deionized water (90 ml). The resulting clear solution was magnetically stirred, and a pH electrode introduced. The pH was adjusted to 8.0 by dropwise addition of a 1N NaOH solution while stirring. 4-Carboxyphenylboronic acid, 99.7% (0.907 g, 5 mmol) was added to the reaction mixture and the resulting suspension was stirred. After 20 minutes of stirring, the pH had dropped to 6.8 and some solid remained suspended in solution. Additional NaOH solution was added in portions with stirring to cause the complete dissolution of the suspension. The pH of the resulting clear solution was 7.5. Solid HOBt-hydrate powder (0.046 g, 0.25 mmol) was then added to the clear reaction solution and dissolved after 20 minutes of stirring. Hydrochloric acid (1N) was added to the reaction mixture to lower the pH to 5.4. The reaction mixture remained clear. EDC-HCl (1.152 g, 6 mmol) dissolved in 10 ml of deionized water was then slowly pipetted into the reaction mixture. The clear reaction mixture had a final volume of 120 ml and a pH of 5.6. This reaction mixture was stirred for 18-hours. The reaction mixture was adjusted to pH = 2.5 with 1N HCl and then subjected to dialysis using tangential flow filtration using a Pall Minimate™ TFF system replenished with an aqueous salt solution (2.5% NaCl, pH = 2.5). After removal of 5-diafiltration volumes, the retentate solution was adjusted to pH = 8.0 with 1N NaOH. Desalting was then performed by

TFF with deionized water replenishment until the filtrate had a conductivity of < 200  $\mu\text{S}/\text{cm}$ . The retentate solution was collected in a lyophilization jar. The purified product solution was frozen in an IPA/dry-ice slurry and lyophilized until dry (3-days). A yield of 1.492 g was obtained as a fluffy white solid. The  $^1\text{H-NMR}$  spectrum ( $\text{D}_2\text{O}/\text{DCI}$ ) confirmed the expected structure (15 mol% substitution) and the absence of small molecule impurities.

**EXAMPLE 2. SYNTHESIS OF PAA<sub>n</sub> modified with 1-Hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxylic acid:** PAA<sub>n</sub> 50.3% solution (0.5017 g, 2.70 mmol of amine equivalents) was placed in a 30 ml glass vial with a magnetic stir bar and deionized water (8.5 ml). The resulting clear solution was magnetically stirred, and a pH electrode was introduced. The solution was adjusted to pH = 8.0 by dropwise addition of a 1N NaOH solution while stirring. 1-Hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxylic acid powder (0.0874 g, 0.491 mmol) was added to the reaction mixture and the resulting suspension was stirred. After 20 minutes of stirring, the pH had dropped to 5.9 and some solid remained suspended in solution. Additional NaOH solution was added in portions with stirring to cause the complete dissolution of the remaining solid. The pH of the resulting clear solution was 7.4. Solid HOBt hydrate powder (0.0084 g, 0.0491mmol) was then added to the clear reaction solution and dissolved after 20 minutes of stirring. Hydrochloric acid (1N) was added to the reaction mixture to lower the pH to 5.4. The reaction solution remained clear. EDC-HCl (0.1097 g, 0.572 mmol) dissolved in 1.0 ml of deionized water was then slowly pipetted into the reaction mixture. The clear reaction mixture had a final volume of 10 ml and a pH of 5.4. This reaction mixture was stirred for 18-hours. The reaction mixture was precipitated into excess acetone. The precipitated solid was dissolved in water, the pH adjusted to 2.8 with 1N HCl and then subjected to dialysis purification using 6 - 8k MWCO cellulose membrane dialysis tubing (Spectrum Laboratories) for 8-hours against 5-gallons of acidified water (pH = 2-3), and then against deionized water over 2-days with three additional water changes. The solution contained within the dialysis bag was collected in a lyophilization jar. The solution was frozen on IPA/dry-ice and place onto lyophilizer until dry (3-days). A yield of 243 mg was obtained as a fluffy white solid. The  $^1\text{H-NMR}$  spectrum

(D<sub>2</sub>O/DCI) confirmed the expected structure (18 mol% substitution) and the absence of small molecule impurities.

**EXAMPLE 3. SYNTHESIS OF PAA<sub>n</sub> Modified With 1-Hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-5-carboxylic acid:** PAA<sub>n</sub> 50.3% solution (5.004 g, 26.90 mmol of amine equivalents) was placed in a 100 ml glass beaker with a magnetic stir bar and deionized water (40.0 ml). The resulting clear solution was magnetically stirred, and a pH electrode was introduced. The solution was adjusted to pH 8.1 by dropwise addition of a 5N NaOH solution while stirring. 1-Hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-6-carboxylic acid powder (0.839 g, 4.71 mmol) was added to the reaction mixture and the resulting suspension was stirred. After 20 minutes of stirring, the pH had dropped to 6.3 and some solid remained suspended in solution. Additional NaOH solution was added in portions with stirring to cause the complete dissolution of the remaining solid. The pH of the resulting clear solution was 8.1. Solid HOBt hydrate powder (0.039 g, 0.22 mmol) was then added to the clear reaction solution and dissolved after 20 minutes of stirring. Hydrochloric acid (4N) was added to the reaction mixture to lower the pH from 7.9 to 5.8. The reaction solution remained clear. EDC-HCl (0.900 g, 4.69 mmol) dissolved in 1.25 ml of deionized water was then slowly pipetted into the reaction mixture. The clear reaction mixture had a final volume of ~50 ml and a pH of 5.9. This reaction mixture was stirred for 18-hours. The reaction mixture was pH adjusted from 5.3 to 2.6 with 4N HCl and then subjected to dialysis purification using 6 - 8k MWCO cellulose membrane dialysis tubing (Spectrum Laboratories) for 18-hours against 5-gallons of acidified water (pH = 2.5), and then against deionized water over 2-days with two additional water changes. The solution contained within the dialysis bag was collected in a lyophilization jar. The solution was frozen with IPA/dry-ice and placed onto lyophilizer until dry (3-days). A yield of 2.72 g was obtained as a fluffy white solid. The <sup>1</sup>H-NMR spectrum (D<sub>2</sub>O/DCI) confirmed the expected structure (15 mol% substitution) and the absence of small molecule impurities.

