



- (51) **International Patent Classification:**
C08F 22/40 (2006.01) C08F 12/30 (2006.01)
- (21) **International Application Number:**
PCT/US2016/051168
- (22) **International Filing Date:**
9 September 2016 (09.09.2016)
- (25) **Filing Language:** English
- (26) **Publication Language:** English
- (30) **Priority Data:**
62/216,335 9 September 2015 (09.09.2015) US
62/216,337 9 September 2015 (09.09.2015) US
62/308,709 15 March 2016 (15.03.2016) US
- (71) **Applicant:** DSM IP ASSETS B.V. [NL/NL]; Het Overloon 1, 6411 TE Heerlen (NL).
- (72) **Inventors:** KONTRA, Justin; 530 North Guthriesville Road, Downingtown, Pennsylvania 19335 (US). RIFFEY, Jacob; DSM Services USA Inc., 735 Pennsylvania Drive, Exton, Pennsylvania 19341 (US). WATTENGEL, William C.; 610 Brainerd Place, Exton, Pennsylvania 19341 (US). RINGEISEN, Timothy A.; 118 Andover Drive, Exton, Pennsylvania 19341 (US). RADANO, Chris; 722 Westcroft Place, West Chester, Pennsylvania 19382 (US).
- (74) **Agent:** LINK, Steven; 735 Pennsylvania Drive, Exton, Pennsylvania 19341 (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, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, 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, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, 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).

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:** BIOMEDICAL ADHESIVE AND SEALANT COMPOSITIONS AND METHODS OF USE

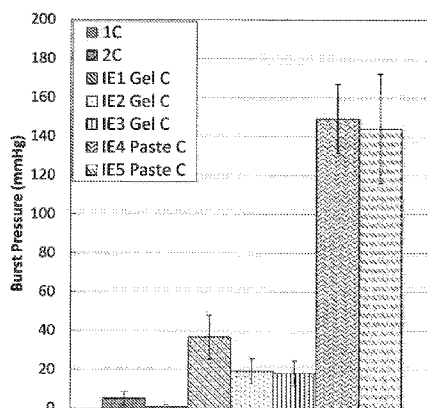


Figure 7. Effective burst pressure of sealant on pre-moistened collagen (condition C).

(57) **Abstract:** The invention relates to polymer materials suitable for use as sealants and adhesives. The polymer formulations provide elasticity, and moisture resistance. They may be employed as in-the-body sealants and adhesives, or alternatively placed against skin, and may secure medical appliances.

BIOMEDICAL ADHESIVE AND SEALANT COMPOSITIONS AND METHODS OF USE**CROSS REFERENCE TO RELATED APPLICATIONS**

[001] This application claims the benefit of the filing date of United States Provisional Patent Application No. 62/216,335 filed September 9, 2015, United States Provisional Application No. 62/216,337 filed September 9, 2015, and United States Provisional Application No. 62/308,709 filed March 15, 2016, the disclosures of which are hereby incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

[002] The invention relates generally to new synthetic medical adhesives and formulations which are capable of undergoing oxidative processes to bond with tissue surfaces, as well as themselves. Specifically, these adhesive formulations are biocompatible, adherent in moisture rich conditions, and are elastic, so as to be able to move with tissue against which it is adhered. The adhesive formulations are capable of being applied to a particular tissue surface and avoid flowing undesirably to adjacent tissue surfaces. The adhesive formulations may be utilized as internal tissue sealants, or as medical adhesives to adhere a medical component to tissue, for internal and external applications; for example the medical adhesive formulations described herein could be employed to affix an ostomy device or appliance to tissue, also contemplated are the affixing of medical devices or appliances to the skin, including bandages and coverings, glucose monitors, continuous injection systems containing micro- needles, diagnostic leads (i.e., – temperature, pulse, respiration, EKG, etc.), diffusion drug delivery patches, skin grafts, resorbable and non-resorbable barrier membranes, etc.

BACKGROUND OF THE INVENTION

[003] [0001] Synthetic, biocompatible polymers functionalized with naturally derived catecholate and guaiacolate-based (e.g. DiHydroxyPhenylAlanine (DOPA)) residues are promising biomaterials for medical applications based on their ability to covalently bind to native tissue, and crosslink with itself to form stable structures with adhesive and sealant-like properties. Such biomaterials may offer a tunable biodegradability. Many examples of these

materials exist in the primary literature and patent art, such as hydrogel-based sealants, elastomeric-like thin film adhesives, and anti-fouling or anti-microbial coatings for implants. In each of these broad categories, modified polymers can interact with a chemical oxidant in water to generate irreversible covalent bonds (i.e., chemical bonds) between any or all of, neighboring polymer chains, specific protein residues, such as those found in soft tissue, and functional groups on biologics or non-biologics. These specific materials have shown notable adhesive character both *in vitro* and *in vivo*. Yet, while many applications are proposed that would benefit from such surgical sealants, adhesives, and coatings, there have been no FDA-approved medical devices that harness the reactivity in the way originally intended. A primary reason is the lack of a comprehensive understanding of the biocompatibility profile of these materials. Also, the structure-property requirements for each application demand more tailored materials. Each of these materials requires some unique synthetic pathway that often economically disfavors commercialization at a large scale. In spite of this, the benefit of these materials in a medical device is still in sight.

[004] Much of the fundamental research surrounding catecholate-modified biomaterials has been directed toward internal surgical applications, where the benefits of wet adhesion to soft tissue are more intuitive. Despite the suitable environments that an internal application creates, such procedures come with drawbacks. For a liquid sealant, the mobility (e.g. running or dripping) of the expressed sealant prior to it setting to a solid or near solid (non-flowable state) leads to contact with adjacent tissue that can create a deleterious inflammatory response. For a thin film adhesive, typically an oxidant-dispersed polymer film is activated upon contact with moist tissue. However, for some of these films, curing is slower and thus leaching of a cytotoxic oxidant can occur more readily. Furthermore, in some cases, ambient moisture or extensive contact with air may lead to pre-oxidation of the film prior to activation, and thus poorer adhesive character upon use. Overall, the challenge of these systems for internal applications is magnified due to the effects of active chemistry on more sensitive soft tissue. For use of these adhesive compositions for in-the-body surgical applications, then, what is needed is an adhesive that is easy to apply and which minimizes flowing to adjacent tissues, thereby also minimizing the deleterious inflammatory response in tissues.

[005] Various tissue adhesives have been described in the past. For example, in US2007/0135606 A1 Belcheva and Hadba teach a polymer composition comprised of terminal

and branched isocyanate-modified polymers in the presence of a diamine to promote a curing reaction that find application in the sealing of tissue. The water sensitivity of the isocyanate groups on the polymers makes it more difficult to control the curing reaction. Additionally, the high concentrations of reactive isocyanate groups can lead to materials that are cytotoxic.

[006] In US 8,652,293 B2 Smith and Beckman disclose an adhesive composition that reacts an isocyanate-functionalized molecule, a hydrogen component, such as a multi-hydroxyl or multi-arm amine to form a crosslinks along with other components that accelerate the curing reaction. A benefit to this system is that the components are in the liquid state so little if any diluents are required to use in a curing reaction. However, the liquid components are low molecular weight, and thus have a low viscosity that leads to a materials that run and drip when applied in heavily contoured geometries. Like other isocyanate systems, these materials contain high concentrations of functional groups that may be aggressively reactive. Additionally, these formulations contain heavy metals such as bismuth and tin, making their application in vivo more challenging. Moreover, handling these adhesives requires cold storage, conditions that can potentially limit the shelf life or lead to premature curing.

[007] In US 2008/0039548A1 and US 2010/0087672 A1 respectively, Zavatsky and Khatri teach a PEG-based sealant that is activated by moisture that based on water activated curing of a isocyanate macromer. The PEG component improves the biocompatibility. Similarly, Abuzaina, in US2009/0131621 A1 teaches the addition of small amine-containing molecules to speed up cure rate in isocyanate sealants, but such an approach is accompanied with a reduction in viscosity, that can lead to uncontrolled placement of the sealant in tight, contoured spaces.

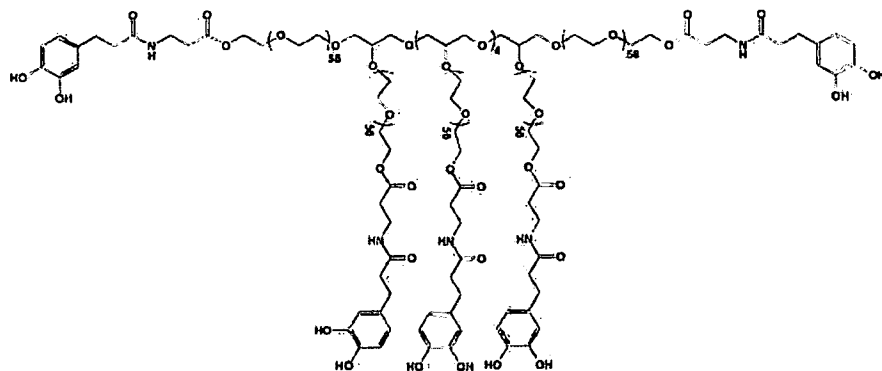
[008] While the fast reactivity of isocyanates with water is the desired characteristic in the aforementioned systems, there are numerous features of the above prior art that are undesirable. In most of these systems the strategic and precise placement of low viscosity sealants in a particular targeted area is much less controlled, leading to an adhesive that runs into and cures within other regions. A further reduction in the viscosity by introducing more reactive components mitigates this to some degree, by relying on the increased viscosity from faster reaction kinetics if that is hopefully achieved. The alternative to this is to employ higher viscosity sealants. However, viscosities that are too high often lead to sealants and adhesives that bind inefficiently to tissue because they are not able to wet the tissue surface as readily as lower viscous solutions.

[009] Another drawback to isocyanate-based sealants is the sensitivity of the isocyanate functionality to adventitious moisture. While much of the desired reactivity of these systems depends on moisture, these groups can be easily consumed, leaving small molecule, low-viscosity byproducts that either never get incorporated into the crosslinked biomaterial and thus lead to highly reactive and cytotoxic substrates. Sealants that avoid isocyanates as the primary mode of reactivity may be less likely to experience these problems.

[010] In US 7,960,498 B2, Chenault teaches the design of multiarm PEG polymers that are chemically linked together that upon reacting with aldehyde-functionalized dextran lead to hydrogels varying elasticity for the purpose of improving greater tissue compliance. In the examples provided this approach can improve elasticity only in certain cases. However, even in cases where there is an improvement, it does not occur to the degree that the sealant in the present invention disclose. Likely this is due to a combination of factors that include 1) the composition of high weight ratios of the modified multi-arm PEGs and their subsequent reaction with the multifunctional saccharides in the described sealant. Ultimately, this approach to modifying elasticity is fairly limited. From our own experience, employing reactivity as described in Chenault (i.e. partial functionalization of multi-arm substrates), leads to a materials that are ill-defined, often too viscous, and thus difficult to hydrate, which precludes its practical use by a wide range of surgeons and nurses that would be preparing these devices.

[011] This disclosure shows how carefully selected materials that are readily soluble and fast curing enhance elasticity and thus introduce a novel way to better match the compliance of a range of tissue-types. Formulations of this type generalize this approach that is required to expand opportunities to tailor biomaterials that meet these elasticity parameters. What is needed is the ability to enhance workability through simpler defined polymeric structures, that are easily hydrated (e.g. after 2 to 3 passes through reciprocating syringe mixing), and when mixed, cure fast enough to reduce the mobility of the sealant after it is dispensed.

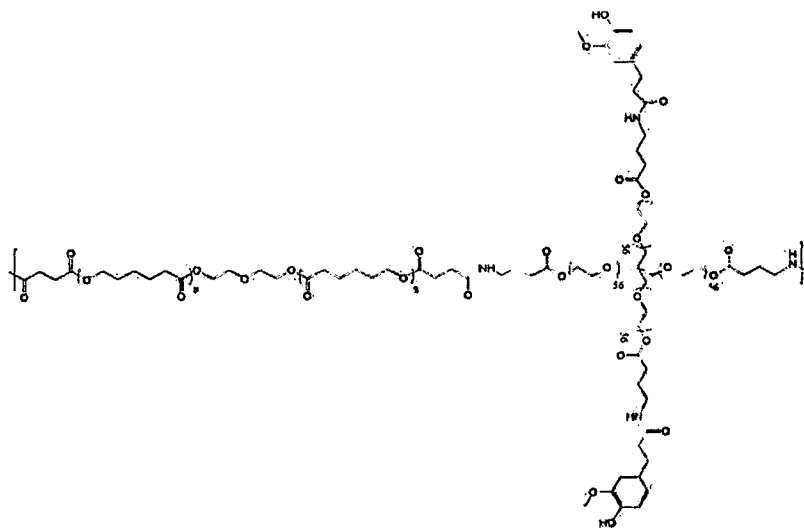
[012] In US2011/0052788A1, US2012/0116424A1, and WO2014/158288 A1, there are disclosed large families of branched PEG-based macromolecules as well as non-branched PEGs, useful, for example, as antifouling coatings and biomaterials, that upon activation crosslink to generate hydrogels that bind to tissue (for example, see Formula I).



Formula I. Polymer M161.

[013] These materials operate by a different mechanism than isocyanate sealants, and thus do well at creating a range of adhesive strength to tissue and cohesive strength through polymer-polymer crosslinks. These materials deliver adequate strength, however, most notably suffer from a lack of elasticity upon curing. This leads to limited use on tissue where the integrity of the sealant or adhesive must stretch with the movement of the tissue to which it is bound.

[014] In light of this, the need for biomaterials that approach or match the compliance of the tissue to which it is applied still remains an important requirement. Unfortunately, the methods previously described do not explain how to achieve this in a simple way. Incorporation of elastomeric components have been disclosed by Dalsin in WO2012/064821 and US2012/0116424A1 (see Formula II below), where the oligomeric polyesters are strategically built within the backbone of the polymer. The class of multi-arm polymers falling into the general structures of Formula I and Formula II, are referred to herein as Polymer 1A.



Formula II. Polymer M141.

[015] The molecule of Formula II was described as having improved elasticity. Yet, while inclusion of polyesters in these materials have the potential to improve elasticity, they do not uptake moisture as readily as materials that are classically hydrophilic, such as PEGs, nor are the molecules incorporating polyesters water soluble enough to be delivered in aqueous solution. Therefore, the previously described molecules incorporating polyesters, as represented by Formula II are not suitably reactive for use as adhesives due to their low moisture uptake. To achieve high elasticities, additional polyester would need to be incorporated and thus lose the benefit of the water-soluble and biocompatible PEG. Intuitively, one would think that a higher incorporation of the plasticizer, e.g., water in the case of a hydrogel or some other components, such as cellulose-based derivatives, may increase elasticity. However, this leads to materials that fracture much easier, and may have a decreased strength profile.

[016] The work of Messersmith, Lee, Murphy, and Dalsin show the improvement over standard amine-isocyanate-based sealants. However, the examples of Messersmith, Lee, and Murphy are formulations that are not able to deliver sealants that are suitably elastic, strong, and possess the controlled mobility that allows for precise placement. Dalsin improves this by introducing elasticity, however at the expense of solubility, making it ineffective as a liquid sealant.

[017] Overall, key considerations when designing a sealant are the strength of the sealant, elasticity of the sealant to mimic the elasticity of the tissue to which it is applied, and the ability

for the sealant to remain where it is applied during the curing step. Such elastic materials are needed for internal surgical applications exposed to tissue stretch or elastic deformation, such as during peristalsis, fluid pressure pulsation, limb flexing or general body movement. Examples would include, but are not limited to, anastomotic procedures (digestive, vascular and nervous system), internal sealants (vascular, digestive, dural) and application of resorbable and non-resorbable medical devices (i.e., meshes, membranes, pace-makers, surgical leads, etc).