**EXAMPLE 4. SYNTHESIS OF PAA<sub>n</sub> Modified With 6-Fluoro-1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-5-carboxylic acid:** PAA<sub>n</sub> 50.3% solution (4.999 g, 26.88 mmol of amine equivalents) was placed in a 100 ml glass beaker with a magnetic

stir bar and deionized water (40.0 ml). The resulting clear solution was magnetically stirred, and a pH electrode was introduced. The solution was adjusted to pH 8.1 by dropwise addition of a 5N NaOH solution while stirring. 6-Fluoro-1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborole-5-carboxylic acid powder (0.829 g, 4.23 mmol) was added to the reaction mixture and the resulting suspension was stirred. After 20 minutes of stirring, the pH had dropped to 6.9 and some solid remained suspended in solution. Additional NaOH solution was added in portions with stirring to cause the complete dissolution of the remaining solid. The pH of the resulting clear solution was 8.1. Solid HOBt hydrate powder (0.038 g, 0.22 mmol) was then added to the clear reaction solution and dissolved after 20 minutes of stirring. Hydrochloric acid (4N) was added to the reaction mixture to lower the pH from 8.1 to 5.5. The reaction solution remained clear. EDC-HCl (0.9057 g, 4.72 mmol) dissolved in 1.25 ml of deionized water was then slowly pipetted into the reaction mixture. The clear reaction mixture had a final volume of ~50 ml and a pH of 5.6. This reaction mixture was stirred for 18-hours. The reaction mixture was pH adjusted from 5.5 to 2.6 with 4N HCl and then subjected to dialysis purification using 6 - 8k MWCO cellulose membrane dialysis tubing (Spectrum Laboratories) for 18-hours against 5-gallons of acidified water (pH = 2.5), and then against deionized water over 2-days with two additional water changes. The solution contained within the dialysis bag was collected in a lyophilization jar. The solution was frozen with IPA/dry-ice and placed onto lyophilizer until dry (3-days). A yield of 2.76 g was obtained as a fluffy white solid. The <sup>1</sup>H-NMR spectrum (D<sub>2</sub>O/DCl) confirmed the expected structure (14 mol% substitution) and the absence of small molecule impurities.

## **II. Mucin-mixing Assay:**

[00133] The scheme for mucin-mixing assay is shown in FIG. 1.

[00134] When a water-soluble mucin glycoprotein is mixed with a soluble polymeric complexing agent, a variety of outcomes may result. The solution may remain clear or become cloudy or even opaque. The physical state of the mixture may remain homogeneous and flowable, or it may contain particles or even take on a gel-like appearance. The degree of opacity and the physical appearance of the mixture

provides a qualitative assessment of the interaction between the complexing agent and mucin, and more importantly, the physical properties of the complex that is formed.

[00135] The inventors seek polymers capable of forming extended network structures when mixed with mucin. They have found that when certain polymers are combined with mucin glycoprotein in solution, complexation may be observed by the appearance of gel-like or opaque mixtures with substantial phase separation. Conversely, in the absence of complexation, the solution may remain clear and flowable. In seeking polymers capable of strong mucin complexation, they are interested in classifying such mixtures according to well-defined descriptors of clarity and physical state.

[00136] For example, in some cases, a dispersion may be formed. In a dispersion, no particulate is visible. Dispersions may be stable for days without settling or aggregation. In other cases, a suspension of small particles may be formed. A suspension may settle out over time (hours, days), but is generally stable and can be re-suspended by mixing. There is literature precedent for use of a turbidity metric derived from optical absorbance at a particular visible light wavelength, and relationship of this metric to assess the degree of complexation in some related experiments involving complex formation involving polymers.

[00137] However, in some cases, mucin complexation by certain polymers results in gross precipitation of larger particles, sometimes with irregular or complex morphology. This may be an indication of extended network formation. In some instances, these precipitated solids have adhesive properties, adhering to the walls of the vial in which the mixing experiment is performed. In some cases, complex fiber-like precipitates or gels are formed. Furthermore, many cases of gross precipitation are accompanied by phase separation (syneresis) where the polymer/mucin complex is deposited as an adherent film or a gel-like mass, and a separate liquid phase (usually clear or only slightly hazy) is observed. In cases of gross precipitation such as these, it is likely that the degree of complexation is very high, and it is informative to classify the morphology and appearance of the mucin/polymer complex in comparison to related materials.

[00138] The objective of the mucin-mixing assay is to determine whether a test polymer forms an insoluble complex when mixed with soluble mucin glycoprotein under a set of standard conditions, and to observe the general properties of the resulting mixture. The assay outputs are: 1) assignment of a clarity descriptor, 2) assignment of a physical state descriptor and 3) optional descriptions and comments.

[00139] **Isolation of a water-soluble fraction of Sigma (cat # 1778) mucin from porcine stomach, Type-3 (MPS-3):** The protocol is as follows. 1.0 g of MPS-3 is mixed with 40 ml of MilliQ deionized water in a 50 mL conical tube. The suspension was left overnight by attaching the tubes to a rotating carousel mixer. The 50 ml conical tube was then centrifuged on a Beckman Avanti centrifuge (5,300 rpm for 60 minutes). The supernatant was poured carefully into a fresh 50 ml conical tube trying to not disturb the solid pellet at the bottom. Centrifugation was then repeated on the supernatant (Beckman Avanti centrifuge, 5,300 rpm for 60 minutes). The supernatant was again collected into a tared 50 ml conical tube. The mucin solution was frozen at -80 °C for at least 2 hrs. The frozen sample was placed on a lyophilizer for at least 3-days. The lyophilized product was collected, the tube weighed, and % yield calculated, with an expected recovery of 0.60-0.65 g. The solid was stored at 2-5 °C in the refrigerator.

[00140] **Preparation of 0.1 M MES-Saline Buffer:** 21.3 g of (2-(N-morpholino)ethanesulfonic acid monohydrate) (MES, J.T. Baker Bioreagent, >98%) was added into a 1-liter bottle. 9.0 g of Sodium Chloride (Fisher Chemical, USP grade) was added into the bottle. A 1-liter graduated cylinder was filled with mQ deionized water (DIW, 18 MΩ). Approximately 750 ml of DIW was added to the bottle, capped and shaken to dissolve all solids. A magnetic stirring bar and a pH electrode were added to the bottle, and stirring initiated. 1N of NaOH solution was added in portions to bring the solution pH to 6.0 (or other desired pH), noting the volume of solution added. The required amount of additional DIW was added to provide a total volume of 1-liter. The bottle was capped and the buffer was stored at 2-5 °C.

[00141] **Polymer/mucin mixing turbidity and observational assay:** A 1.0% w/w solution was made of each test polymer using MES-Saline buffer, pH adjusted to

6.0 (or other desired pH). A 1.0% w/w solution of water-soluble MPS-3 was made using MES-Saline buffer, pH adjusted to 6.0 (or other desired pH). The mucin solution was slightly hazy. 0.25 – 0.5 mL of the MPS-3 solution was placed into a 2-dram (4 mL) vial. An equivalent volume of the test polymer solution was slowly added to the vial. The vial capped and slowly rotated to mix while observing any physical changes. One of the following descriptors for the clarity of the mixtures can be selected to read the resulting mixture: clear (only slight hazy, similar to initial mucin solution); hazy (more hazy than initial mucin solution, can read text through it); cloudy (non-transparent, can't read through it, but transmits light well); opaque (like milk, no transparency, does not transmit much light) and not applicable (material shows gross phase separation). One of the following descriptors on the physical state of the mixtures can be selected to read the resulting mixture: clear; dispersion (no visible particles); suspension (very fine particulate is observable), precipitate (large irregular particles, may be adherent) and phase separation (films, gels are deposited, a clear or hazy supernatant fluid may be seen). The mixtures in capped vials were observed for approx. 1 hour to note any changes.