[018] Elastic adhesive materials are also needed for external surgical and non-surgical applications, wherein said adhesive materials are utilized to hold medical devices or appliances to the skin including bandages and coverings, glucose monitors, continuous injection systems containing micro- needles, diagnostic leads (I.e., – temperature, pulse, respiration, EKG, etc.), diffusion drug delivery patches, skin grafts, resorbable and non-resorbable barrier membranes, etc. Ostomy, as a teaching example related to use of adhesive for external surgical and non-surgical applications, represents one such situation where the need for a sealant that adhesively and cohesively binds could be beneficial. Though it is contemplated by the applicants that the chemistries and formulations described herein could suitably be employed for any external or non-surgical medical applications, much in the same way it could be used for ostomy applications. The benefits of using a biologically functional, biocompatible, and “softer” sealant could significantly improve upon the raw performance criteria of harsher, more traditional external sealants. With an ostomy, a portion of the intestine (or ureter in the case of urostomy) is surgically re-routed to exit the body of a being, typically through the abdomen of the individual. The soft tissue of the intestine is folded over and sutured to the skin to create a stoma in the form of an opening where intestinal fluid or urine is discharged and may be collected in a bag or container. The collection container is then exchanged routinely by the individual. With this procedure, there is the high potential for the corrosive stomal effluent to leak as it exits the body and to be absorbed by the skin. Creating a suitable barrier to leakage for a person who requires an ostomy is an ongoing challenge, due to the varieties of ostomy environments (e.g. ileostomy, colostomy, urostomy) as well as the physical condition of the person. The effluent that breaches the common sealants and adhesives used in ostomy care may be corrosive, and often leads to painful skin irritation and wounds that require more extensive care. Leakage occurs by a few prevailing mechanisms. First, absorbent materials become saturated with stomal effluent and come into contact with skin. This saturation can lead to delamination of the adhesive used to

adhere the collection container to the stoma. Alternatively, leakage can occur when there is not a strong or continuous seal between the stoma and the ostomy appliance. Leakage can then delaminate the adhesive and come into contact with the skin. Another root cause of breaching the seal between an ostomy appliance and skin is the effects of perspiration of some patients, as moisture may negatively affect the performance of many known adhesives. Additionally, a sealant or adhesive that lacks sufficient flexibility, combined with excessive patient movement, can lead to a poorer or delaminated seal, leaving the patient vulnerable to any of the aforementioned leakage scenarios. In any case, disruption of the adhesive seal due to effluent leakage or perspiration is a problem that is necessary to be overcome. What is needed is a technology that can address directly the failings described above, specifically by providing an improved adhesive, such as may be used in various applications, including ostomy applications, where the adhesive provides improved adhesion under wet conditions, enhanced cohesiveness, and flexibility.

[019] Currently, numerous strategies have been employed for developing a sealant possessing a stronger, more effective barrier. Absorbent and adhesive materials are a well-developed portion of these strategies. Materials such as hydrocolloids are effective at absorbing the effluent, so that the leak can be prevented. Pressure sensitive adhesives (PSAs) have been used to create contact with the skin next to the stoma-skin interface, and provide a barrier against leakage, while helping to bear the load of the appliance itself. Elastomeric components help keep the flexibility so that repetitive motion does not lead to delamination (the separation of the adhesive layer from the container). Hydrophobic tackifiers are often used to assist the adhesive seal, while also providing a hydrophobic barrier against aqueous effluent. Some examples of synthetic polymers that are used in the patent literature are copolymers of ethylene and vinyl acetates, poly(alkylvinyl ethers), polyvinyl alcohols, polyisobutylenes, styrene-butylene copolymers and polysaccharides. Most adhesive materials use a strategic combination of these general types of materials: an absorbent; an elastomer; and a tackifier. The mode of action is to absorb via hydrophilicity, repel via hydrophobicity, remain tacky, or reshape to maintain an impermeable barrier, until the appliance is changed and a new one is introduced.

[020] Enhancing the mechanical strength and degradative stability of adhesive materials to effluent exposure can also be done through various forms of polymer crosslinking. Crosslinking of the aforementioned polymers has been described in US4477325 by Osburn, US4738257 by

Meyer. Additionally, a bilayer sealant approach with distinct functionality for each layer has been described previously (see US 5496296). Furthermore, incorporating small amounts of fumed or colloidal silica (see US 4578065) into a sealing composition has been described to produce a composition with increased mechanical endurance when exposed to intestinal fluids and/or urine, without appreciably reducing its wet tack while still providing a satisfactory dry tack. In spite of these enhancements, these materials suffer from an inability to create a tight seal when it becomes too wet or just an inability to fully coat the surface around heavily contoured stoma geometries.

[021] Shah in US6068852 and Lam in US 8436121 employ dual component, epoxy-like materials, to address shortcomings in the current sealants. These sealants claim to fill gaps more effectively since the materials start as liquids and cure over time. However, as these material are largely organic, the proclivity for delamination still exists in the presence of excess moisture and further, excessive moisture is thought to inhibit polymer crosslinking, reducing the effectiveness of the seal. Additionally, the active chemistry components used in the crosslinking reaction can be toxic to skin. Also, if the polymer is not sufficiently hydrophilic, the compositions may not absorb moisture, but rather trap moisture as they cure, and thus promote irritation. Moreover, while these materials are effective in crosslinking to create a stronger material, they do not possess the reactivity to form chemical bonds with tissue residues on skin or on soft tissue of the stoma.

[022] Previous adhesives using catechols have been described previously, for example, see work published by Phil Messersmith and Bruce Lee, at Northwestern University and Nerites Corporation. These adhesives are based on the adhesive proteins secreted by mussels, living in marine conditions, and occasionally exposed to dry conditions. Research into the mussel proteins has described the protein as being rich in catechol groups. These previously known dihydroxyphenyl (e.g., catechol-based) adhesives, while effective at adhering in various conditions, including wet aqueous conditions, are not necessarily capable of functioning as an ostomy sealant material that must be able to maintain a liquid proof seal, despite the movement of the patient, as previously described prior art aqueous compatible adhesives do not possess all of the required qualities suitable for such an application, for example, elasticity, burst pressure, desired set time range, and material integrity, *inter alia*, that would make an ideal ostomy sealant material. The applicants have surprisingly discovered that by including an active inorganic filler,

the characteristics of the sealant material are improved, for example, in terms of burst pressure, integrity, elasticity, additionally, the amount of functionalized polymer as a percentage is reduced significantly.

[023] Furthermore, none of the prior art approaches, however, seemingly provide a combined solution for leakage prevention, freedom of patient motion, and patient convenience and ease of use.

BRIEF SUMMARY OF THE INVENTION

[024] In an embodiment, the various aspects described herein provide an adhesive material suitable for use in various applications requiring elasticity, such that they can accommodate movement of the patient. Such applications include, but are not limited to internal surgical applications, particularly where exposed to tissue stretch, or elastic deformation, such as during peristalsis, fluid pressure pulsation, limb flexing or general body movement. Examples where the various adhesive embodiments described herein could be utilized include, but are not limited to, anastomotic procedures (digestive, vascular and nervous system), internal sealants (vascular, digestive, dural) and application of resorbable and non-resorbable medical devices (i.e., meshes, membranes, pace-makers, surgical leads, etc.). External surgical and non-surgical applications, wherein the various embodiments of adhesive materials described herein are utilized to hold medical devices or appliances to the skin, include, but are not limited to bandages and coverings, glucose monitors, continuous injection systems containing micro- needles, diagnostic leads (i.e., temperature, pulse, respiration, EKG, etc.), diffusion drug delivery patches, skin grafts, resorbable and non-resorbable barrier membranes, etc.

[025] Some of the various compounds described herein are able to be applied as a liquid, but are characterized by being resistant to excessive run-off, commonly occurring in other liquid adhesives, prior to curing.

[026] In other embodiments, and as a teaching example for use of adhesive for external surgical and non-surgical applications, the various teachings herein provide for an ostomy device, having an ostomy sealant that is suitable for use in ostomy applications. It is contemplated by the applicants that the chemistries and formulations described herein could suitably be employed for any external or non-surgical medical applications, much in the same

way it could be used for ostomy applications. In various embodiments, a functionalized polymer is combined with an active filler material form mixture that is capable of reacting, in the presence of an aqueous solvating fluid, to form a hydrogel sealant. The filler material may be an inorganic material, such as a ceramic material, and in an embodiment, the filler material is calcium phosphate. In another embodiment, these materials are used in ostomy applications. In an embodiment, the sealant is to be adhered to a tissue surface, such as mucosal tissue or dermal tissue.

[027] One embodiment is an ostomy device, comprising a mixture of one or more functionalized polymers, that is combined with an activator. The mixture may optionally further include an active inorganic filler material. The mixture may be hydrated with an aqueous solvating fluid, and upon hydration will be in a first form that is a malleable gel, and as the functionalized polymer reacts, will set to a second form that is a hydrogel. This hydrogel may then be arranged to create a biocompatible seal between a first and second surface, such as between opposing tissue surfaces, or between a tissue surface on one side, and a component of an ostomy appliance on the other. It is also contemplated the hydrogel could create a seal between two surfaces that are components of a medical device, such as an ostomy appliance.

[028] In an embodiment, the aqueous solvating fluid is able to solubilize the activator within the mixture. In an embodiment, the functionalized polymer has at least one phenyl derivative molecule attached to the polymer, the functional group would be activated by the activator. In some embodiments, the functional group is a reactive functional group that is capable of maintaining adhesion and cohesion in the presence of an aqueous environment. In some embodiments, the phenyl derivative is a catechol, guaiacol, diamine, or syringol.

[029] It is contemplated that in various embodiments described herein, the activator may be an oxidant or chelating agent, capable of causing the functional groups attached to the polymer to react. The activator may be one or more of: NaIO_4 , tetra-alkyl ammonium periodate, tetrabutylammonium periodate), AgNO_3 , Ag_2CO_3 , tetrabutylammonium permanganate, tetrabutylammonium dichromate, iron(III) acetylacetonate, iron(III)nitrate, potassium ferrate, di-tert-butyl peroxide, cumene hydroperoxide, or 2-butanone peroxide.

[030] In various embodiments, the inorganic filler material is one or more of: calcium carbonates, magnesium carbonates, silicates, silicic acids, aluminum hydrates, calcium sulfates, calcium phosphates, hydroxyapatite, alumina silicate, bioglasses, glass ceramics, and silica, and

combinations thereof. It is contemplated that the bioglass is selected from the group consisting of: 45S5; 45S5F; 45S5.4F; 40S5B5; 52S4.6; and 55S4.3. Additionally, it is contemplated that the glass ceramic is one of KGC; KGS, KGy213, A-W GC, MB GC. Suitable bioglasses and glass ceramics suitable for the uses contemplated herein are described in Biomaterials Science 2nd edition, edited by Ratner et al., page 159.

[031] In various embodiments, the active inorganic filler is incorporated into the mixture as a percentage exceeding 50% by weight of filler in the weight of the dry mixture. The filler may be present in the dry mixture as greater than 75%, greater than 90% or greater than 91%, greater than 92%, greater than 93%, greater than 94%, greater than 95%, greater than 96%, greater than 97%, or greater than 98% by weight of the dry mixture.

[032] In various embodiments, the functionalized polymer is incorporated into the mixture as a percentage of less than 50% by weight of functionalized polymer in the weight of the dry mixture. The functionalized polymer may be present in the dry mixture as less than 25%, less than 10%, less than 9%, less than 8%, less than 7% less than 6%, less than 5%, less than 4%. less than 3%, or less than 2% by weight of the dry mixture.

[033] In various embodiments, the functionalized polymer is a linear, branched, or multi-arm polymer molecule. It is contemplated that in various embodiments, the functionalized polymer is a polyalkylene. In various embodiments, the functionalized polymer is polyethyleneglycol.

[034] In another embodiment, an ostomy appliance is provided having a sealant material capable of sealing the appliance to at least one of the peristomal area tissues, and the stoma tissues, wherein the appliance has a body waste collector component, such as a bag, and the sealant component is a mixture of functionalized polymer, and an active inorganic filler, along with an activator. This mixture can be stored dry, and later mixed with an amount of aqueous solvating fluid, such as water, saline, or buffered aqueous liquid. The hydrated mixture initially forms a malleable gel, and the activator causes the functional groups on the polymer to react, whereupon a hydrogel is formed, to create a biocompatible seal between the body waste collector component and the tissue. The hydrogel is pliable, and elastic, such that it is able to move with the patients movement, without leakage occurring at the seal. The sealant may also serve as an adhesive to secure the ostomy appliance against the wearer.

[035] In an embodiment, the hydrogel material is characterized by having a measured strain of at least 50% without breaking, relative to the hydrogel material prior to being placed under tensile stress. In another embodiment, the hydrogel has a measured strain of at least 100%. In still another embodiment, the hydrogel material is elastic returning to nearly its original dimensions upon release from force causing strain.

[036] In an embodiment, the hydrogel material has a measured integrity value greater than 80%. In an embodiment, the hydrogel material has a measured integrity value greater than 85%. In an embodiment, the hydrogel material has a measured integrity value greater than 90%. In an embodiment, the hydrogel material has a measured integrity value greater than 95%.

[037] It is contemplated that for various embodiments of the materials described herein, when the hydrogel is utilized to form a seal, the seal integrity will not be negatively impacted by continued exposure to aqueous fluid.

[038] For the various embodiments described herein, the mixture, when exposed to aqueous solvating fluid will set to a hydrogel form in less than 30 minutes.

[039] It is contemplated that for various embodiment the mixture of functionalized polymer, activator, and inorganic active filler, may further comprise an additive, such as an agent to modulate pH, for example, citric acid, acetic acid, buffering agents, may be incorporated into the mixture, and upon hydration adjust the pH of the hydrated gel. In some embodiments, it is contemplated that the inorganic filler is able to modulate pH upon addition of hydrating fluid to the mixture including the inorganic filler. It is further contemplated that the aqueous solvating fluid may contain a pH modulator, for example, buffers may be included in the aqueous mixture, or alternatively, the aqueous solvating fluid may itself be of desired pH, thereby controlling the rate of reaction of the functionalized groups on the polymer, and affecting the rate at which the gel sets to a cured hydrogel material. It is also contemplated that the mixture may further comprise an additive material, which may be in the form of a second filler material incorporated into the mixture, for example the mixture may further incorporate one or more of inorganic fillers, organic fillers, biologically active agents and drugs, vitamins, soothing agents, odor absorbers, pain reducers, deodorants, and antiperspirants, for example. It is contemplated that alternatively, one or more of the additives described above may instead be added to the mixture along with the aqueous solvating fluid. In various embodiments, the aqueous solvating fluid may

comprise one of a slurry, suspension, or solution. In some embodiments, the aqueous solvating fluid may further incorporate salts, clays, or starches.

[040] In another embodiment, there is provided is an ostomy device, comprising a plate having a sealant material thereon, the sealant being made of a mixture of one or more functionalized polymers, that is combined with an activator. The mixture may optionally further include an active inorganic filler material. The mixture may be hydrated with an aqueous solvating fluid, and upon hydration will be in a first form that is a malleable gel, and as the functionalized polymer reacts, will set to a second form that is a hydrogel. This hydrogel may then be arranged to create a biocompatible seal between opposing first and second surfaces, such as between a tissue surface on one side, and the plate component of an ostomy device on the other. In an embodiment, the seal is created between the plate and an ostomy containment. In another embodiment, the sealant material is applied against an adhesive material applied to the ostomy device, such that the sealant material and the ostomy adhesive are able to work in concert to maintain the ostomy device in position and prevent leakage of fluid at the ostomy site. In an embodiment, the sealant material may be applied as a layer over the ostomy adhesive. In another embodiment, the sealant material is applied over or against a portion of an ostomy adhesive.

[041] In the various embodiments described herein, the functional groups on the polymer will chemically react upon being activated by an activator, wherein the chemical reaction of the functional groups creates covalent bonds between functionalized polymer molecules, and between functionalized polymers and an adjacent surface, the former being an example of a cohesive reaction, and the latter being an example of an adhesive reaction.

[042] In various embodiments described herein, the mixture may further comprise a second functionalized polymer, wherein the second functionalized polymer has an average molecular weight that is greater than the average molecular weight of the first functionalized polymer.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. Burst Pressure of cured hydrogel vs. % polymer 2B.

Figure 2. % Elongation at break of cured hydrogel vs. % polymer 2B.

Figure 3. Delivery syringe with static mixer.

Figure 4. 60 degree ramp for testing sealant flow.

Figure 5. Effective burst pressure under conditions with increasing moisture. Product 1: Brava ostomy ring. Product 2: Coloplast Bag wafer. Product 3: Eakin ostomy ring. Condition A: Accessory on dry mylar (PET). Condition B: Accessory on dry collagen casing. Condition C: Accessory on pre-moistened collagen.

Figure 6. Effective burst pressure under conditions with increasing moisture. Product 4: Coloplast ostomy paste. Product 5: Stomahesive ostomy paste. Product 6: Adapt ostomy paste. Product 7: NuHope ostomy paste. Condition A: Paste on dry mylar (PET). Condition B: Paste on dry collagen casing. Condition C: Paste on pre-moistened collagen.

Figure 7. Effective burst pressure of sealant on pre-moistened collagen.

Figure 8. Effective burst pressure of Medhesive sealant on pre-moistened collagen.

Figure 9. Effective burst pressure of ostomy sealants on pre-moistened collagen.

Figure 10. Schematic diagram for Burst Pressure Test.

Figure 11. Photos of burst pressure test fixture containing a cured paste on casing test sample.

Figure 12. Depicts general structure of Medhesive-209.

Figure 13. Depicts general structure of Medhesive-222.

Figure 14. Depicts general structure of Medhesive-223.

Figure 15. Depicts general structure of Medhesive-224.

Figure 16. Depicts general structure of Medhesive-225.

Figure 17. Depicts general structure of Medhesive-231.

Figure 18. Depicts general structure of Medhesive-239.

Figure 19. Depicts general structure of Medhesive-240.

Figure 20. Depicts general structure of Medhesive-243.

DETAILED DESCRIPTION

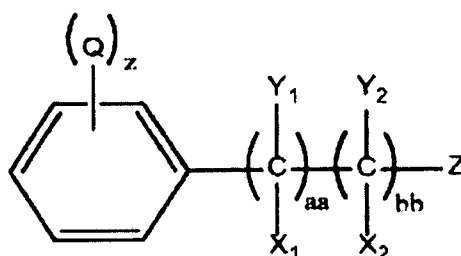
[043] In the specification and in the claims, the terms "including" and "comprising" are open-ended terms and should be interpreted to mean "including, but not limited to. . . ." These terms encompass the more restrictive terms "consisting essentially of" and "consisting of."

[044] It must be noted that as used herein and in the appended claims, the singular forms "a", "an", and "the" include plural reference unless the context clearly dictates otherwise. As well, the terms "a" (or "an"), "one or more" and "at least one" can be used interchangeably

herein. It is also to be noted that the terms "comprising", "including", "characterized by" and "having" can be used interchangeably.

[045] The term "residue" is used to mean that a portion of a first molecule reacts (e. g., condenses or is an addition product via a displacement reaction) with a portion of a second molecule to form, for example, a linking group, such an amide, ether, ester, urea, carbonate or urethane linkage depending on the reactive sites on the PA and PD. This can be referred to as "linkage".

[046] The denotation "PD" refers to a phenolic derivative, such as a mono-hydroxy, mono- or di-methoxy phenyl derivative, for example, a 3-methoxy—4-hydroxy phenyl moiety, or 3,5-dimethoxy—4-hydroxy phenyl moiety. Suitable PD derivatives include the formula:



wherein Q is an OH, NH₂ or OCH₃;

"z" is 1 to 5;

Each X₁, independently, is H, NH₂, OH, or COOH;

Each Y₁, independently, is H, NH₂, OH, or COOH;

Each X₂, independently, is H, NH₂, OH, or COOH; Each Y₂, independently, is H, NH₂, OH, or COOH;

Z is COOH, NH₂, OH or SH;

aa is a value of 0 to about 4;

bb is a value of 0 to about 4; and

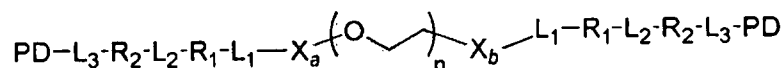
[047] Optionally provided that when one of the combinations of X₁ and Y₁, and X₂ and Y₂, X₁ and Y₂ or Y₁ and X₂ are absent, then a double bond is formed between the C_{aa} and C_{bb}, further provided that aa and bb are each at least 1 to form the double bond when present.

[048] Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs. All publications and patents specifically mentioned herein are incorporated by reference in their entirety for all purposes including describing and disclosing the chemicals, instruments, statistical analyses and methodologies which are reported in the publications which might be

used in connection with the invention. All references cited in this specification are to be taken as indicative of the level of skill in the art. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

Elastic tissue adhesives and sealants

[049] One embodiment of the invention described herein is an elastic, fluid resistant, strong adhesive, capable of adhering to tissue. It has surprisingly been discovered that the blends of phenyl derivative (PD)-modified multi-arm polymers, in combination with one or more linear PD-modified polymers of the general structure (Formula III below), wherein the class of polymers falling into this general structure are referred to herein as Polymer 2A, enable water-soluble sealants and adhesives that achieve high strength and elasticity, without the use of elastomers. Furthermore, sealants that incorporate polymers with the inventive structures described herein exhibit minimal flow when introduced, for example, when applied to steeply angled surfaces, making their placement in highly contoured spaces readily achievable, as the sealant would tend to stay where it is applied, rather than readily flow onto adjacent tissue surfaces where the sealant might not be desirable.



Formula III. Polymer 2A

[050] In one embodiment;

X_a = C=O;

X_b = NH or O, or C=O;

L₁ is selected to be either ester or amide linkages;

R₁ is selected from a group of □, □-amino acids, □, □-dicarboxylic acids, or □, □-diamines, □, □-hydroxyl carboxylic acid, as a way to influence performance properties that include but are not limited to, tuning degradability, tuning the hydrophilic/hydrophobic character, altering swelling behavior, inducing anisotropic reactivity through sterics or electronics;

L₂ is selected to be either ester or amide linkages;

R₂ and L₃ are not present;

PD is selected from a group of PDs, such as catechol or guaiacol;

PD is bonded to L₂ when R₂ and L₃ are not present.

[051] The value of n can be any value from 4 to 25000, preferably, 15 to 11500, more preferably, 30 to 5000, most preferably 50-2300, where variations in the molecular weight of PEG used a wide range can be achieved with a minimal amount of multi-arm polymer. Surprisingly, these polymers, alone or in combination with other polymers led to sealants that were significantly more elastic than sealants found in the art, and specifically the cases of polymer 1A.

Table 1. Sealant formulations using polymer 2A at 20% solids, 0.75 molar ratio of NaIO_4 to PD, and pH of sealant = 7.4. ^a Comparative example. ^b pH of sealant = 6.6. M217 uses a 10kg/mol hydroxylated PEG as a starting material.

Formulation	1A	2A	% 1A	% 2A	% Polymer Solids	Burst Pressure (mmHg)	% Elongation at break
1	M161 ^{a,b}	-	100	0	20	259	42
2	M161 ^a	-	100	0	10	148	63
3	M141 ^a	-	100	0	polymer not soluble in PBS buffer		
4	M161	M217	75	25	20	225	-
5	M161	M217	50	50	20	208	95
6	M161	M217	25	75	20	179	112
7	M161	M217	0	100	20	67	231

[052] Table 1 shows how the incorporation of linear polymer (polymer 2A) can improve the elasticity of the material as defined by its percentage of elongation at break. A comparative example, in formulation 1 not only has a very poor elongation, but requires the working of the materials at a pH lower than ideal. Alternatively, if pH is held the same at 7.4 (formulation 2), the percent polymer in the formulation must be reduced to 10% solids to completely mix and dispense the adhesive formulation through a syringe. In either of these instances (formulations 1 or 2), elasticity of the final sealant is not able to match those of the invention. The use of Polymer 2A described in this invention allows us to access elasticities that are inaccessible using standard approaches of those in the art. Prior attempts to improving elasticity through the incorporation of a polyester in the backbone as in formulation 3 (

[053] Formula II) led to a formulation that was not soluble in aqueous buffer systems, and thus could not be used as a liquid sealant as described in this invention. An appropriate organic solvent would likely solubilize the molecule, however would not be desirable because of the in vivo toxicity.

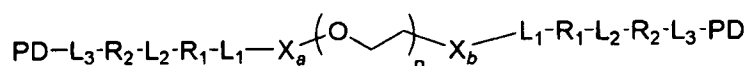
[054] In addition to sealant formulations where the phenyl derivative (PD) is a catecholate structure, it is possible to extend the features of this invention to polymers that contain guaiacolate PD derivatives, such as ferulate as shown in Table 2.

Table 2. Sealant formulations using polymer 2A at 20% solids, 0.75 molar ratio of NaIO₄ to PD, and pH of sealant = 7.4. M219 uses a 10kg/mol hydroxylated PEG as a starting material.

Form.	1A	2A	% 1A	% 2A	% Polymer Solids	Burst Pressure (mmHg)	% Elongation at break
8	M161	M219	75	25	20	226	
9	M161	M219	50	50	20	166	101
10	M161	M219	25	75	20	140	
11	-	M219	0	100	20	24	

[055] These sealants offer improved elasticity without the need to incorporate polyester-based additives or design of elaborate polyester-PEG copolymer components. As a blend component these materials may be easily added to achieve the desired property. Additionally, as modified PEGs, these components not only have tuneable degradation profile that is similar to those used commonly in literature, they also possess comparable polarities and hydrophilicities that make their dissolution in aqueous buffers straightforward.

[056] In another feature, sealants that contain blends of catecholate- and guaiacolate-modified multi-arm polymers are blended with catecholate-/guaiacolate-modified polymers of the following structure (Formula IV, below). The class of polymers falling into the general structures of Formula IV, are referred to herein as Polymer 2B.

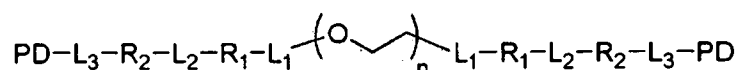


Formula IV. Polymer 2B

(e.g. M222, M231, M239)

[057] In various embodiments, the functionalized polymer is a polymer backbone that has been functionalized, for example, with 2 or more reactive functional groups (for example, catechols, syringols, diamine phenyl derivative or guaiacols). The functionalized polymer backbone may be linear or branched. In a specific embodiment, the polymer backbone is a linear backbone, that is bi-functionalized with catechol groups. In another embodiment, the polymer backbone is a multi-arm molecule, with 3 or more functional catechol groups.

[058] An example polymer utilized in the practice of various embodiments described herein is represented by the sealant material incorporating functionalized polymers of the following structure:



wherein:

PD is a phenyl derivative, such as guaiacol, catechol or syringol, diamine phenyl derivative,

L_1 is selected to be either urethane, urea, ester, or amide linkages,

R_1 is selected from a linear, cyclic, branched, aryl, or substituted aryl group as a way to influence performance properties that include but are not limited to, tuning degradability, tuning the hydrophilic/hydrophobic character, altering swelling behavior, inducing anisotropic reactivity though sterics or electronics, for example, R_1 may derived from a group of linear, cyclic, branched, aryl, or substituted aryl diisocyanates, or R_1 may be selected from a group of α,ω -amino acids, α,ω -dicarboxylic acids, or α,ω -diamines, α,ω -hydroxyl carboxylic acid, as a way to influence performance properties that include but are not limited to, tuning degradability, tuning the hydrophilic/hydrophobic character, altering swelling behavior, inducing anisotropic reactivity though sterics or electronics.

L_2 is selected to be either urethane, urea, or amide linkages.

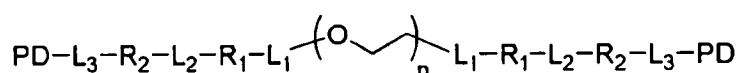
R_2 may be selected from a linear, cyclic, branched, aryl, or substituted aryl group as a way to influence performance properties that include but are not limited to, tuning degradability, tuning the hydrophilic/hydrophobic character, altering swelling behavior, inducing anisotropic reactivity though sterics or electronics, for example, R_2 may derived from a group of linear, cyclic,

branched, aryl, or substituted aryl diisocyanates, or R_2 is selected from a group of $\square$, $\square$ -amino acids, $\square$, $\square$ -dicarboxylic acids, or $\square$, $\square$ -diamines, $\square$, $\square$ -hydroxyl carboxylic acid, as a way to influence performance properties that include but are not limited to, tuning degradability, tuning the hydrophilic/hydrophobic character, altering swelling behavior, inducing anisotropic reactivity through sterics or electronics.

L_3 is selected to be either an amide, urea, or a urethane, where R_2 is derived from a diisocyanate, alternatively L_3 may further be an ester.

when L_3 is not present R_2 becomes the PD terminating group.

[059] Alternatively, Polymer 2B is described by the following



L_1 is selected to be either ester or amide linkages,

R_1 is selected from a group of $\square$, $\square$ -amino acids, $\square$, $\square$ -dicarboxylic acids, or $\square$, $\square$ -diamines, $\square$, $\square$ -hydroxyl carboxylic acid, as a way to influence performance properties that include but are not limited to, tuning degradability, tuning the hydrophilic/hydrophobic character, altering swelling behavior, inducing anisotropic reactivity through sterics or electronics.

L_2 is selected to be either amide, urea, biuret, urethane.

R_2 is selected from a linear, cyclic, branched, aryl, or substituted aryl group as a way to influence performance properties that include but are not limited to, tuning degradability, tuning the hydrophilic/hydrophobic character, altering swelling behavior, inducing anisotropic reactivity through sterics or electronics.

R_2 is derived from a group of linear, cyclic, branched, aryl, or substituted aryl diisocyanates.

L_3 is selected to be either a urea, amide, or urethane.

[060] The value of n can be any value from 4 to 25000, preferably, 15 to 11500, more preferably, 30 to 5000, most preferably 50-2300, where variations in the molecular weight of PEG used a wide range can be achieved with a minimal amount of multi-arm polymer.

Surprisingly, these polymers, alone or in combination with other polymers led to sealants that were significantly more elastic than sealants found in the art, and specifically the cases of polymer 1A.

[061] Intuitively, one would expect these polymers to contribute similar sealant properties to those sealants that are derived from polymer 2A, and that incorporating more of polymers 2B

would also simply lead to improved elasticity and a decrease strength as measured by burst pressure (Table 1 and Table 3). However, it has surprisingly been observed that the incorporation of linking groups possessing urethane and urea functionality provide a boost of strength and elasticity. Comparison of formulation 6 against 16 most clearly demonstrates this, where at comparable polymer solids, the formulation 16 has a burst pressure that is 34mmHg higher and is ca. 37% more elastic than formulation 6. So, while polymer 2B leads to the design of sealant formulations that behave according to a similar strength and elasticity trend, sealants that incorporate polymer 2B provide yet additional strength, that in some cases may recapture the strength that may be lost as a consequence of incorporating 2A or 2B.

[062] Furthermore, Table 4 provides examples of increased sealant burst strength as the concentration of polymer 2A or 2B in the formulation increases. Notably, this boost in strength is achieved while retaining the high degree of elasticity.

Table 3. Sealant formulations using polymer 2B at 10% solids, 0.75 molar ratio of NaIO₄ to PD, and pH of sealant = 7.4. M222 uses a 10kg/mol hydroxylated PEG as a starting material. ^a Sample was prepared but unable to be tested.

For m.	1A	2B	% 1A	% 2B	% Polymer Solids	Burst Pressure (mmHg)	% Elongation at break
2	M161	-	100	0	10	148	63
12	M161	M222	75	25	10	126	121
13	M161	M222	50	50	10	127	131
14	M161	M222	25	75	10	109	234
15	-	M222	0	100	10	^a	^a

Table 4. Sealant formulation 14 at variable polymer solids with a 0.75 molar ratio of NaIO₄ to PD, and pH of sealant = 6.6. ^a pH of sealant = 7.4.

For m.	1A	2B	% 1A	% 2B	% Polymer Solids	Burst Pressure (mmHg)	% Elongation at break
2	M161	-	100	0	20	259	42 ^a

16	M161	M222	25	75	19	213	153
17	M161	M222	25	75	16	161	156
18	M161	M222	25	75	13	130	222
19	M161	M222	25	75	10	109	234
2	M161		100	0	10	148	63

[063] In order to expand the utility of this invention and to access an even broader window of sealant properties, we have incorporated polymers 2A or 2B using starting PEG raw materials of variable molecular weights. Table 5 shows representative examples of polymer that utilize a 20kg/mol catecholate-modified PEG (formulations 22-25) and a 6kg/mol catecholate-modified PEG (formulations 26-27). We envision the possibility of using polymers of molecular weights ranging between 600g/mol to 500kg/mol; preferably, 1kg/mol to 300kg/mol; more preferably 4.5kg/mol to 100kg/mol; more preferably 6kg/mol to 50kg/mol, and most preferably 10kg/mol to 35kg/mol.