**[00142] Results of mucin-mixing observational assay:** Following the protocol above, a set of test compounds were tested for their ability to form insoluble complexes with mucin in MES buffer at pH = 5.5, 6.0, and 6.5. Polymer solutions were made at least 1-hour before the experiment and allowed to mix gently on a rotisserie. Total dissolution was confirmed for all test polymer before beginning the experiment.

**[00143]**

**Table 1: Mucin Mixing Observational Assay Results**

Polymer	Mucin-Mixing Result (clarity/physical-state)		
	pH = 5.5	pH = 6.0	pH = 6.5
PAA <sub>n</sub> -HCl	2/B	2/B	2/B
Example-1	2/B	2/B	5/E

Example-2	5/E	5/E	5E
Example-3	5/E	5/E	5/E
Example-4	5/E	5/E	5/E

**[00144]** The results of the mucin-mixing assay show that when the parent polymer, PAA<sub>n</sub>-HCl, is mixed with mucin, a hazy dispersion is obtained at all pH values. This result suggests that in this case, the polymer/mucin complex does not form an extended network structure. When the modified PAA<sub>n</sub> of Example-1 is mixed with mucin, a similar hazy dispersion is observed at pH = 5.5 and 6.0. However, at pH = 6.5 strong phase separation is observed with a white film depositing on the vessel walls. At this higher pH value, the polymer of Example-1 is capable of acting as a mucin crosslinking agent, forming an extended network structure.

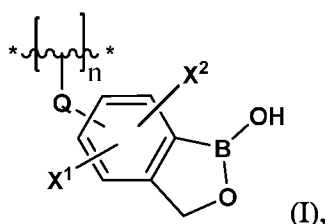
**[00145]** The polymers of Example-2, Example-3 and Example-4 are structurally related to Example-1. However, the boronic acid group is present as a cyclized benzoxaborole functionality. For polymers modified with benzoxaboroles, such as Example-2, Example-3 and Example-4, strong phase separation behavior is observed at all pH values examined in this experiment. The benzoxaborole functionality represents an activated phenylboronic acid group capable of a stronger interaction with mucin at lower pH. This stronger interaction causes the observed stronger and more robust extended network formation at pH = 6.0 and at pH = 5.5.

**[00146]** Additionally, there is even a stronger observed interaction at pH = 5.5 with Example-4 when compared to Example-2 and Example-3. This is due to the presence of an electron withdrawing fluoro substituent which acts to further lower the pK<sub>a</sub> of the boronic acid moiety.

While the invention has been particularly shown and described with reference to specific preferred embodiments, it should be understood by those skilled in the art that various changes in form and detail may be made therein without departing from the spirit and scope of the invention as defined by the appended claims.

What is claimed is:

1. A polymer comprising a pendant benzoxaborole repeat unit of Formula (I)



wherein

\*~~~~\* is a polymer repeat unit;

Q is a direct bond or a linker;

$X^1$  and  $X^2$  are independently selected from a group consisting of hydrogen, halo,  $-CN$ ,  $-NO_2$ ,  $-CF_3$ ,  $-SO_2CF_3$ ,  $-SO_3(R^1)$ ,  $-SO_2(R^1)$ ,  $-N^+(R^1)(R^2)(R^3)$ ,  $-CON(R^1)(R^2)$ ,  $-COO(R^1)$ , substituted or unsubstituted alkyl,  $-NHCO(R^1)$ ,  $-(CH_2)_m-N(R^1)(R^2)$ ,  $-OCO(R^1)$  and  $-O(R^1)$ ;

$R^1$ ,  $R^2$  and  $R^3$  in each occurrence are independently hydrogen or substituted or unsubstituted alkyl (preferably a substituted or unsubstituted  $C_1$ - $C_6$  alkyl);