Table 5. Sealant formulations using polymer 2B at 10% solids, 0.75 molar ratio of NaIO₄ to DHPD, pH = 7.4. PD based on dopamine. M223 uses a 20kg/mol hydroxylated PEG as a starting material. M224 uses 6kg/mol hydroxylated PEG as a starting material.

For m.	1A	2B	% 1A	% 2B	% Polymer Solids	Burst Pressure (mmHg)	% Elongation at break
20	M161	M223	75	25	10	129	103
21	M161	M223	50	50	10	105	146
22	M161	M223	25	75	10	60	314
23	-	M223	0	100	10	17	-
24	M161	M224	50	50	10	130	133
25	M161	M224	25	75	10	124	161

[064] At equivalent % polymer solids and polymer 1:polymer 2 weight ratios, lower molecular weight versions of polymers 2B lead to higher strengths, as demonstrated by the graph of Figure 1.

[065] With respect to elasticity, there seemed to be an equivalent and gradual increase in elasticity as more of polymer 2B was added up to 50%. Beyond 50% of polymer 2B, sealants derived from 20kg/mol were more elastic than those of 6kg/mol., as demonstrated by the graph of Figure 2.

[066] One would expect that higher molecular weights would lead to higher strengths, given the possibility for more chain entanglements, higher (and more rapid) molecular weight build-up during the crosslinking reaction. However, the opposite was surprisingly observed, leading to a very unique system.

[067] The site-specific application of a sealant is important when used in tightly contoured surfaces or tissue surfaces that are not readily accessible. If a sealant is unable to remain where it is placed, whether due to slow reactivity or too low of a viscosity, the liquid can drip and ultimately cure to adjacent tissue and bond to tissue where it was not intended, leading to the possibility of adverse effects. Hence, the post-dispensed mobility of any liquid sealant that cures is an important consideration. Remedies to this problem are achieved in a few ways; the use of a much thicker sealant solution prior to mixing, where the high viscosity limits the mobility of the sealant during the curing step; a propellant-like spray, where the curing occurs so rapidly that it doesn't have a chance to drip; or highly reactive systems whose kinetics are fast enough to overcome the mobility of the sealant. The advantages in each of these scenarios is met with numerous disadvantages. The handling properties of highly viscous liquid sealants do not often meet the handling properties and requirements needed for nurses and doctors to easily prepare and use such a sealant system. Furthermore the higher viscosities are not often able to sufficiently wet the surface of the tissue and therefore not able to form a good adhesive seal with tissue, in spite of the strong cohesive strength of the cured sealant. Propellant-like sprays are often limited in the relatively large target diameter of the spray as it hits the tissue and are not as useful in tight spaces. Thirdly, as described previously in the prior art, identifying a liquid system where the effects of exceedingly fast reaction kinetics outweigh the mobility of the dispensed sealant is still too difficult.

[068] In view of the limitations known in the art, we disclose two ways to overcome this challenge. First, the use of a multi-arm that utilizes a unique sequence of linking groups to enhance the set time of the sealant. Second, the ability to use the foaming properties of our hydrated sealant formulations to achieve a higher "virtual viscosity" while retaining the ability to

mix the components at an easily handled and comfortable, low viscosity. The ability to reduce the post-dispensed flow of our sealant using either of these strategies was quantified by mixing the formulation components through a static mixer using a syringe mixing device assembly such as the one shown in **Error! Reference source not found.** onto a 60 degree angled ramp as shown in **Error! Reference source not found.**.

[069] It is theorized that the stable foam of the sealant originates from the use of isophorone diisocyanate molecule as a linker that leads to the complex distribution of intermediates (i.e. polymers). Specifically, the incorporation of *cis*- and *trans*- isomers of isophorone diisocyanate, anisotropic reactivity of primary and secondary isocyanates, as well as the potential formation of dimer and trimer PEG-Isocyanates leads to partial solubility of the final DOPA-modified polymers in water, which is capable of trapping (micro)air (bubbles) within the matrix, thus increasing its resistance to flow, and taking the form of a foam paste.

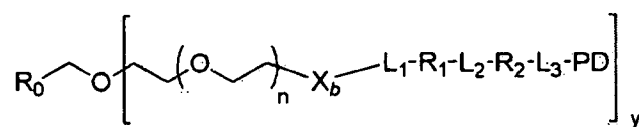
[070] Thus, the partial solubility of the above described materials, traps air during the incomplete solvation of the sealant material, forming a stable suspension of small bubbles that are prevented from coalescing into adjacent bubbles thus avoiding the formation of larger bubbles, due to the presence of the insoluble or partially soluble components. This results in the formation of a unique elastic sealant foam. The easiest way to trap the air in the materials and create the foam paste is through use of a reciprocating syringe, or static mixing tip, although other mixing forms, such as whipping, or aggressive blending could achieve similar results, so long as the action sufficiently traps air within the composition. This foam paste material can be delivered to the target site during open surgical procedures, or through a syringe, cannula or spray device.

[071] This same foam paste material can also work as a carrier for drugs, biologics, ceramics, bioactive glasses and other materials listed throughout this disclosure. This will allow the foam material to function as a unique low density adhesive tissue bone void filler or drug delivery material.

[072] Both the quick setting and foaming properties of the curing sealant prevent the movement of the liquid such that we are able to dispense this on a 60 degree angled surface with little to no movement. We achieved this by leveraging the unique properties of the linking groups of the polymers in our formulation to create a quicker setting mixture or a stable foam that cures without the assistance of air or inert gas, salt porogen, frozen solvent porogen (e.g. benzene),

surfactant, or gas-producing reactivity typically used to create a foam (e.g. carbon dioxide formation). Though, it is contemplated that any of these may beneficially be used, if so desired, with the formulations described herein.

[073] In the first approach, blends of PD-modified linear polymers with PD-modified polymers of the following structure (Formula V) are able to deliver notable reduction in the post-dispensed mobility of the cured sealant.

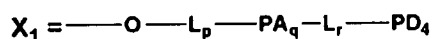
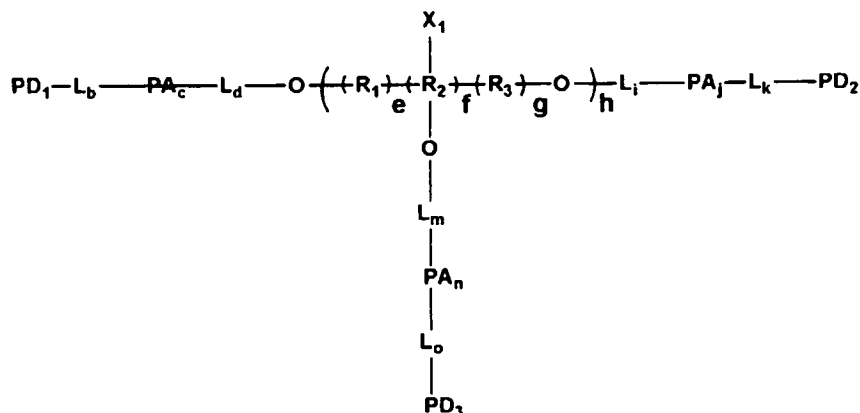


Formula V

R₀ = Hexaglycerin, tripentaerythritol, pentaerythritol, or other commonly utilized starting cores for building multi-arm polyethylene glycols, as known in the art.

$$y = 3\text{--}10$$

In an alternate depiction, the molecule of Formula V above may also be depicted as follows (Formula VI):



Formula VI. Polymer 1B.

wherein

X_1 is optional;

each PD_1 , PD_2 , PD_3 , and PD_4 , independently, can be the same or different;

each L_b , L_k , L_o and L_r , independently, can be the same or different;

optionally, each L_d , L_i , L_m and L_p , if present, can be the same or different and if not present, represent a bond between the O and respective PA of the compound;

each PA_c , PA_j and PA_n , independently, can be the same or different;

e is a value from 1 to about 3;

f is a value from 1 to about 10;

g is a value from 1 to about 3;

h is a value from 1 to about 10;

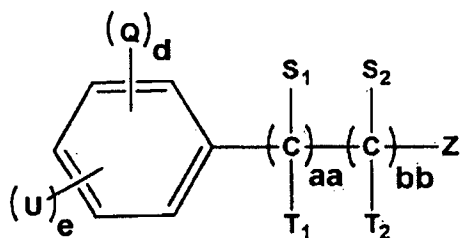
each of R_1 , R_2 and R_3 , independently, is a branched or unbranched alkyl group having at least 1 carbon atom;

each PA, independently, is a substantially poly(alkylene oxide) polyether or derivative thereof;

each L, independently, is a linker or is a suitable linking group selected from amide, ether, ester, urea, carbonate or urethane linking groups; and

each PD, independently, is a phenyl derivative, wherein

each of PD₁, PD₂, PD₃, and PD₄, independently, is a residue comprising:



wherein Q is a OH, SH, or NH₂

“d” is 1 to 5

U is a H, OH, OCH, O-PG, SH, S-PG, NH₂, NH-PG, N(PG)₂, NO₂, F, Cl, Br, or I, or combination thereof;

“e” is 1 to 5

“d+e” is equal to 5

each T₁, independently, is H, NH₂, OH, or COOH;

each S₁, independently, is H, NH₂, OH, or COOH;

each T₂, independently, is H, NH₂, OH, or COOH;

each S₂, independently, is H, NH₂, OH, or COOH;

Z is COOH, NH₂, OH or SH;

aa is a value of 0 to about 4;

bb is a value of 0 to about 4; and

optionally, when one of the combinations of T₁ and T₂, S₁ and S₂, T₁ and S₂ or S₁ and T₂ are absent, then a double bond is formed between C_{aa} and C_{bb}, aa and bb are each at least 1 to form the double bond when present.

Table 6 shows a series of formulations that were prepared that reveal the improvements in reducing post-dispensed flow.

Table 6. Polymer Composition and performance data for sealant formulations. [Oxidant]:[Catecholate] = mol NaIO₄ : mol PD = 0.75. ^a Measured by stretching a line of dispensed and cured polymer parallel to the direction of the line. ^b Average distance that 0.5mL of sealant travelled down a 60 degree ramp. ^c Comparative example. ^d Average distance travelled down a 30

degree ramp of 0.5mL sealant. ^e Cure time was too fast and sealant was not able to be expressed out of the syringe.

Form	1A	1B	2B	2C	%1 A	% 1B	% 2B	%2 C	% Polymer Solids	pH	% Elongation at break ^a	Flow (cm) ^b
26 ^c	M16 1		-		100	-	-		35	6.1		>45.5
27		M22 5	-		-	100	-		35	6.1	^e	^e
28	M16 1		M22 2		10		90		35	6.1	300	17.5

30		M22 5		M231	-	30	-	70	35	6.1		2.5
31		M22 5		M231	-	30	-	70	35	6.4	100	3.0
32		M22 5		M231	-	30	-	70	35	6.7	100	3.3
33		M22 5		M231	-	20	-	80	35	6.1	100	3.5
34		M22 5		M231	-	20	-	80	35	6.7		
35		M22 5		M231	-	10	-	90	35	6.1		6.0
36		M22 5		M231	-	10	-	90	35	7.0	500	2.0
37		M22 5		M231	-	10	-	90	35	7.4		
38		-		M231	-	0	-	100	35	6.1	800	11.0
39		-		M231	-	0	-	100	35	6.7	>800	7.0
40		-		M231	-	0	-	100	35	7.4		

[074] Comparison of formulations 26 and 27 in Table 6 show how high concentrations of either M161 and M225 alone result in vastly different flow behaviors. In the case of M161, the sealant dripped off the ramp when it was dispensed, whereas the M225 solution was not able to be expressed through the static mixer as it cured much too quickly. This was surprising given that these two polymers differ only in the linking groups that connect the PD with the core PEG molecule. Therefore, in order to evaluate the benefit of M225 more quantitatively, formulations 28 and 29 were prepared and expressed onto the ramp. This comparison more clearly revealed the benefit of Med225 over Med161 by reducing the distance travelled from 17.5cm when using M161, compared to 11cm when using M225. Notably, the elongation, or functional elasticity, of the M225-M222 hydrogel was the same as M161-M222, revealing that the difference in linking group was responsible for reducing the flow *without* impacting the overall elasticity of the hydrogel.

[075] In another feature of this invention, blends of PD-modified multi-arm polymers with a PD-modified polymer of the following structure:

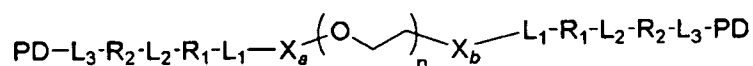


Figure 1. Polymer 2C. (aka Polymer 2B where R₁ is an isophorone derivative). (e.g. M231) where L₁ is selected and L₂ are selected urethane and urea, and R₁ is derived from isophorone, such that when it is dissolved in water exists as a stable foam and upon mixing with an oxidant, cures as a foam, with a reduced flow.

[076] To highlight the benefit of a formulation containing polymer 2C (i.e. isophorone-modified polymer 2B), the flow of formulations 28, 29, and 35 are presented in Table 6. These reveal the initial effect of including polymer 1B, and further by polymer 2C. The additive effect of using polymer 2C in conjunction with polymer 1B to reduce the post-dispensed flow of the cured sealant is particularly beneficial to both achieve a quicker setting formulation as well as a sealant with minimal flow. Moreover, the combination of polymer 1B and polymer 2C yield sealants with high degrees of elasticity, and formulations that pass ISO 10993 for in vitro cytotoxicity. Compared to relevant sealant formulations known in the art, the incorporation of polymer 1B, and particularly polymer 2C show a vast improvement in reducing the flow down a 60 degree ramp after being dispensed.

[077] Since highly concentrated sealants may not be advantageous for all applications, we have evaluated formulations that are run at a reduced solids as well as different levels of oxidant. This can have beneficial impact on handling as well improving the sealant's in vitro cytotoxic profile.

Table 7. Sealant formulations using polymer 1B and polymer 2C at 20% and 25% solids and burst strength data for sealant formulations. ^amol NaIO₄ : mol PD = 0.5. pH = 7.4.

Form	1B	2C	% 1B	% 2C	% Polymer Solids	Burst Pressure (mmHg)	% Cell viability
41	M22 5	M23 1	15	85	20	77	93
42	M22 5	M23 1	15	85	25	95	23
43	M22 5	M23 1	10	90	20	58	99
44	M22 5	M23 1	10	90	25	86	50
45	M22 5	M23 1	0	100	20	42	90
46	M22 5	M23 1	0	100	25	48	86

Table 8. Sealant formulations using polymer 1B and polymer 2C at 20% and 25% solids and burst strength data for sealant formulations. $\mu\text{mol NaIO}_4 : \text{mol PD} = 0.75$. pH = 7.4.

Form	1B	2C	% 1B	% 2C	% Polymer Solids	Burst Pressure (mmHg)	% Cell viability
47	M22 5	M23 1	15	85	20	114	29
48	M22 5	M23 1	15	85	25	145	25
49	M22 5	M23 1	10	90	20	99	30
50	M22 5	M23 1	10	90	25	130	59
51	M22 5	M23 1	0	100	20	71	61
52	M22 5	M23 1	0	100	25	119	49

[078] The important feature in these formulations is the presence of a stable dense foam that remains when hydrated and then when mixed. The presence of this foam can be dependent upon pH and polymer concentration. Data in

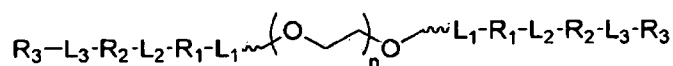
Table 9 shows that the majority of formulations show a stable foam that holds. This feature is important for the sealant to remain where it is dispensed. Again, it is noteworthy that the foaming capability is achieved simply by the composition of the linking group, which occurs in the polymer at a weight percentage of less than 5%.