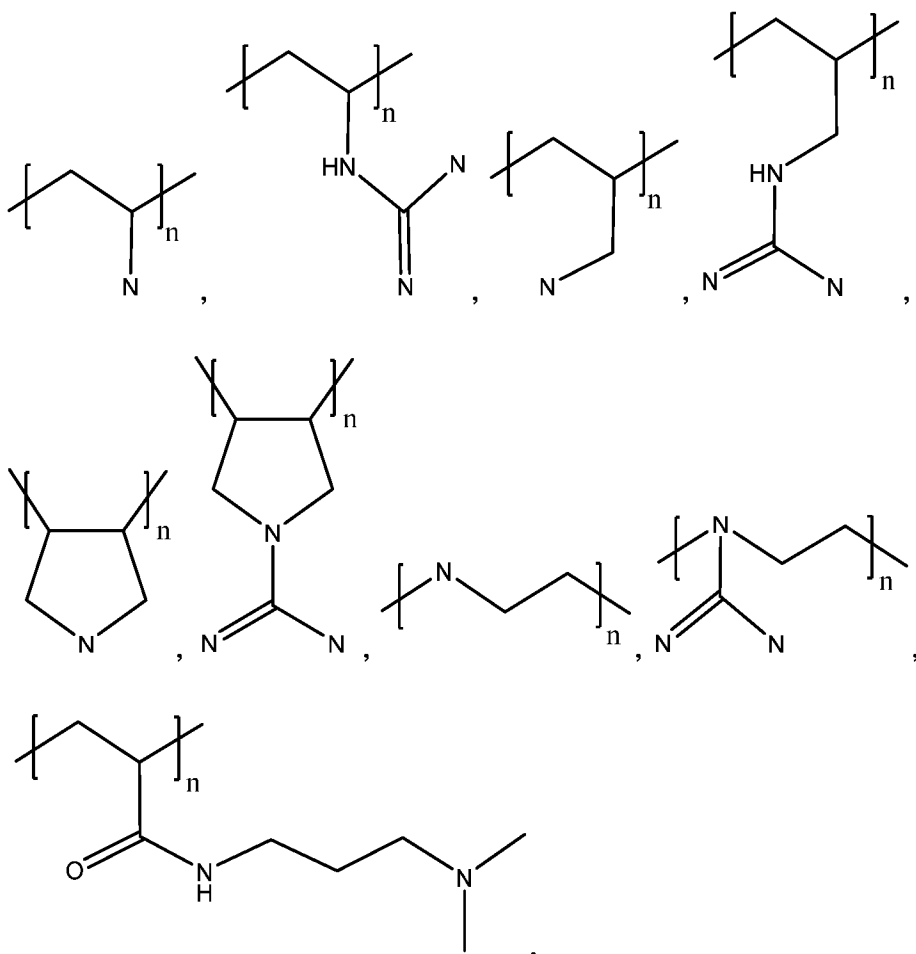
n is an integer from 1 to 100,000 and

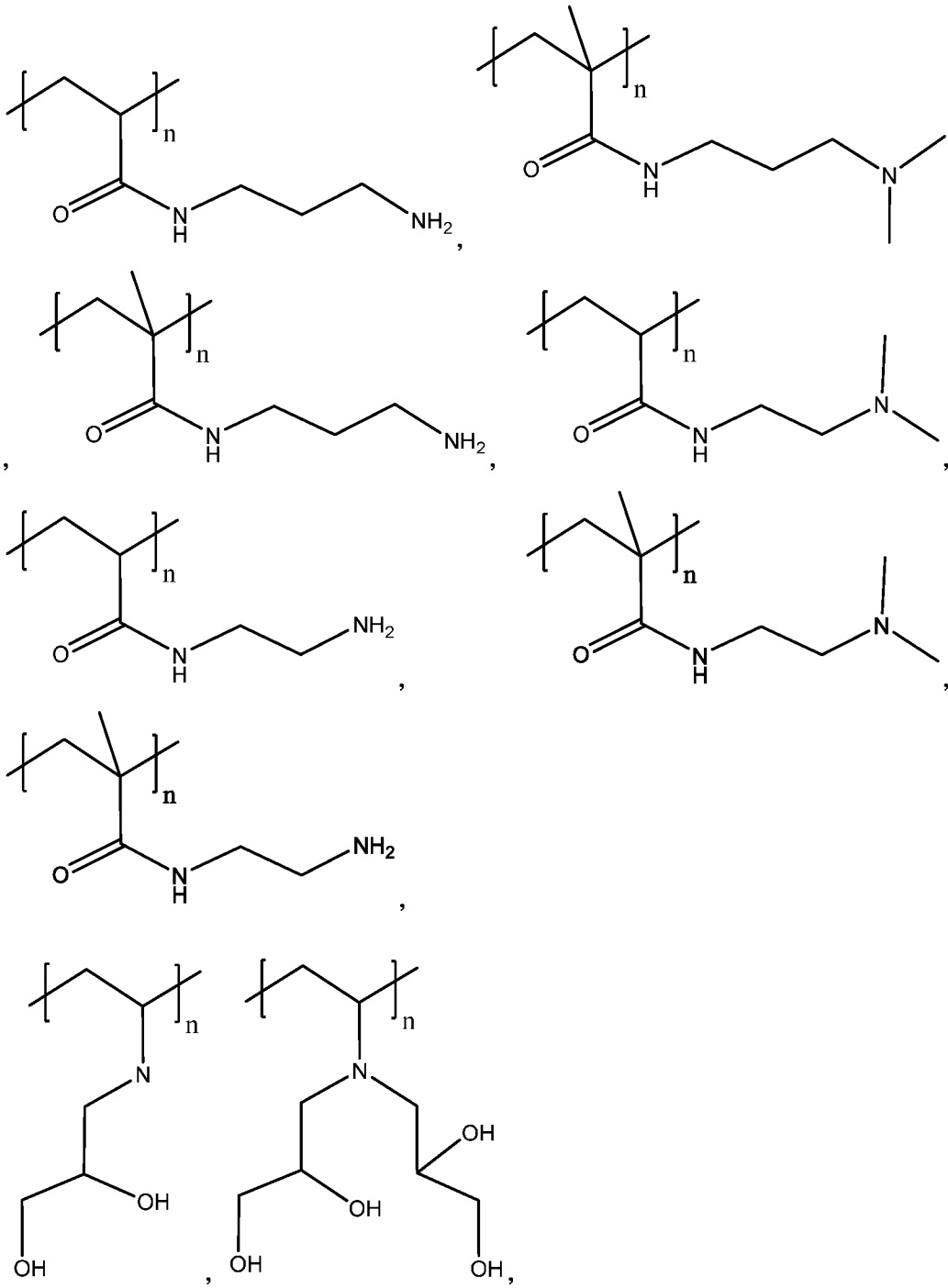
m is an integer from 0 to 4.

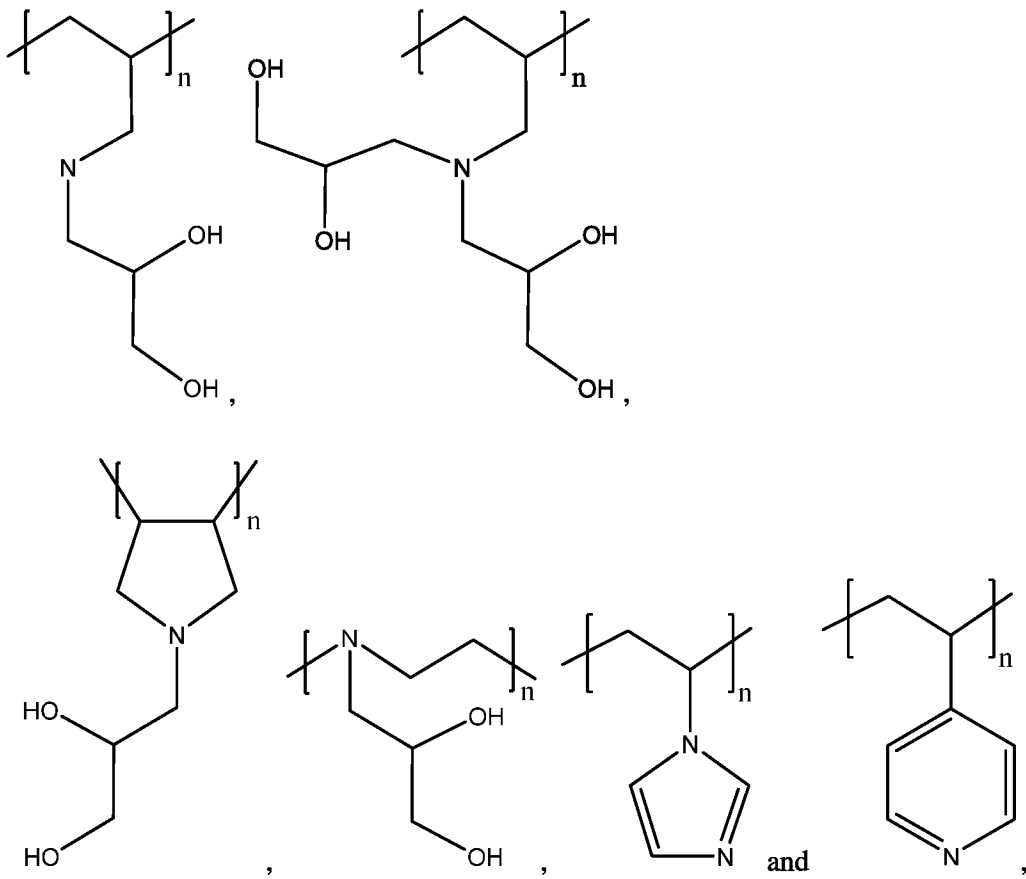
2. A polymer comprising a pendant benzoxaborole repeat unit of Formula (I) according to claim 1, wherein the polymer repeat unit comprises of cationic repeat units, amine-functionalized repeat units and repeat units that contain nitrogen.
3. A polymer comprising a pendant benzoxaborole repeat unit of Formula (I) according to claim 2, wherein the polymer repeat unit comprises of repeat units that contain nitrogen.
4. A polymer comprising a pendant benzoxaborole repeat unit of Formula (I)

according to claim 1, wherein the Q is a linker selected from a group consisting of  $-\text{N}(\text{R}^1)-(\text{CH}_2)_m-$ ,  $-(\text{CH}_2)_m-\text{N}(\text{R}^1)-\text{C}(\text{O})-$ ,  $-\text{C}(\text{O})-\text{N}(\text{R}^1)-$ ,  $-\text{C}(\text{O})-(\text{CH}_2)_m-$ ,  $-\text{C}(\text{O})-\text{N}(\text{R}^1)-(\text{CH}_2)_m-\text{N}(\text{R}^1)-$ ,  $-(\text{CH}_2)_m-$ ,  $-\text{O}-(\text{CH}_2)_m-$ ,  $-\text{S}-(\text{CH}_2)_m-$ , and  $-\text{OC}(\text{O})-(\text{CH}_2)_m-$ .