Table 9. Foam stability data for sealant formulations with varying polymer composition, concentration, and pH. [Oxidant]:[Catecholate] = mol NaIO₄ : mol PD = 0.75. ^aTime for foam to fully disappear. ^bComparative example. ^cDid not form a foam.

Form	1B	2B	% 1B	% 2B (or 2C)	% Polymer Solids	pH	Time ^a
26 ^b	M16 1	-	100	-	35	6.1	^c
27	M22 5		100	-	35	6.1	^c
28	M16 1	M22 2	10	90	35	6.1	^c
29	M22 5	M22 2	10	90	35	6.1	^c

30	M22 5	M23 1	30	70	35	6.1	<3 min
31	M22 5	M23 1	30	70	35	6.4	>60 min
32	M22 5	M23 1	30	70	35	6.7	>60 min
33	M22 5	M23 1	20	80	35	6.1	>60 min
35	M22 5	M23 1	10	90	35	6.1	>60 min
36	M22 5	M23 1	10	90	35	7.0	>60 min
38	-	M23 1	0	100	35	6.1	>60 min
39	-	M23 1	0	100	35	6.7	>60 min

[079] In another embodiment, the blends of a PD modified multi-arm polymers with dihydroxyphenylalanine (DOPA)-modified polymers of the following structure (Formula VII), with constituent units as described previously:



Formula VII

[080] In another embodiment, it is contemplated that any of the structures described herein could be used in other applications, especially surgical applications. For example, there may be a benefit in using the multi-arm structures to seal an opening in tissue, where the elasticity of the molecule allows it to adhere to the tissue, even if the tissue is continually moving. These adhesives may be optionally be combined with a filler material, to add bulk, for example, a ceramic, a calcium phosphate, or alternatively collagen or decellularized tissue matrices may serve to provide additional structure in the adhesive material. This filler material may be faster resorbing than the polymer, and may create interconnecting porosity extending through the adhesive material, as the filler material is absorbed.

Ostomy Sealants and Pastes

[081] An embodiment of the invention described herein is an elastic, fluid resistant, strong sealant material useful for ostomy applications (e.g., ileostomy, urostomy, and colostomy), where the sealant is comprised of a dry mixture of a functionalized polymer, an active inorganic filler, and an activator. To this dry mixture, may be added an amount of water, or other aqueous liquid, that when incorporated into the mixture initially forms a malleable gel material, and further the addition of the liquid allows the activator to initiate a reaction. As the reaction of the functionalized polymer proceeds, the hydrated mixture will transition from its initial malleable gel form to a hydrogel form, that while elastic, is no longer malleable/amorphous.

[082] The initially hydrated mixture may be in a malleable, gel form, such as a material that may be injected through a syringe with less than 30 Newtons, according to the testing method described below. In an embodiment, the gel will have a volume of liquid added to the dry mixture so that it forms a material that exhibits little to no flow when in a steady state. In another embodiment, the hydrated mixture may have a viscosity that is not self-supporting in

steady state. Preferably, the aqueous fluid added to the dry mixture will be an amount that is capable of solvating the activator, but not so much that it causes the dilution of the functionalized polymer to the point that it will not react to form a cross-linked matrix.

In one embodiment, the sealant material comprises:

[083] a) a functional oligomer of generic structure: C-D-X-D-C wherein C has a functional group capable of binding, such as by having ligand forming capability, and wherein C has an additional moiety capable of reacting with group D and wherein C is also capable of initiation and subsequent polymerization by an oxidant; wherein D is a reactive linking group which can react with both C and X and has a functionality of 2 or greater, and wherein X is a moiety, which may be hydrophilic, and is capable of reacting with D and having a reactive functionality of at least 2;

[084] b) an inorganic active filler, which may be an inorganic salt, the inorganic active filler being capable of being chelated, or hydrogen bonded, or combination thereof, with the functional group moieties of component a), , and wherein the inorganic active filler is present in an amount exceeding 50% (dry weight particle to polymer weight); the inorganic filler may be present in an amount exceeding 75%, in an amount exceeding 90%, in an amount exceeding 95%, in an amount exceeding 96%, in an amount exceeding 97%, or , in an amount exceeding 98%;

[085] c) an aqueous solvating fluid, such as water, saline, buffered aqueous solution, or biological fluids;

[086] d) an oxidant capable of initiating the reaction of said oxidant initiatable species C in component a) wherein C is capable of initiation and subsequent polymerization and the entire composition forms a set polymer in a controlled length of time.

In some embodiments, the functional group for C may be bidentate or polydentate.

[087] In one specific embodiment, the ostomy sealant material, comprises a functional hydrophilic oligomer, and upon being hydrated by addition of an aqueous solvating fluid, the functional oligomer is to be activated by the activator, and is a reaction product of a hydroxyl modified molecule (e.g., dihydroxyphenylalanine (DOPA)), a diisocyanate, and a polyethylene glycol polyol, and the sealant material further comprises an inorganic active filler, such as a calcium phosphate. The aqueous fluid added is water, and the oxidant is sodium periodate.

[088] In an embodiment, the functionalized polymer in the dry mixture can be a polymer backbone with at least two functional groups that can react in the presence of an activator. The reaction of the functional groups may cause the polymer backbone units to bind to each other in a manner that makes the material cohesive, such as by cross-linking. The reaction of the function groups may further may cause the polymer backbone units to bind to external features, such adjacent surfaces or tissue surfaces, rendering the material adhesive. In the case where the material is utilized in an ostomy application, the polymer backbone units are arranged to react with eachother, by interactions of the reactive functional groups, to form a cohesive material, and further, the reactive functional groups react to bind to adjacent surfaces adhesively, where the adjacent surface could be a tissue surface, whether dermis or mucosa, or alternatively the material of the ostomy appliance.

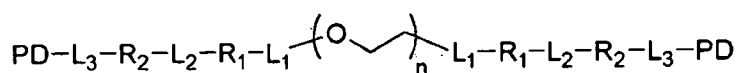
[089] In some embodiments, the polymer unit may be a linear molecule, or alternatively, a branched, multi-armed molecule. The polymer may be any suitable biocompatible backbone molecule, capable of being functionalized to, so that it can react to form a cross-linked matrix. Suitable examples of molecules for use in accordance with the various embodiments described herein include polyalkylene oxides, polyacrylates, polymethacrylates, and polyurethanes. It is expected that one skilled in the art of oligomer synthesis would understand and adjust the oligomer physical and chemical structure with the teachings herein and that no limitation to said structure functionality number is per se expected. In one embodiment, said oligomer is difunctional and linear.

[090] The functionalized polymers described herein present adhesive qualities, due to the presence of reactive functional groups, such as catechol, syringol, diamine phenyl derivative or guaiacol functional groups. Functionalized polymers, may further be combined with one or more active filler materials. These active filler materials are characterized by being able to interact with the reactive functional groups of the functionalized polymers, and effect the binding characteristics of the functionalized polymer. An active filler is one where the inclusion of the active filler in the composition affects the physical characteristics and performance of the resultant hydrogel for at least one of the physical properties of the hydrogel, when contemplated for use as an ostomy sealant, when contrasted with same functionalized polymer also set to a hydrogel, with the same activator, only without the active filler. Essentially, the inclusion of the active filler provides a benefit to the hydrogel, in terms of enhanced performance characteristics

as a ostomy sealant over the same hydrogel lacking the active filler. Factors of the active inorganic filler that cause the enhanced performance of the hydrogel as an ostomy sealant could include the average and mean particle size of the filler particles, the effect on pH of the particle, solubility of the particle, water holding ability of the particle. Without being bound by theory, it is thought that the nature of interaction of the active filler and the reactive functional groups is such that, there is considerable reversible bonding character, such that the extensibility of the adhesive is surprisingly large.

[091] In various embodiments, the functionalized polymer is a polymer backbone that has been functionalized, for example, with 2 or more reactive functional groups (for example, catechols, syringols, diamine phenyl derivative or guaiacols). The functionalized polymer backbone may be linear or branched. In a specific embodiment, the polymer backbone is a linear backbone, that is bi-functionalized with catechol groups. In another embodiment, the polymer backbone is a multi-arm molecule, with 3 or more functional catechol groups.

[092] An example polymer utilized in the practice of various embodiments described herein is represented by the sealant material incorporating functionalized polymers of the following structure:



wherein:

n is an integer from 75 to 800;

PD is a phenyl derivative, such as guaiacol, catechol or syringol, diamine phenyl derivative;

L₁ is selected to be either urethane, urea, ester, or amide linkages;

R₁ is selected from a linear, cyclic, branched, aryl, or substituted aryl group as a way to influence performance properties that include but are not limited to, tuning degradability, tuning the hydrophilic/hydrophobic character, altering swelling behavior, inducing anisotropic reactivity though sterics or electronics, for example, R₁ may derived from a group of linear, cyclic, branched, aryl, or substituted aryl diisocyanates, or R₁ may be selected from a group of □, □-amino acids, □, □-dicarboxylic acids, or □, □-diamines, □, □-hydroxyl carboxylic acid, as a way to influence performance properties that include but are not limited to, tuning degradability,

tuning the hydrophilic/hydrophobic character, altering swelling behavior, inducing anisotropic reactivity though sterics or electronics;

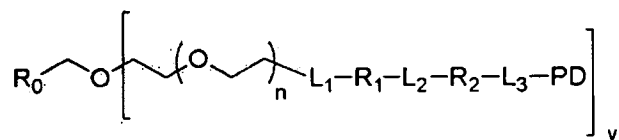
L₂ is selected to be either urethane, urea,, or amide linkages;

R₂ may be selected from a linear, cyclic, branched, aryl, or substituted aryl group as a way to influence performance properties that include but are not limited to, tuning degradability, tuning the hydrophilic/hydrophobic character, altering swelling behavior, inducing anisotropic reactivity though sterics or electronics, for example, R₂ may derived from a group of linear, cyclic, branched, aryl, or substituted aryl diisocyanates, or R₂ is selected from a group of □,□-amino acids, □,□-dicarboxylic acids, or □,□-diamines, □,□-hydroxyl carboxylic acid, as a way to influence performance properties that include but are not limited to, tuning degradability, tuning the hydrophilic/hydrophobic character, altering swelling behavior, inducing anisotropic reactivity though sterics or electronics;

L₃ is selected to be either an amide, urea, or a urethane, where R₂ is a derived from a diisocyanate,, alternatively L₃ may further be an ester;

when L₃ is not present R₂ becomes the PD terminating group.

[093] In another embodiment, an example polymer utilized in the practice of various embodiments described herein is represented by the sealant material incorporating functionalized polymers of the following structure:



Wherein R₀ is, for example, *Hexaglycerin, tripentaerythritol, pentaerithrytol, or other cores suitable for forming multi-armed PEGS, as known to those skilled in the art;*

y is an integer from 3 to 20;

PD is a phenyl derivative, such as guaiacol, catechol or syringol, diamine phenyl derivative;

L₁ is selected to be either urethane, urea, ester, or amide linkages;

R₁ is selected from a linear, cyclic, branched, aryl, or substituted aryl group as a way to influence performance properties that include but are not limited to, tuning degradability, tuning the hydrophilic/hydrophobic character, altering swelling behavior, inducing anisotropic reactivity though sterics or electronics, for example, R₁ may derived from a group of linear, cyclic, branched, aryl, or substituted aryl diisocyanates, or R₁ may be selected from a group of □,□-

amino acids, □,□-dicarboxylic acids, or □,□-diamines, □,□-hydroxyl carboxylic acid, as a way to influence performance properties that include but are not limited to, tuning degradability, tuning the hydrophilic/hydrophobic character, altering swelling behavior, inducing anisotropic reactivity though sterics or electronics;

L₂ is selected to be either urethane, urea,, or amide linkages;

R₂ may be selected from a linear, cyclic, branched, aryl, or substituted aryl group as a way to influence performance properties that include but are not limited to, tuning degradability, tuning the hydrophilic/hydrophobic character, altering swelling behavior, inducing anisotropic reactivity though sterics or electronics, for example, R₂ may derived from a group of linear, cyclic, branched, aryl, or substituted aryl diisocyanates, or R₂ is selected from a group of □,□-amino acids, □,□-dicarboxylic acids, or □,□-diamines, □,□-hydroxyl carboxylic acid, as a way to influence performance properties that include but are not limited to, tuning degradability, tuning the hydrophilic/hydrophobic character, altering swelling behavior, inducing anisotropic reactivity though sterics or electronics;

L₃ is selected to be either an amide, urea, or a urethane, where R₂ is a derived from a diisocyanate,, alternatively L₃ may further be an ester;

when L₃ is not present R₂ becomes the PD terminating group.

[094] The functional group, (e.g., diamine phenyl derivative, catechol, syringol and guaiacol) modified polymer creates a cohesive network upon oxidation with a chemical oxidant, and provides a rubbery and pliable feel, capable of adapting to irregular surfaces, that is capable of stretching 4-5 times its length under tensile stress and will adhere to wet or dry skin surface very well. It is believed that this combination of properties is not known, but is particularly well suited to the needs of ostomy patients. It is envisioned by the inventors that this combination of adhesive properties could suit a wide variety of internal and external biomedical needs.

[095] The sealant material may initially form a gel or paste composition when first hydrated, prior to substantial oxidation reaction occurring; and in some embodiments, are intended to be delivered as aqueous based pastes or gels, wherein the sealant material is malleable and is able conform to irregular surfaces, thereby able to fill contoured gaps, folds and creases that accompany a wide variety of stoma geometries, making these sealant materials useful in ostomy applications. In various embodiments described here, the sealant material, as the activator causes the reaction of the functional groups, will set to a second form as a hydrogel.

This setting to a hydrogel is attributable to the sealant material curing occurs over a span of time, preferably one that allows adequate handling of the material for application to the patient, typically 5-10 minutes of curing, whereupon the sealant material transitions from a malleable gel or paste, to become soft, elastic, and pliable. The cured hydrogel sealants are able to provide more sealant strength, especially in aqueous environments, than commercially available rings, wafers, and pastes as known in the art, such as Stomahesive, Coloplast Ostomy Paste, and Hollister Adapt paste, when tested according to a standard test burst pressure method.

The ligand forming hydrophilic oligomer

[096] In various embodiment, the functionalized polymer has a base structure of C-D-X-D-C. The C groups are generally described as capable of ligand formation, and are bidentate or greater, and which are capable of initiation and subsequent polymerization by an oxidant. Non-limiting examples of the ligand forming portion of said C groups are: diamine phenyl derivative, catechol, guaiacol, and syringol. Other examples would include chemical species that would form the hydroquinoidal species in the presence of oxidants. Non-limiting examples of the moieties capable of reacting with the D groups are: branched or unbranched alkanols, branched or unbranched alkyl amines, branched or unbranched alkyl ether alcohols, branched or unbranched alkyl ether amines.

[097] The D groups are described as linking groups capable of reacting with C and X and has a functionality of 2 or greater. Non-limiting examples are: toluene diisocyanate, isophorone diisocyanate, alkyl dicarboxylates, alkyl ether dicarboxylates, □,□-amino acids, □,□-dicarboxylic acids, or □,□-diamines, □,□-hydroxyl carboxylic acid and the like.

[098] The X groups are described as hydrophilic moiety capable of reacting with D and having a reactive functionality of greater than 2. Non-limiting examples are: polyethylene glycol with a number average molecular weight between 1000 and 35000 Daltons, methyl substituted polyoxazolidones, ethyl substituted polyoxazolidinones, propyl substituted polyoxazolidinones, butyl substituted polyoxazolidinones, polyvinyl alcohols, polymethacrylates, polyacrylates, polysaccharides.

[099] It is expected that one skilled in the art having this teaching can conceive of many different combinations of C, D, and X groups such that the functions cited are performed. These combinations are not exhaustively disclosed and one skilled in the art would be able to select

useful combinations based on the teachings described herein as long they perform the functions described.