5. A polymer comprising a pendant benzoxaborole repeat unit of Formula (I) according to claim 1 and at least one cationic monomeric repeat unit selected from the group consisting of

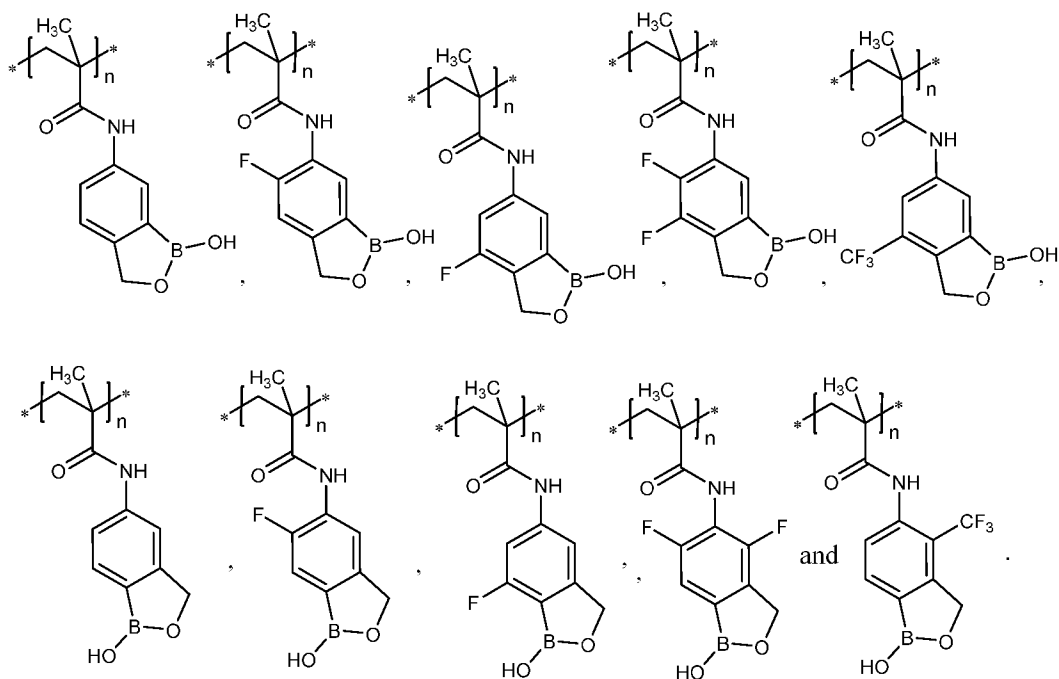






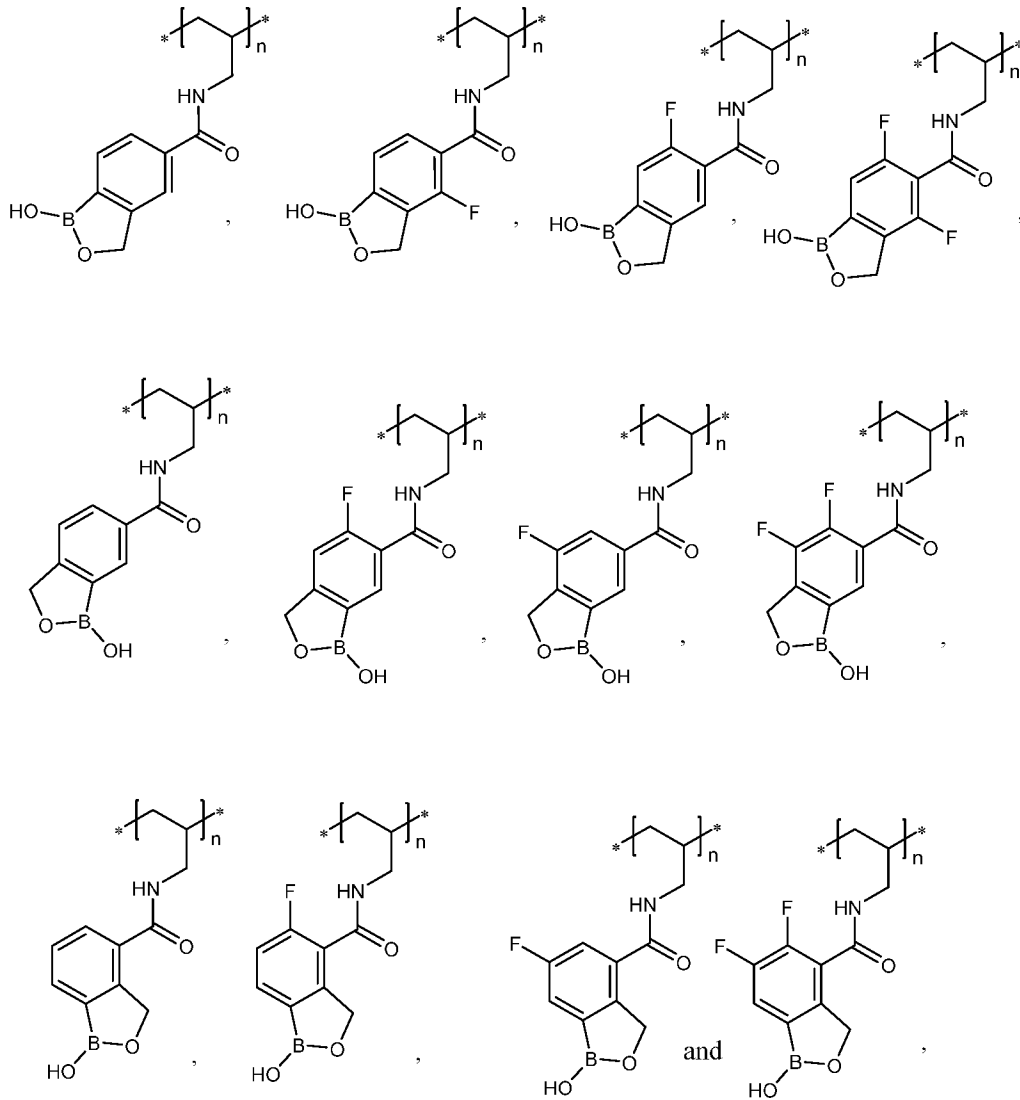
where "n" represents an integer from 1 to 100,000.