The inorganic active filler

[0100] The inorganic active filler is described as one which can be subsequently successfully chelated or hydrogen bonded or a combination thereof with the ligand moieties of a) and wherein the inorganic active filler is present in an amount exceeding 50%. In an embodiment, the inorganic active filler is present from 51% to 98% (dry particle weight to polymer volume). In another embodiment, the inorganic active filler is a reactive salt incorporated into the functionalized polymer, and activator mixture, which upon exposure to an amount of aqueous fluid, the activator will be free to initiate the reaction of the functional groups, causing the material to set, such as by cross-linking, to a pliable, elastic hydrogel form. Non-limiting examples of the inorganic active fillers are: monocalcium phosphate, dicalcium phosphate, tricalcium phosphate, Mg_3PO_4 , MgPO_4 , BaPO_4 , SrPO_4 , SrSO_4 , BaCO_3 , MgCO_3 , MgSO_4 , BaSO_4 , CaSO_4 , CaCO_3 and the like. It is expected that, with this teaching, one skilled in the art could select a wide variety of useful materials which are contemplated. Especially surprising is that particle amounts, in any amount exceeding 50%, such as from exceeding 51% to exceeding 98% (dry particle weight to polymer volume), seem to be unusually effective for use as contemplated herein, considering that such high levels of inorganic materials would be expected to reduce the overall concentration of reactive functional groups, and it would be anticipated that with a lower concentration of reactive groups, the hydrated mixture would not be expected to set as effectively to a strong, cohesive, elastic material. This is surprising, as one skilled in the art would be motivated to minimize the concentration of fillers, as the effect of excessive fillers is recognized, for example, in the field of latex paints, where the latex paint is required to cross-link, however, when the filler concentration is high, it has been observed to interfere with the cross-linking of the latex paint. Similarly, one would expect the cross-linking of the functionalized polymers to behave in a similar manner. Applicants have surprisingly noticed that adding inorganic filler materials that are at concentrations exceeding 50%, for example at concentrations above 75%, at concentrations above 90%, and at concentrations above 95%, are able to enhance the physical characteristics of the hydrogel material that results when the functionalized polymers have set to a hydrogel form, as has described herein.

[0101] Another additional filler, which may, or may not be an active filler, could be included in various embodiments described herein is one that is an absorbent filler. Such an absorbent filler could provide a moldable and/or injectable sealant material that will conform to the site of application without the need to be a thin, low viscosity, liquid-like material, and that can set up quickly once applied to the site. The solution to this identified need is to establish a way to temporarily retard the reaction rate of the functionalized polymer, by absorbing the hydration fluid away from the reactive components, isolating the hydration fluid long enough from the reactive components so that it does not set too quickly into unmoldable/non-injectable mass, but also provide for sufficient hydration so that the material can be easily molded/injected. Essentially, a way of providing fluid-like properties, without free fluid is needed. The absorbent filler could serve as a particulate hydrogel entrapped within the functionalized polymer as it is setting to an elastic hydrogel matrix. The additional absorbent filler would be capable of swelling as it imbibed water and bound it within its polymer matrix, and would only release the water when exposed to drying conditions. The incorporation of an absorbent hydrogel solves the problems of prior art by placing hygroscopic particles within the mixture that adsorb fluid and prevent the fluid partaking in the reaction of the functionalized polymer to a hydrogel, until after the mixture has been injected and/or applied to a site. Once the polymer and activator mix is thoroughly combined, the hygroscopic absorbent filler materials will absorb the excess fluid, to leave a more viscous gel, which can then set to a hydrogel as previously described. Non limiting examples of such additional fillers include:: Carboxymethyl cellulose, Alginate, Chitosan, clays (e.g., laponite, kaolin, zeolite), Bioglass, glass ceramics, Chitin, SiO₂, and the like.

Aqueous Solvating Fluid

[0102] The aqueous solvating fluid may be added to the mix of at least functionalized polymer and activator, and optionally active inorganic fillers, with sufficient concentration of solvent which is capable of solvating the activator in sufficient quantities to enable the of formation of reaction between functional groups on the polymer. The amount of aqueous solvating fluid added to the functionalized polymer and activator must not be so much that it dilutes down the concentration of mix ingredients to the point where they are non-reactive, or not able to set up properly. Non-limiting examples of these sorts of aqueous solvents are: water,

saline, phosphate buffered saline, buffered aqueous solutions, or biological fluids, such as blood, autologous fluids, and the like. It should be understood that in the case of most of the functionalized polymers, the rate at which the reactions proceed may be affected by the pH, accordingly, the hydronium ion concentration can be increased by increasing the pH by the introduction of a wide variety of pH adjusting ingredients. It is expected that one skilled in the art having this teaching can conceive of many different aqueous fluids, such that the functions cited are performed. These combinations are not exhaustively disclosed and one skilled in the art would be able to select useful combinations based on the teachings described herein as long they perform the functions described.

Activator

[0103] The activator is described as one which is capable of initiating the reaction of said species in component a) capable of initiation and subsequent polymerization and form a set polymer in a controlled length of time. The activator may be an oxidant that initiates an oxidant intitiatable species of component a). Non-limiting examples of these activators are: tetramethyl ammonium periodate, tetraethyl ammonium periodate, tetrapropyl ammonium periodate, tetrabutyl ammonium periodate, Fe(II)Cl_2 , Fe(III)Cl_3 , Cu(I)Cl , Cu(II)Cl_2 , AgNO_3 , AgO , Ag_2CO_3 , and the like. It should be understood, that chelated forms of the metallic ions are also usable and that EDTA or other ligands could be used in place of the counteranions cited.

[0104] Varying the concentration of the oxidant incorporated into the mix with functionalized polymer would allow some control over the rate at which the hydrated material will set to a hydrogel, during this set, the material transitions from a malleable gel, to an elastic hydrogel. By controlling the starting concentration of the oxidant, one is able to control the workable time that the hydrated gel remains shapeable, before setting to the elastic hydrogel form. The oxidant concentration typically is less than 1% by weight of the dry reagents.

[0105] Moisture build up around the adhesive seal of presently available ostomy devices is a well-documented problem for ostomy patients. Whether due to perspiration or effluent leakage, moisture is the primary cause for breakdown of the seal that leads to skin irritation and pain. Commercial suppliers of adhesives and sealant have previously attempted to alleviate this tendency by developing products that absorb moisture or provide a barrier against the moisture. In nearly all cases, preparation of the skin and excessive drying of the skin is critical to the

effectiveness of the adhesive or sealant. Unfortunately, moisture introduced by perspiration or effluent leakage negates these laborious efforts and can lead to chronic discomfort. In order to understand the impact of trace moisture on the ostomy seal, we tested a few different ostomy products under a few different conditions where moisture is gradually introduced. We have developed a test method that allows us to quantitatively measure the seal on a defined substrate by measuring a final pressure of water that causes the seal to break. A high burst pressure reading generally correlates to a strong seal, where a low pressure reading generally correlates to a weaker seal. Figure 5 shows three commercial products: Coloplast Brava Ring; the wafer from a Coloplast ostomy bag; and a ConvaTec Eakin Ring; all tested under three conditions that reflect increasing moisture.

[0106] With reference to Fig. 5, Condition A refers to the commercial sealant sample applied on a piece of dry mylar (oriented polyethylene terephthalate). Condition B refers to the sealant applied onto a piece of collagen casing that is patted to dryness. In this condition, while the casing is dry to the touch, there still remains trace amounts of inherent moisture to the casing. Condition C refers to collagen casing that has been patted dry as in condition B, but is then followed by adding a single drop of PBS buffer to the casing. In this condition, we show the effect of intentionally adding a small amount of moisture. The most notable feature seen in Figure 5 is that for each commercial product tested, the burst pressure on the dry substrate is significantly high – most for the Coloplast bag wafer (col. 2A). Although mylar is not a substitute for human skin, in our evaluation, this would represent the best case sealability that one might expect. In this test, Coloplast bag wafer outperforms the other ostomy sealants we evaluated. As moisture is introduced, a precipitous drop in strength for each of these existing commercial products is observed, as depicted in condition B for all of the samples. The ConvaTec Eakin Ring does retain some of its strength over the Coloplast ring or bag wafer, however, a progressive drop in strength of *ca.* 50% is still observed with even small amounts of moisture.

[0107] An evaluation of commercially available ostomy pastes under the same conditions as the accessories yielded a similar behavior, only with burst pressures starting at a much lower value (**Error! Reference source not found.**).

[0108] To assess the sealing performance of various sealant material embodiments described herein, we evaluated samples according to the same burst pressure test method as above. For a

given composition, a number of samples were tested and the mean burst pressure with error is reported in **Error! Reference source not found.**⁷ For this evaluation, the decision was made to be conservative, by measuring the burst pressure – and consequent sealability – according to a scenario where the skin is not completely dry corresponding to condition “C”, described above. By intentionally adding a small amount of moisture to the collagen casing material for the test, the burst pressure test method would most closely represent a scenario where the skin is not exhaustively dried and even allows for some moisture. Also, by using collagen casing substrate, we have a substrate with reactive tissue residues, similar to skin, that can demonstrate the ability of our sealant to adhere to the stoma as well as the skin of the patient, thereby serving as a suitable model for enhanced protection of the peristomal skin.

[0109] The left-most bar (1C) on the graph in Figure 6 is the Brava ring tested under condition C. Under the conditions of the test method, the casing was patted dry and a single drop of PBS buffer was placed onto the casing. The substrate was then placed onto the moist casing and conditioned for 30 minutes before testing. This control served as a baseline for many of the other compositions. The second bar (2C) from the left in **Error! Reference source not found.**⁷ is the wafer from a Coloplast bag appliance. The burst pressure in both of these cases was poor. The wafer on the ostomy bag (2C), was the same testing material that provided the strongest dry burst pressure in Figure 5 (sample 2 from Fig. 5), and here, upon testing in condition C, dropped substantially with a small amount of moisture.

[0110] With reference to Figure 7, we then evaluated various embodiments as sealants, which were comprised of a filler material and a functionalized synthetic polymer at a 90/10 weight ratio respectively. In this embodiment, the functionalized polymer is catecholate-modified. The inorganic filler materials chosen were: a 3% aqueous solution of carboxymethylcellulose (IE1 Gel); a 3% aqueous solution of tragacanth gum (IE2 Gel); and a 3% aqueous solution of laponite, which is a clay (IE3 Gel). Each of these sealants, when hydrated adequately, initially had the consistency of a malleable gel, where their effectiveness of filling in contoured or creased skin was envisioned. The functionalized polymer was allowed to react and set to a hydrogel, using sodium periodate as an activator, at less than 1%. In each case, a notable improvement in the burst pressure was observed, showing that in a moist environment, these newly developed sealants could be as effective or even more effective than existing commercial sealant materials (the controls 1C and 2C). A benefit of the various embodiments of the sealants

described herein is they differ from those known in the art in that they are not dry, but rather inherently contain a substantial amount of water. Where the negative impact of just small amounts of moisture on existing commercial sealants is dramatic, these various embodiments of novel gel sealants do not exhibit the same effect, thus demonstrating how a sealant that contains >90% water can still be effective.

[0111] In an even more surprising result, when the filler material chosen was an inorganic material, such as a calcium phosphate salt, an even greater increase in burst pressure was noticed. Under similar test conditions as with the previously tested ring, bag adhesive wafer, and flowable gels of Inventive Examples 1, 2, and 3, various paste embodiments according to the teachings herein were prepared, comprised of at least 95% calcium phosphate and up to 5% of a catecholate-modified synthetic polymer. As can be seen in Fig. 7, these paste embodiments (IE4 and IE5) resulted in a burst pressure approximately ten times greater than the controls (1C and 2C). The most notable features of this class of sealant are the enhanced strength over commercial wafers and bag adhesives, and more flexibility as measured by the elongation at break of these adhesives (4-5x stretch). The strength is important to maintain a seal for the effluent, while the flexibility is critical for resistance to delamination from the skin or the appliance, considering the active lifestyle of the patient, as the flexibility and elasticity will move with the tissue surface of the patient. A third notable feature of the sealant embodiments described herein is the amount of synthetic polymer that is used to achieve the aforementioned properties. One would expect materials comprised of *ca.* 96% inorganic content and *ca.* 4% polymeric binder content to be relatively brittle, however, when prepared with the various embodiments of catechol, syringol, diamine phenyl derivative, and guaiacol containing adhesive molecules, the samples according to the embodiments herein, even with the high inorganic content, greater than 50%, and according to these particular samples, approximately 96%, are capable of high flexibility, elasticity, and strength, making them suitable for use in various applications, such as ostomy applications. As with the previously described flowable gels (IE1, 2, and 3), these sealant paste materials were designed to have an initial flowable consistency that could fill in skin creases and contours, prior to setting as a hydrogel. It is believed that a critical amount of phenyl derivatives, (e.g., synthetic catecholate or guaiacolate polymer, etc.) is required for the paste to remain cohesive. By contrast, example pastes that were prepared with less than 4% catecholate-modified PEG, had

drawbacks such as reduced strength, cured too slow to be practical (≥ 30 minutes cure time) or did not cure at all (*vide infra*).

[0112] In order to learn more about this system, we considered two addition experiments: one where the catecholate-modified PEG was substituted with a dihydroxylated PEG (containing no catechol), and one where the catecholate-modified PEG was substituted with a PEG-diacrylate. The dihydroxylated PEG substitution was chosen to confirm that the catechol-based crosslinking mechanism was in fact responsible for the unique properties. The PEG-diacrylate was chosen to assess the breadth of other crosslinking mechanisms that may also be responsible for the unique properties. The dihydroxylated PEG was activated with oxidant, in this case, sodium periodate, while the diacrylate was crosslinked via addition of an initiator azobisisobutyronitrile (AIBN) and UV light. The burst pressure of each resultant paste was measured, with the results provided in Table 10. The burst pressure for the dihydroxyl PEG was negligible and couldn't be measured reliably since it did not cure. Similarly, the PEG-diacrylate took too long for a cohesive mass to be obtained. These experiments revealed that the catecholate-based crosslinking reaction is essential in creating a soft, pliable elastic ostomy paste incorporating an active inorganic filler, in this particular example, calcium phosphate, to yield a paste with exceptional properties, and suitable for a variety of uses, including medical applications, such as in ostomy applications. Also, it demonstrated that there are limitations to the type of crosslinking mechanisms that can be applied to these systems and yield the type of properties that ostomy applications require, e.g. curing in less than 30 minutes. It is anticipated that a guaiacolate-based cross-linking reaction would perform similarly to a catecholate based cross-linking reaction.

Table 10. Data for Calcium phosphate/catecholate-modified PEG pastes.

PEG-(Z)₂	activator	Cohesive mass (Y/N)	Burst Pressure (mmHg)	Elongation at Break
PEG-(OH) ₂	NaIO ₄	N	0.7	- ^a
PEG-(Acrylate) ₂	AIBN/UV light	Y	- ^b	- ^a

^a Not able to be tested due to the poor handling. ^b Did not fully cure after 30 minutes.

[0113] In order to demonstrate the breadth of inorganic fillers suitable as effective base materials for improved ostomy sealants, by their property of being an active inorganic filler, we prepared and tested an additional series of pastes under different conditions using the following inorganic components: alpha and beta-tricalcium phosphates, hydroxyapatite, a zeolite (alumina silicate), a bioglass, and silica. The data shown in Table 11, reveals that alpha and beta tricalcium phosphates, hydroxyapatite and a representative zeolite, all have substantially comparable or superior burst pressures. This suggests that they also could be used as a curable, soft, and pliable ostomy paste.

Table 11. Composition and Burst pressure data for ostomy pastes that utilize different inorganic components. ^a Condition A. ^b Condition B. ^c Condition C. ^d Samples did not cure cohesively due to immiscibility of calcium and water. NT = not tested.

	IE6	IE7	IE8	IE9	IE10	IE11	IE12
Filler material	□- TCP	□- TCP	□-TCP ^d	□-TCP ^d	□-TCP ^d	Hydroxy Apatite	zeolite
average particle size (□m)	< 15	< 15	50-100	300- 500	> 500	< 15	< 15
mass filler material (g)	20	20	20	20	20	20	20
mass adhesive polymer M222 (g)	1.28	1.28	1.28	1.28	1.28	1.28	1.28
mass water (g) PBS	7.0	7.0	7.0	7.0	7.0	7.0	7.0
g activator (g)							
Burst Pressure (mmHg) ^a	262.0	NT	13.1	2.4	5.9	207.4	63.7
Burst Pressure (mmHg) ^b	127.9	NT	3.1	3.4	1.3	101.0	37.2
Burst Pressure (mmHg) ^c	132.3	NT	1.7	3.2	1.5	97.1	45.7

[0114] While the compositions of inorganic components is far from exhaustive, it demonstrates that this is not limited to dicalcium phosphate salts alone. In fact, we noticed a stronger correlation between burst strength and particle size of inorganic components than identifying only similar compositions. For example, □-TCPs of higher particle size had lower burst than those of lower particle size. In fact, inorganic components with particle sizes < 100□m were far more suitable pastes for the applications considered herein, due to their more

desirable burst pressure results, than those inorganic components with larger particle sizes. It was noted that silica-based pastes led to grainy gels that showed no cohesiveness.

[0115] While not explicitly tested, the pH of these pastes can be mildly acidic to strongly basic, the pH is anticipated to be largely dependent upon the aqueous solvating fluid used, and the influence upon the pH from the filler material, or a pH modifying agent that may be added in some embodiments. For example, a dicalcium phosphate paste has a mildly acidic pH, similar to normal human skin, whereas the tricalcium phosphate pastes are much more basic. It is known that for the catecholate functionalized polymers, the reaction rate for the catechol functional group will be faster in an elevated pH, thus a filler which tends to adjust pH more basic, will cause the material to cure much faster in the presence of a catecholate-modified synthetic polymer. Beyond affecting how fast the paste cures, pH maybe used to introduce anti-fungal or anti-bacterial properties. Thus, the use of citric acid in conjunction with faster curing pastes, not only slows down the rate of curing, but also introduces beneficial anti-fungal and anti-bacterial features. Therefore, the dicalcium phosphate salt (being mildly acidic) is able to introduce this benefit, without incorporating an additional acidic component.

[0116] Pastes based on classic organic curing mechanisms, such as previously described acrylic functionalized PEG, and isocyanate-based sealants such as Gorilla glue, were tested with filler materials. Additionally, poly(methyl)methacrylate (PMMA) was tested without filler material. Neither the PEG-acrylate material, nor the PMMA material examples displayed appropriate burst pressure; thus we did not consider them as suitable barrier materials useful for an ostomy application. The isocyanate based gorilla glue exhibited adequate burst pressure, however was not elastic enough to allow appropriate patient movement, nor would it be easily removed from the patient's tissue surfaces. Furthermore, repeated exposure to excessive isocyanates may cause bio-incompatibility issues. See Table 12.

Table 12. Composition and Burst pressure data for ostomy pastes that utilize different organic chemistries. ^a Condition A. ^b Condition B. ^c Condition C. NT = not tested.

	IE12	IE11	IE6
Filler material	PEG-diacrylate	PMMA	gorilla glue

mass filler material (g)	20	0	20
mass adhesive polymer <i>M222</i> (g)	1.28	1.28	1.28
mass water (g)	7.0	7.0	7.0
g activator (g)			
Burst Pressure (mmHg) ^a	63.7	NT	262.0
Burst Pressure (mmHg) ^b	37.2	7.0	127.9
Burst Pressure (mmHg) ^c	45.7	3.3	132.3

[0117] While the aforementioned Inventive Examples tested were prepared with a linear difunctionalized PEG molecule, in order to demonstrate the effectiveness of this approach across different architectures of catecholate-modified PEGs, an additional series of pastes were prepared and tested, using various multi-arm catecholate-modified PEGs as well.

[0118] In order to demonstrate the effectiveness of this approach across a range of molecular weights of catecholate-modified PEGs, we prepared and tested an additional series of pastes, where the molecular weight of the catecholate-modified PEG ranged from 4.5KDa to 20KDa. We observed no significant difference in burst pressure between the pastes containing different molecular weight PEG (**Error! Reference source not found.**). It is applicants' belief that the most important feature of this system is good mixing and intimate contact between the filler material and the functionalized polymer, so as to form an interconnected network, whereby a cohesive mass can be held together. It is believed that as long as there is solubility for the functionalized polymer molecule, and an adequate density of functional groups on the functionalized polymer, molecular weight should not inhibit its effectiveness. The control is column labelled CE3, and comprises a 10KDa polymer lacking the functional groups.

[0119] When comparing the various sealant embodiments described herein against additional commercial products, we clearly see the enhancement of the burst pressure in a moist environment (**Error! Reference source not found.**). We evaluated these novel sealant embodiments in a slightly moist environment, to demonstrate its effectiveness even in the absence of excessive drying. The ConvaTec Eakin ring (3C) does show a burst pressure superior to the other comparative example ring/wafer and paste materials tested, and nearly similar to the inventive paste examples 4 and 5 (IE4 & IE5) disclosed herein. The ConvaTec Eakin ring

material is able to absorb moisture, and as the ConvaTec Eakin ring becomes warm with body heat, or hydrated with moisture and stomal effluent absorbed into the material of the Eakin ring, the ring softens and begins to lose mechanical integrity due to the increasing moisture content. This softening of the ring material allows it to reshape to fill in gaps, as it is degrading. This reshaping action is what sets the ConvaTec product apart from other existing barrier materials. For the inventive paste embodiments described herein, it is believed that one of the benefits over the ConvaTec Eakin ring is that the paste embodiments described herein, at the time of initial application, are better able to fill gaps and conform to uneven tissue surfaces due to the gel nature of the initially hydrated material. Then, once cured by the reaction of the functional groups to an elastic hydrogen form, the inventive paste embodiments herein are able to retain their shape and maintain an effective seal, by absorbing little moisture, and maintaining an effective bond to the tissue surfaces; something that the Eakin ring cannot do.

[0120] In addition to burst testing and tensile testing of these materials, the stability of the inventive sealant materials described herein were evaluated in harshly acidic (pH~2), basic (pH~11), and mildly acidic saline solutions. While the intestinal tract will never see a consistent pH of 2 or 11, these sealants were submitted to these conditions as extreme cases, as well as to highlight the overall stability of the inventive examples. The evaluation of the sealants under mildly acidic saline solution (pH~6.2) represents the conditions normally found in the small intestine or large intestine. Testing at this pH further demonstrates the stability of these sealant materials for colostomy, urostomy, or ileostomy applications. Where the saline solutions were found to cause the commercial products to swell or completely fall apart, the various embodiments of the sealants and pastes described herein remain intact and shape-stable.

Conclusion

[0121] Based on these results, we have discovered a new class of ostomy sealant materials to be used in various ostomy applications, e.g., colostomy, urostomy and ileostomy applications. The sealant materials are designed to be used as a replacement or alternatively, as an adjunct to the existing pressure sensitive adhesives that hold the ostomy appliances close to the body. The composition of the sealant material is a mixture of a functionalized polymer, and an activator. In many embodiments, the mixture may optionally incorporate in excess of 50% an active inorganic filler. In some embodiments, the active inorganic filler is an inorganic salt. In an embodiment,

the active inorganic filler is dicalcium phosphate. The functionalized polymer in an embodiment is a functionalized PEG molecule. In another embodiment, the PEG molecule of the functionalized polymer is linear, branched or multi-armed PEG. In some embodiments, the functionalized polymer is functionalized with at least one catechol, guaiacol, or syringol functional group. The mixture of polymer, activator, and optionally active inorganic filler may be hydrated with an aqueous fluid, which is incorporated or mixed into the mixture to form a malleable gel material. Once hydrated to a smooth gel form, the activator will cause the functional groups to react, and while still in gel form, may be applied to the stoma or peristomal skin and held against an appropriate ostomy appliance where it cures as a sticky, soft, pliable, and elastic cohesive paste. The curing will cause the gel to become a hydrogel, and also bind to adjacent surfaces, be it tissue, or other surfaces, such as ostomy appliance. Under application-relevant standardized testing, the stability of these materials to acidic conditions representing intestinal pH, the sealability under a dynamic flow of water, and the flexibility exceed the state of the art products currently on the market.

Sealant Examples and Compositions (TBD)**Table 13.**

	1 ^a	2 ^b	IE1	IE2	IE3	IE4	IE5
Filler material			Carboxymethyl cellulose	Tragacanth Gum	Laponite	Dicalcium phosphate	Dicalcium phosphate
mass filler material (g)	-	-	2.867	2.867	2.867	70.8	70.8
mass adhesive polymer (g)	-	-	4.425	4.425	4.425	4.425	4.425
mass water (g)	-	-	92.708	92.708	92.708	24.78	24.78
g activator (g)	-	-	0.040	0.040	0.040	0.040	0.040
Burst Pressure (mmHg) ^c	17.1	22.5	37.5	14.6	26.8		
Burst Pressure (mmHg) ^d	5.1	0.8	36.6	18.8	18.2	86.7	103.9

^a Brava ring. ^b Coloplast ostomy bag wafer. ^c Condition B. ^d Condition C.

	CE3	IE14	IE15	IE17	IE18	IE19
Filler material	Dicalcium phosphate	Dicalcium phosphate	Dicalcium phosphate	Dicalcium phosphate	Dicalcium phosphate	Dicalcium phosphate
adhesive groups/molecule	2	2	2	4	2	8
MW of adhesive polymer	10 KDa	4.5 KDa	7.5 KDa	10KDa	20KDa	20KDa
mass filler material (g)	-	-	-			
mass adhesive polymer (g)						
mass water (g)						

g activator (g)						
Burst Pressure (mmHg) ^a	-	68.9	55.1			
Burst Pressure (mmHg) ^b	0.7	85.6	70.3			

	IE21	IE22	IE23	IE24	IE25	IE26 ^d
Filler material	Dicalcium phosphate	Dicalcium phosphate	Dicalcium phosphate	Dicalcium phosphate	Dicalcium phosphate	Dicalcium phosphate
mass filler material (g)	20	20.23	20.44	20.67	20.89	21.10
mass adhesive polymer (g) ^{M222}	1.28	1.06	0.85	0.63	0.42	0.21
mass water (g) (PBS 6.6)	7.0	7.0	7.0	7.0	7.0	7.0
g activator (g)	0.040	0.033	0.026	0.020	0.013	0.006
Burst Pressure (mmHg) ^a	493.1	357.4	238.5	217.6	124.1	-
Burst Pressure (mmHg) ^b	90.9	76.9	70.4	61.4	37.5	-
Burst Pressure (mmHg) ^c	92.6	80.1	85.3	59.5	40.8	-

^a Condition A. ^b Condition B. ^c Condition C. ^d Did not set after 30min.

[0122] In another embodiment, it is contemplated that any of the adhesive molecules described herein could be employed as an adhesive layer added to any existing medical device, such as an ostomy device. In this form, the bulk of a filler material would likely not be required, though it is contemplated that the filler may be incorporated, if so desired. It is contemplated

that the adhesive materials described herein could be applied, whether as a spray coating, or a thin-film, onto an existing device, at any point prior to application of the device to the patient, wherein the enhanced adhesion in moist conditions provided by the adhesives described herein could enhance the performance of another device.

[0123] Thus since the inventive process and inventions disclosed herein may be embodied by additional steps or other specific forms without departing from the spirit of general characteristics thereof, some of which steps and forms have been indicated, the embodiments described herein are to be considered in all respects illustrative and not restrictive. The scope of the invention is to be indicated by the appended claims, rather than the foregoing description, and all changes which come within the meaning and range of equivalency of the claims are intended to be embraced therein.

Examples

[0124] Commercial adhesives and sealants were obtained to be used as comparative examples. These materials are identified as follows:

[0125] Comparative Example 1 is ConvaTec Stomahesive® Paste (REF No 183910)

[0126] Comparative Example 2 is Coloplast Ostomy Paste (REF No 2650),

[0127] Comparative Example 3 is Hollister Adapt Paste (REF No 79301),

[0128] Comparative Example 4 is Trio Ostomy Care Silken™ silicone-stoma gel (REF No 1070)

[0129] Comparative Example 5 is Nu Hope Ostomy Paste

[0130] Comparative Example 6 is Convatech Eakin Ring

[0131] Comparative Example 7 is Coloplast Brava Ring

[0132] Comparative Example 8 is Coloplast Bag

Inventive Example 5

[0133] M231 + Ca₂PO₄ + water + NaIO₄

[0134] Combine 20.0g dicalcium phosphate, 1.25g M231, 40.0mg NaIO₄ in a plastic 100mL beaker. With a glass stir rod, the solids are blended until a homogenous powder is observed. In a 20mL glass vial, 7.0g phosphate buffer solution is massed out and transferred to the dry components. Upon the addition of the buffer, a timer is started. The paste is stirred by hand with a glass stir rod aggressively for 60 seconds beginning at the time of fluid addition. The product

can be dispensed directly following this step into the specific test protocols. In addition citric acid may be added in the initial dry component mixing step in order to increase set time.

Test Methods

Extensibility Testing

[0135] Take the prepared paste and transfer 10.0 grams into a plastic mold with dimensions 104mm x 26 mm x 7 mm. The mold is then lightly tapped 20 times on the benchtop to afford an evenly filled mold with no visible bubbles or surface perturbations. The paste filled mold is then allowed to react at 25°C with 50% relative humidity for 15 minutes, before being covered with a 12" square Kim Wipe evenly wetted with about 11 grams of deionized water for an additional 15 minutes at 25°C. The final thickness of the material is between 5.5 cm and 7.0 cm.

[0136] The cured polymer is left in the mold and cut with Dogbone Type I - ASTM D1708 Steel Rule Die. The position of the die is optimized to avoid imperfections in the putty slab and maximize the number of test specimens. Any imperfection over 0.5 mm in length present in the sample is considered defective and discarded. All specimens are cut at least 1 cm from the edge of the putty slab. Cut specimens are then removed from the mold with tweezers via the dogbone tab, careful to not stress or perturb the material prior to testing. Specimens are then placed between layers of 12" square Kim Wipes that have been wetted with roughly 11 grams of deionized water to prevent dehydration prior to testing.

[0137] The specimens are then tested on an Instron 5965 Dual Column Test Stand with a static load cell of +/- 100N, and a gauge length of 22 mm with standard Instron 1 kN Pneumatic Grips with 10 PSI. After a specimen is clamped into place as outlined in ASTM D1708, a Digital Thickness Gauge (VWR CAT. NO.: 10111-906) is used to verify an appropriate sample thickness of 0.5 mm to 0.7 mm. After testing the sample as outlined in ASTM D1708, the specimen was examined to make sure the break was in the gauge (5 mm) portion of the sample. If the break occurred outside the gauge area, in either the transition zone or the tab, the data is not considered valid. The overall extension was calculated by looking at the difference between the starting grip distance of 22 mm (D_i), and the grip distance at failure (D_f). Testing was performed with a sample size of $n = 6$, and a standard deviation of 25.

[0138] Percent Extension = $((D_f - D_i)/D_i) \times 100$

[0139] Ostomy Paste Injectability Force Testing Method

[0140] The injectability force of the Ostomy Paste was determined by measuring the force required to push the paste through a 3 mL BD luer lock syringe (Supplier No 309606) with and without an attached 14G tapered needle (Catalogue No KDS14TNP, Cooper Tools). The test was performed at a constant injection speed of 0.01 inch/min using an Instron Single Column Test Stand (Model No 5542) couple with a Static Load Cell (± 100 N) (Model No 2525-807) at a temperature of 20-25°C.

DSM Ostomy Paste preparation

[0141] All inventive example sample pastes were loaded into a 3mL BD syringe to a volume of 2.5mL.

[0142] Comparative example ostomy pastes preparation

[0143] All comparative examples were also directly loaded into a 3mL BD syringe to a volume of 2.5mL.

[0144] When each sample was loaded, the injectability force test was initiated 3 min after the paste was mixed with PBS (for Inventive Example 1 only) or 3 min after the paste was loaded into the syringe (for commercial available ostomy pastes) and was stopped when the applied force reached 100 N. Three specimens were tested for each formulation. The compressive load vs time were graphed and reported. The non-injectable point was determined by averaging the points where the samples exhibited a compressive load larger than 30N.

[0145] A non-injectable point of 6-180min, preferably 6-60min, more preferably 8-12 min was determined to be acceptable considering the working time requirement for the device usage by the patients.

Integrity Testing of Ostomy Products

[0146] The integrity of an ostomy device is defined as its ability to resist breakdown by simulated biological fluids. This test measures the weight percentage, otherwise known as integrity value of the ostomy device retained after exposure to simulated biological fluid under specified conditions.