6. A polymer comprising a benzoxaborole repeat unit selected from the group consisting of



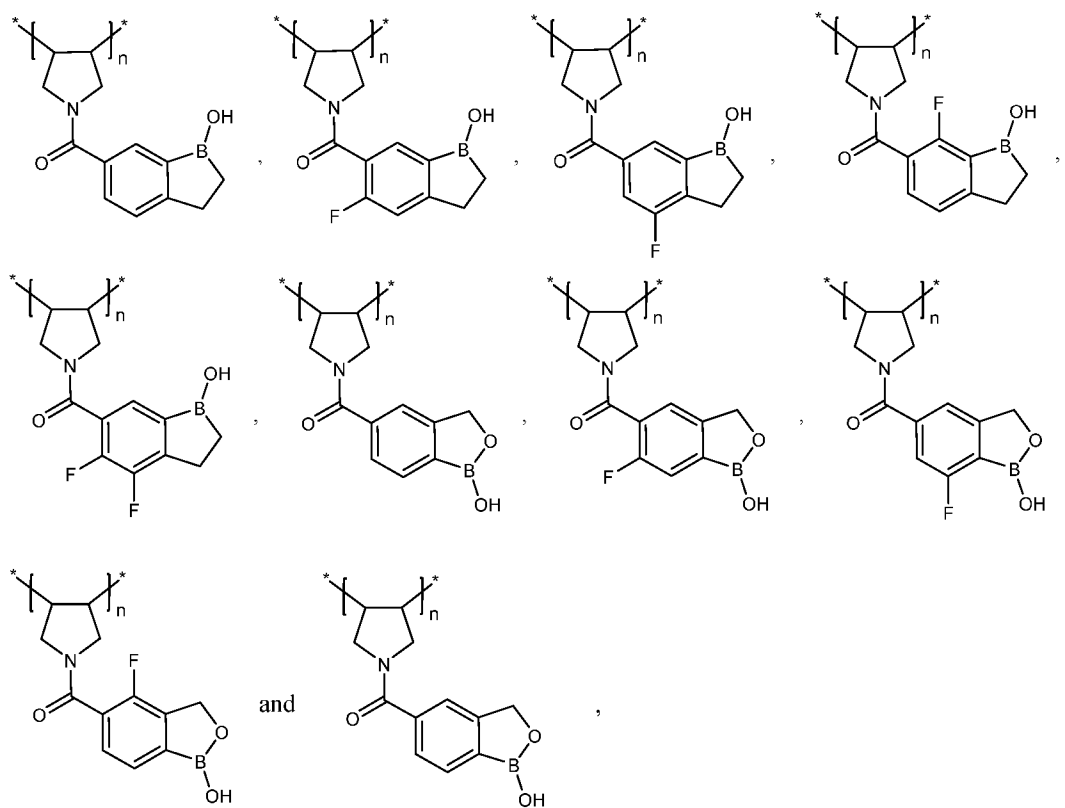
wherein n is an integer from 1 to 100,000.

7. A polymer comprising a benzoxaborole repeat unit selected from the group consisting of



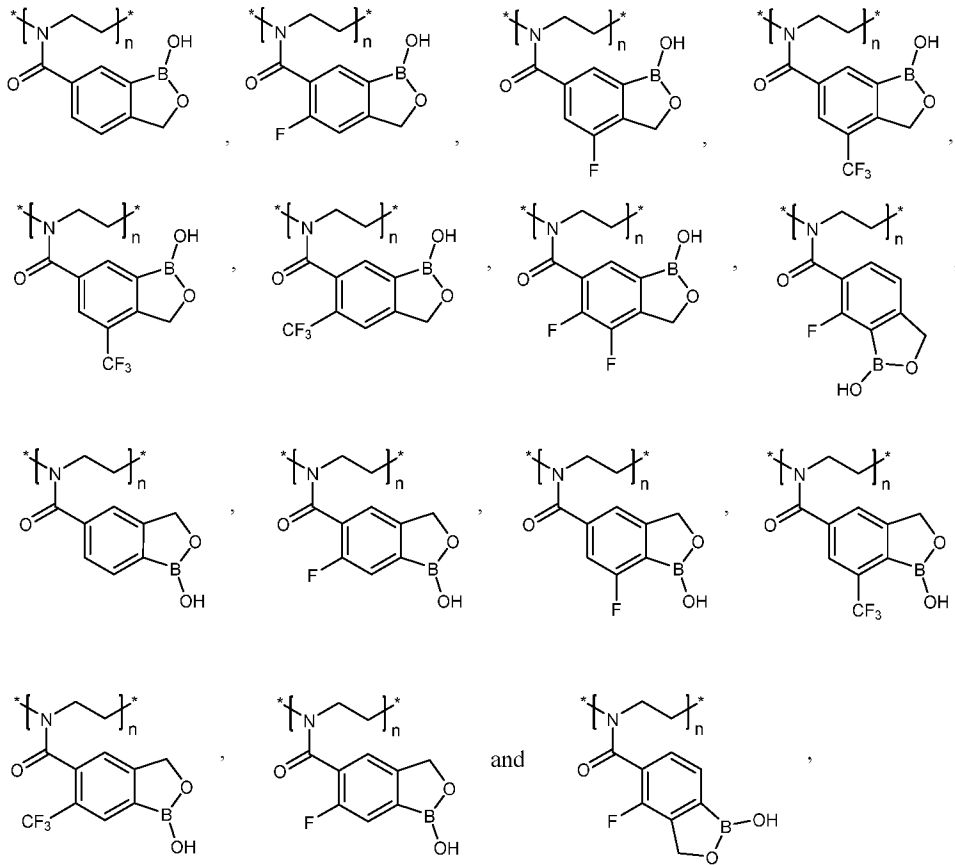
wherein n is an integer from 1 to 100,000.

8. A polymer comprising a benzoxaborole repeat unit selected from the group consisting of



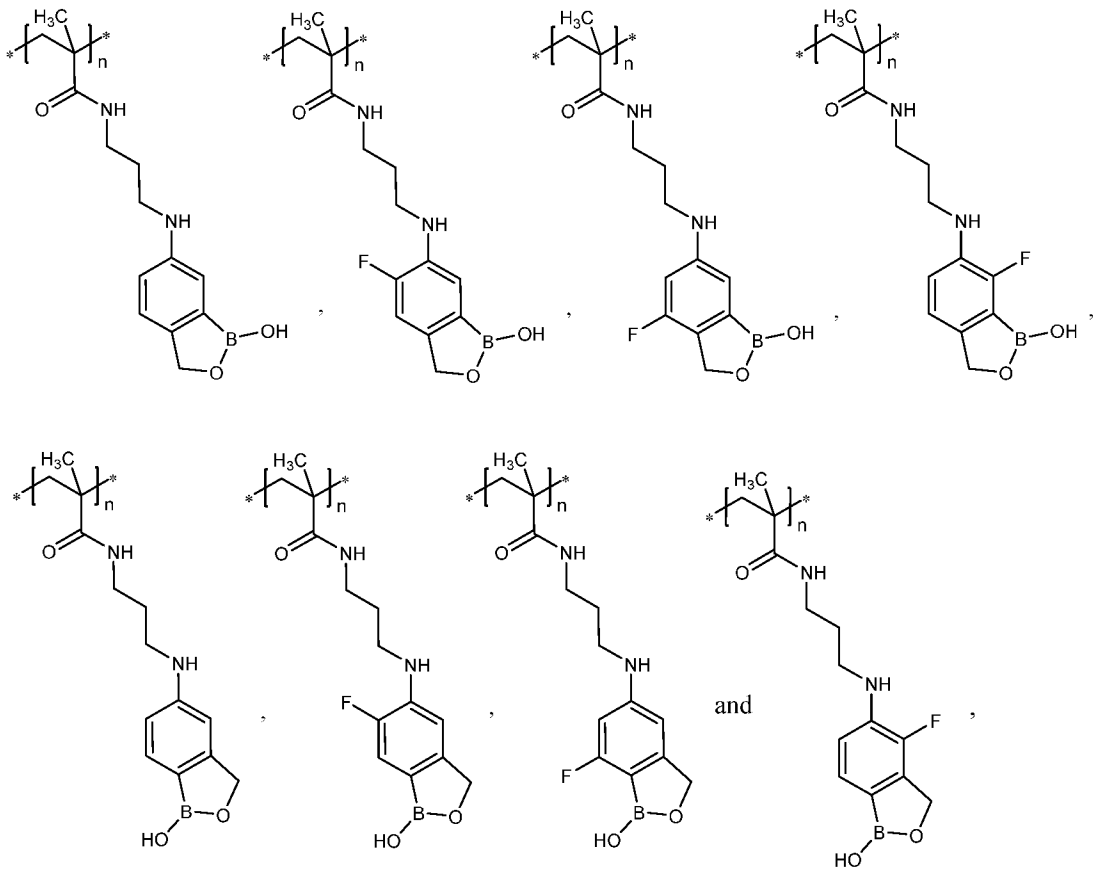
wherein n is an integer from 1 to 100,000.

9. A polymer comprising a benzoxaborole repeat unit selected from the group consisting of



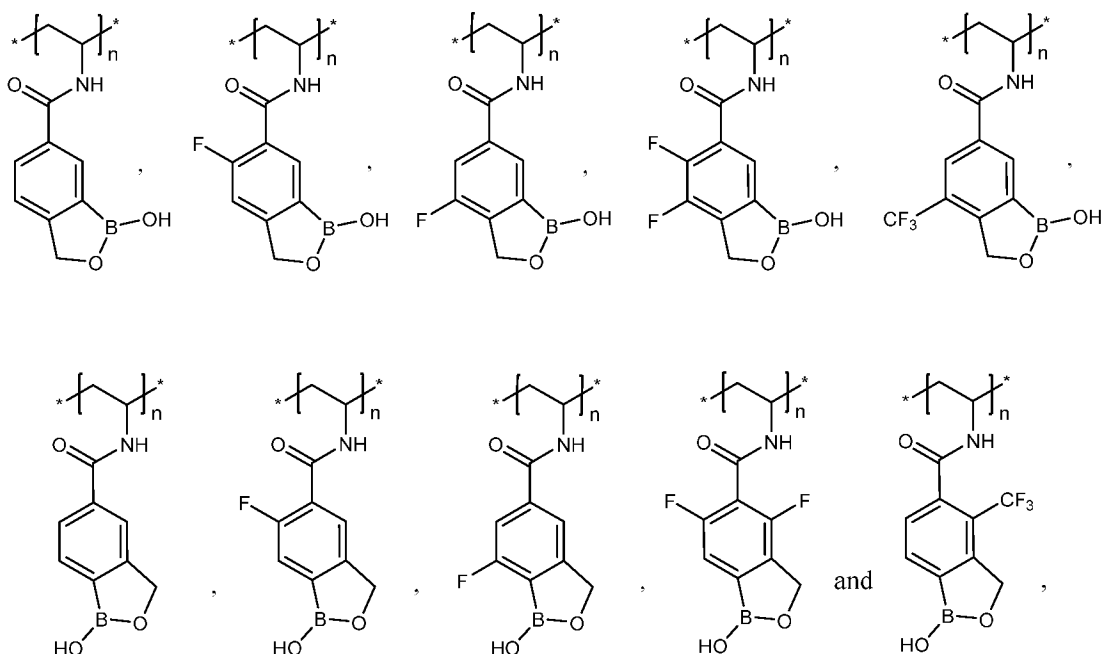
wherein n is an integer from 1 to 100,000.

10. A polymer comprising a benzoxaborole repeat unit selected from the group consisting of



wherein n is an integer from 1 to 100,000.

11. A polymer comprising a benzoxaborole repeat unit selected from the group consisting of



wherein  $n$  is an integer from 1 to 100,000.

12. A pharmaceutical composition comprising a polymer of any one of the preceding claims and a pharmaceutically acceptable excipient.

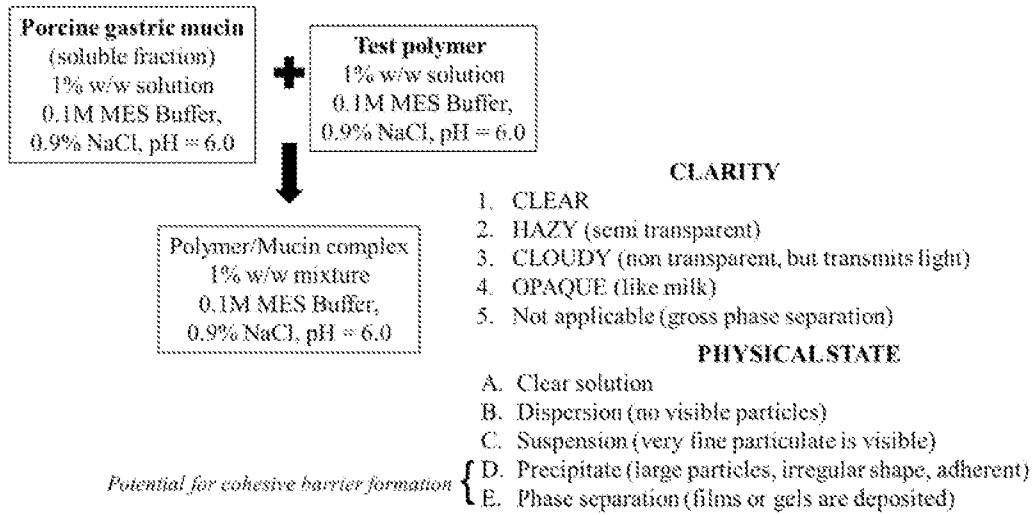
13. The pharmaceutical composition of claim 12, wherein the composition is a liquid, tablet, caplet or capsule.

14. The pharmaceutical composition of claim 12, wherein the composition is an enteric coated tablet, caplet or capsule.

15. The pharmaceutical composition of claim 14, wherein the enteric coated tablet, caplet or capsule is for targeted deliver to the duodenum.

16. A method for treating a metabolic disorder in a subject, comprising administering to a subject in need thereof a therapeutically effective amount of a polymer according to any one claims 1-11 or a pharmaceutical composition according to any one of claims 12-15.

17. The method of claim 16, further comprising administering another therapeutic agent to the subject in need thereof.
18. The method of claim 16 or claim 17, wherein the metabolic disorder is glucose intolerance, T1DM, T2DM, prediabetes, hyperlipidemia, obesity, overweight, dyslipidemia, hypertension, hyperglycemia, impaired glucose tolerance, insulin resistance, metabolic syndrome, non-alcoholic steatohepatitis (NASH), non-alcoholic fatty liver disease (NAFLD) and polycystic ovary syndrome (PCOS).
19. The method of claim 16 or claim 17, wherein the metabolic disorder is type-2 diabetes mellitus.
20. A method for treating gastrointestinal disorder in a subject, comprising administering to a subject in need thereof a therapeutically effective amount of a polymer according to any one claims 1-11 or a pharmaceutical composition according to any one of claims 12-15.



**FIG. 1**

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US20/51499

## A. CLASSIFICATION OF SUBJECT MATTER

IPC - C07F 5/02; A61K 31/69 (2020.01)

CPC - C07F 5/02; A61K 31/69

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History document

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	(KUDO, Y et al.) 'Controlled water-soluble properties of poly(vinyl alcohol) films via the benzoxaborole-containing temperature-responsive copolymers'; 30 April 2019, Polymer; Volume 175, pages 1-7; page 2, figure 1	1, 12-15
A	US 2006/0134062 A1 (HUVAL, CC et al.) 22 June 2006; paragraph [0160]	1, 12-15
A	US 2011/0059176 A1 (MORO, T et al.) 10 March 2011; paragraph [0031]	1, 12-15
A	(KOTSUCHIBASHI, Y et al.) 'Temperature, pH, and Glucose Responsive Gels via Simple Mixing of Boroxole- and Glyco-Based Polymers'; 07 March 2013, ACS Macro Letters; Volume 2, pages 260-264; abstract; page 261, figure 1	1, 12-15
A	WO 2017/061435 A1 (NAT INST FOR MATERIALS SCIENCE) 13 April 2017; original - paragraph [0020]	1, 12-15

 Further documents are listed in the continuation of Box C. See patent family annex.

\* Special categories of cited documents:

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

"D" document cited by the applicant in the international application

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

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

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

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

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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

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

"&amp;" document member of the same patent family

Date of the actual completion of the international search

30 November 2020 (30.11.2020)

Date of mailing of the international search report

08 FEB 2021

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents

P.O. Box 1450, Alexandria, Virginia 22313-1450

Facsimile No. 571-273-8300

Authorized officer

Shane Thomas

Telephone No. PCT Helpdesk: 571-272-4300

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US20/51499

**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
3.  Claims Nos.: 16-20  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Groups I+, Claims 1-15; and a compound of Formula I wherein \*wavy line\* is a polymer repeat unit; Q is a direct bond; X1 and X2 are hydrogen; and n is 1 (compound structure) are directed toward compounds and compositions.

\*\*\*-Continued on supplemental page-\*\*\*

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
  
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:  
1 (in-part) and 12-15 (in-part); a compound of Formula I, wherein \*wavy line\* is a polymer repeat unit; Q is a direct bond; X1 and X2 are hydrogen; and n is 1 (compound structure)

**Remark on Protest**

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

----Continued from Box No. III: Observations where unity of invention is lacking----

The compounds and compositions will be searched to the extent they encompass a compound of Formula I, wherein "wavy line" is a polymer repeat unit; Q is a direct bond; X1 and X2 are hydrogen; and n is 1 (first exemplary compound structure). Applicant is invited to elect additional compound(s), with fully specified structure(s) thereof (e.g. no optional or variable atoms, bonds, or substituents) for each, to be searched. Additional compound(s) will be searched upon the payment of additional fees. It is believed that claims 1 (in-part) and 12-15 (in-part) encompass this first named invention and thus these claims will be searched without fee to the extent that they encompass a compound of Formula I, wherein "wavy line" is a polymer repeat unit; Q is a direct bond; X1 and X2 are hydrogen; and n is 1 (compound structure). Applicants must specify the claims that encompass any additionally elected compound structure(s). Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined. An exemplary election would be a compound of Formula I wherein "wavy line" is a polymer repeat unit; Q is a direct bond; X1 and X2 are hydrogen; and n is 2 (compound structure).

Groups I+ share the technical features including: a polymer comprising a pendant benzoxaborole repeat unit of Formula (I), as shown, wherein "wavy line" is a polymer repeat unit; Q is a direct bond or a linker; X1 and X2 are independently selected from a group consisting of hydrogen, halo, -CN, -NO<sub>2</sub>, -CF<sub>3</sub>, -SO<sub>2</sub>CF<sub>3</sub>, -SO<sub>3</sub>(R<sub>1</sub>), -SO<sub>2</sub>(R<sub>1</sub>), -N+(R<sub>1</sub>)(R<sub>2</sub>)(R<sub>3</sub>), -CON(R<sub>1</sub>)(R<sub>2</sub>), -COO(R<sub>1</sub>), substituted or unsubstituted alkyl, -NHCO(R<sub>1</sub>), -(CH<sub>2</sub>)<sub>m</sub>N(R<sub>1</sub>)(R<sub>2</sub>), -OCO(R<sub>1</sub>) and -O(R<sub>1</sub>); R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> in each occurrence are independently hydrogen or substituted or unsubstituted alkyl (preferably a substituted or unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl); n is an integer from 1 to 100,000 and m is an integer from 0 to 4; and a pharmaceutical composition comprising a polymer and a pharmaceutically acceptable excipient.

However, these shared technical features are previously disclosed by the article entitled "Controlled water-soluble properties of poly(vinyl alcohol) films via the benzoxaborole-containing temperature-responsive copolymers" by Kudo, et al. (hereinafter 'Kudo').

Kudo discloses a polymer comprising a pendant benzoxaborole repeat unit of Formula (I), as shown, wherein "wavy line" is a polymer repeat unit; Q is a linker; X1 and X2 are hydrogen; n is an integer from 1 (benzoxaborole-containing copolymers as shown in figure 1; page 2, figure 1); and a pharmaceutical composition comprising a polymer and a pharmaceutically acceptable excipient (composition comprising a benzoxaborole-containing copolymer and water (pharmaceutically acceptable excipient); page 2, figure 1; page 4, first column, second paragraph).

Since none of the special technical features of the Groups I+ inventions is found in more than one of the inventions, and since all of the shared technical features are previously disclosed by the Kudo reference, unity of invention is lacking.