Sample Preparation for curable pastes

[0147] A minimum of 20g of inventive example 1 is prepared. Immediately following preparation the paste is transferred into a plastic mold with dimensions 104mm x 26mm x 7mm. The mold is then lightly tapped 20 times on the benchtop to afford an evenly filled mold with no

visible bubbles or surface perturbations. The paste filled mold is then allowed to react at 25°C with 50% relative humidity for 15 minutes. Circular samples with a diameter of about 10mm are obtained by cutting with a die cutter. The samples height must be in the 5.5-7.0mm range.

[0148] Sample Preparation for free flowing ostomy adhesives

[0149] For a free flowing ostomy device such as commercially available pastes or gels without the ability to cure, dispense samples until a 10-20mm diameter with a 5.5-7.0mm height is achieved. For solid form ostomy devices obtain 10mm diameter circular samples by cutting with a die cutter. The samples height must be 5.5-7.0mm.

Integrity Testing of prepared samples

[0150] Condition samples at 37±1°C and about 50% relative humidity for 24 hours. Weigh and record the samples mass (Mi) to four significant figures. Place each sample in a 20mL scintillation vial with screw cap (VWR Catalog Number 66020-326). Dispense 15mL of physiological saline (NaCl 0.9% wt in water adjusted to pH 6.2 using 1N HCl and 1N NaOH) into each vial. Cap the vial and agitate the vials using an orbital shaker (VWR Catalog Number 58816-121 Model: 945300) set to setting 6 for 24 hours. Remove the samples from the vials and pat them dry to remove any excess moisture. Dry the samples at 37±1°C and about 50% relative humidity for 24 hours. Weigh and record the samples mass (Mf) to four significant figures. The integrity value of each individual sample is calculated using the following equation:

[0151] Integrity Value (%) = $100 \times ((Mf)/(Mi))$

[0152] Each sample group tested must contain eight samples per unique sample group. The standard deviation of each unique sample groups integrity values must be ≤5 for the sample set to be valid.

Burst Strength Test Method

[0153] To test the ability of these paste formulations to function as viable ostomy sealants, they were used to seal an opening (3 mm diameter) on a wetted collagen substrate under pressure. The burst strengths of various ostomy formulations were tested using a protocol based on ASTM Standard F 2392-04 (*Standard Test Method for Burst Strength of Surgical Sealants* 2004) as well as US 8030413B2, US8673286 B2) as well as this disclosure. The test involves the tissue preparation as well as the testing of the material. The paste was prepared according to the previously described procedure, see schematic (**Error! Reference source not found.**).

[0154] Bovine collagen casing (purchased from Vista International) was removed from the refrigerator (*ca.* 4 deg C), and gently rinsed under cool tap water until slightly softened. The casing is further rinsed by being placed in a 71oz. bucket 2/3 of the volume filled with tap water which is then placed in an incubator shaker at 90rpm and 37degC for 15 minutes. Discard tap

water and cut casing lengthwise using bandage scissors. Transfer casing to empty bucket and fill with 1000mL of freshly prepared 0.1% w/v SDS in process water.

[0155] Bucket is placed in an incubator shaker (New Brunswick, Model - Inova 44R) at 90rpm and 37deg C for 15minutes. Discard the SDS solution and thoroughly rinse casing and container with cool tap water. Return casing to container and fill bucket 2/3 of the volume with process water and place on incubator shaker at 90rpm, and 37degC, for 15minutes. Discard the process water from the container and add 1000mL 1X PBS (pH 7.4) buffer. Soak for a minimum of 30min before cutting for testing.

[0156] The collagen material is cut into 30 mm dia. circular pieces. In each piece a 3 mm circular defect is created on-center using a leatherworking punch. In parallel an small dab of grease (3-4mm in diameter) is applied to release liner and spread evenly into a thin circle *ca.* 30mm in diameter. The casing is placed onto the release liner. The freshly activated ostomy pastes are transferred to a 3 ml Becton Dickinson syringe and onto the collagen substrate with complete coverage, and filled inside a PTFE (or silicone) washer (id = 15.0mm, thickness = 1.0mm). The pastes were allowed to cure at ambient for 30 min to yield cured discs having a thickness between 5.0 and 7.0mm before testing. Sealed defects were tested by removing the casing with cured paste from the release liner and onto a custom built apparatus consisting of a syringe pump, syringe, test fixture (Figure 11), water bath (Oakton, Model: U-12501-10), and pressure gauge (Fisher Scientific, Model: 06-664-19). The system was pressurized with water (37deg C) delivered by a syringe pump (brand and model or syringe and pump) at a flow rate of 2 mL/min until the paste failed. The maximum pressure attained was recorded.

[0157] Comparative burst strength measurements for an ostomy paste of this invention versus other ostomy pastes, rings, or adhesive products are shown in this invention. The measurements were made in accordance with ASTM Test Standard F 2392-04. The data obtained is from a sample size of 8 cured discs for each paste prepared. Standard deviation and %RSD are collected, where the %RSD is calculated by $[SD]/[Average Burst Pressure] \times 100$.

[0158] The inventive pastes described herein exhibited a surprising and unexpected improvement over existing products.

[0159] Various formulation of molecules, per the components in an ostomy paste were prepared as set forth below, and tested, where M231 and M232 are patent example 1 and 2 respectively. Results of the testing are provided in Table 14. Additionally, Table 14 provides the

actual amounts measured for creation of the formulations, where the both the weight percentages and the masses of components are provided.

Table 14

Patent Example	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Excel Component	-	-	A	B	C	D	E	F	G	H	I	J	K	L	M
Poly (g)	0.56	0.56	5.24%	5.12%	5.44%	3.51%	2.82%	3.44%	3.34%	3.51%	3.51%	3.51%	4.00%	3.81%	4.42%
Filler (g)	10.72	10.72	62.99%	61.51%	65.45%	71.76%	57.60%	70.35%	68.20%	71.73%	71.73%	71.73%	63.92%	61.00%	70.6
Citric (g)			0.77%	0.09%	0.10%	0.04%	0.03%	0.03%	0.10%	0.00%	0.00%	0.00%	0.00%	0.00%	0.07
Activator (g)	0.018	0.018	0.18%	0.18%	0.19%	0.12%	0.10%	0.36%	5.01%	0.19%	0.19%	0.19%	0.12%	0.12%	0.13
Water (g)	3.7	3.7	30.82%	33.10%	28.82%	24.58%	39.45%	24.09%	23.36%	24.57%	24.57%	24.57%	31.96%	35.07%	24.7
cosolv (g)								1.72%							
Total	15.00	15.00	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100

N			7	2	6	5	7	6	6	3	4	4			
Modulus			0.195	0.059	0.235	0.188	0.130	0.208	0.619	0.913	1.756	0.808			
SD			0.034	0.004	0.105	0.069	0.031	0.045	0.054	0.093	0.079	0.049			
% Extension			532	255	268	369	123	268	228	132	90	79			
SD			101.6	49.3	67.4	57.5	18.9	51.7	21.2	32.9	10.3	9.6			

N			1	3	2	3	2	3	3	3	3	3			
t(min) to 30N			46	22.1	13.8	7.8	13.2	13.9	11.8	5.3	2.5	4.3		1.0	
SD				4.40	1.10	2.91	0.30	1.08	0.74	0.76	0.16	1.70			

N (Mylar)			8	8	8	8	8	8	8	8	8	8	5	8	6
BP (mmHg)			253.8	68.8	77.3	290.3	140.5	322.0	350.8	181.9	157.4	133.8	262.0	394.3	207
SD			49.8	20.5	14.1	108.3	35.6	61.4	84.7	43.9	74.6	24.9	41.8	108.2	24.

N (Casing)			8	8	8	8	8	8	8	8	8	8	5	8	4
BP (mmHg)			86.5	37.6	25.3	120.6	53.8	183.5	198.5	220.3	180.4	198.7	132.3	84.7	97.
SD			14.1	4.7	7.5	36.7	11.5	13.5	44.5	40.4	19.2	27.3	25.1	12.3	24.

16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
N	O	P	Q	R	S	T	U	V	W	X	Y	Z	AA	AB
4.42%	3.26%	3.26%	3.26%	4.52%	3.74%	3.00%	2.22%	1.48%	0.74%	3.81%	3.81%	3.81%	3.81%	3.81
70.70%	52.24%	52.24%	52.24%	70.62%	71.43%	72.19%	72.99%	73.76%	74.52%	60.99%	60.98%	60.97%	60.95%	60.9
0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	0.02%	0.03%	0.05%	0.08%	0.15
0.13%	0.10%	0.10%	0.10%	0.14%	0.12%	0.09%	0.07%	0.05%	0.02%	0.12%	0.12%	0.12%	0.12%	0.12
24.75%	44.40%	44.40%	44.40%	24.72%	24.71%	24.72%	24.72%	24.71%	24.72%	35.07%	35.06%	35.06%	35.05%	35.0
100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100

										3.5	5.0	6.8	10.0	25.0	

6	6	8	5	8	8	8	8	8	8						
63.7	13.1	2.4	5.9	493.1	357.4	238.5	217.6	129.2	DNS						
20.4	3.0	1.7	2.2	85.0	99.5	72.3	75.9	124.1	DNS						

8	6	8	6	8	8	8	8	8	8						
45.7	3.2	3.2	1.5	92.6	80.1	85.3	59.5	40.8	DNS						
11.2	1.9	1.9	0.9	8.8	17.5	23.7	19.8	9.0	DNS						

31	32	33	34	35	36	37	38			
AC	AD	AE	AF	AG	AH	AI	AJ	Low	High	Delta
3.80%	3.78%	3.76%	4.42%	4.42%	4.42%	3.00%	3.00%	0.74%	5.44%	4.70%
60.81%	60.54%	60.08%	2.87%	2.87%	2.87%	72.12%	72.17%	2.87%	74.52%	71.65%
0.30%	0.76%	1.50%	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%	1.50%	1.50%
0.12%	0.12%	0.11%	0.04%	0.04%	0.04%	0.19%	0.12%	0.02%	5.01%	4.98%
34.97%	34.81%	34.55%	92.67%	92.67%	92.67%	24.70%	24.71%	23.36%	92.67%	69.31%
								1.72%	1.72%	0.00%
100%	100%	100%	100%	100%	100%	100%	100%			

								Low	High	Delta
								0.059	1.756	1.697
								79	532	453.003

								Low	High	Delta
90.0	140.0	150.0						2.5	46.0	43.5

			8	8	8	8	8	Low	High	Delta
			37.5	14.6	26.8	68.9	55.1	68.8	350.8	281.9
			14.6	5.9	10.0	34.6	22.3			

			8	8	8	8	8	Low	High	Delta
			36.6	19.1	18.2	85.6	70.3	1.500	220.338	218.838
			11.3	6.4	6.4	22.1	21.5			

Product Candidates	RE31	Formulation (g)	15g mass (g)	%
	MSI1	0.36	0.54	1.77%
	DCE	10.72	3.64	71.54%
	Citric Acid	0.00	0.00	0.00%
	NaHCO ₃	0.018	0.01	0.12%
	DI Water	3.7	1.95	24.62%

RE32	Formulation (g)	15g mass (g)	%
MSI2	0.36	0.54	3.71%
DCE	10.72	5.64	71.45%
Citric Acid	0.00	0.00	0.00%
NaHCO ₃	0.018	0.01	0.12%
DI Water	3.7	1.95	24.82%

Inorganic Nern	A	Formulation(g)	15g mass (g)	%
	MSI1 (Polar B1)	1.000	0.780	5.21%
	Filler: CaCO ₃	20.44	9.44	52.57%
	Citric Acid	0.010	0.116	0.77%
	Peroxide	0.050	0.028	0.18%
	DI Water	10.0	4.62	30.82%
Inorganic Nern	D	Formulation(g)	15g mass (g)	%
	MSI2 (Polar B1)	1.00	0.52	3.51%
	Filler: CaCO ₃	20.44	10.74	71.74%
	Citric Acid	0.01	0.005	0.04%
	Peroxide	0.054	0.018	0.12%
	DI Water	7.0	3.86	24.59%

B	Formulation (g)	15g mass (g)	%
MSI1 (Polar B1)	1.00	0.77	5.17%
Filler: BaSO ₄	20.44	9.23	61.51%
Citric Acid	0.010	0.01	0.09%
Peroxide	0.080	0.03	0.18%
DI Water	11.0	4.97	33.10%

C	Formulation (g)	15g mass (g)	%
MSI1 (Polar B1)	1.00	0.82	5.44%
Filler: CaSO ₄	20.44	9.82	65.65%
Citric Acid	0.010	0.01	0.10%
Peroxide	0.050	0.03	0.18%
DI Water	9.0	4.32	28.82%

Organics	F	Formulation (g)	15g mass (g)	%
	MSI1 (Polar B1)	1.00	0.52	3.44%
	Filler: DCP	20.44	10.54	70.34%
	Citric Acid	0.010	0.01	0.07%
	TPAP	0.005	0.00	0.03%
	DI Water	7.0	1.61	10.69%
	Acetone	0.500	0.26	1.72%

G	Formulation (g)	15g mass (g)	%
MSI1 (Polar B1)	1.00	0.50	3.34%
Filler: DCE	20.44	10.33	68.79%
Citric Acid	0.010	0.01	0.10%
Ac2CO ₃	3.5	0.25	1.61%
DI Water	7.0	3.50	23.36%

H	Formulation (g)	15g mass (g)	%
MSI2	1.00	0.53	3.51%
DCE	20.44	10.76	71.73%
Citric Acid	0.002	0.00	0.00%
NaHCO ₃	0.054	0.02	0.12%
DI Water	7.0	3.68	24.57%

PEG Core, Adhesive Group, Bonding	M	Formulation (g)	15g mass (g)	%
	MSI40	1.00	0.53	3.51%
	DCE	20.44	10.76	71.73%
	Citric Acid	0.002	0.00	0.00%
	NaHCO ₃	0.054	0.03	0.19%

Sample d'd not form a smooth paste

Table 15 provides testing results from comparative examples, as described above. The term “UTT” indicates that the sample was unable to be tested.

Table 15

Patent Example	CE1	CE2	CE3	CE4	CE5	CE6	CE7	CE8	CE9	CE10	CE11	12			
Product	COP	Sto	Ada	NuH	SH	Eak	Bra	Mio	M096	Ex 1-4	PMMA		Low	High	Def
Poly (g)											3.00%		3.00%	100.00%	97.0
Filler (g)	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%					0.00%	0.00%	0.00%
Citric (g)													0.00%	0.00%	0.00%
Activator (g)													0.00%	0.00%	0.00%
Water (g)													0.00%	0.00%	0.00%
cosolv (g)													0.00%	0.00%	0.00%
Total	100%	100%	100%	100%	100%	100%	100%	100%	0%	0%	3%	0%			
N													Low	High	Def
Modulus	UTT	UTT	UTT	UTT	UTT	UTT	UTT	UTT					0.000	0.000	0.00
SD															
% Extension	UTT	UTT	UTT	UTT	UTT	UTT	UTT	UTT					0	0	0.00
SD															
N													Low	High	Def
t(min) to 30N	>30	>30	>30	>30	>30	UTT	UTT	UTT					0.0	0.0	0.0
SD															
N (Mylar)	8	8	8	8	8	8	8	8			8		Low	High	Def
BP (mmHg)	33.6	43.5	20.4	5.5	31.8	160.5	160.3	422.8			7.0		5.5	422.8	417
SD	4.7	9.9	2.6	2.5	6.0	44.9	44.7	122.4			4.8				
N (Casing)	8	8	8	8	8	8	8	8			8		Low	High	Def
BP (mmHg)	2.6	2.3	2.6	2.3	4.2	80.6	5.1	0.8			3.3		0.800	80.600	79.8
SD	1.6	1.4	1.6	0.4	2.2	18.9	3.4	1.2			3.0				

UTT - Unable to test

Synthesis of molecules:

Linear molecules: Representative synthetic procedure for M231

[0160] 500.00g (0.1mol hydroxyl group) PEG10K(OH)₂ was added to a 5.0L jacketed reactor, dissolved in 1950mL of chloroform, and stirred under a nitrogen atmosphere using an overhead stirrer. To the PEG solution was added 222.30g (1.0mol) of isophoronediiisocyanate. 0.500g of dibutyltin dilaurate (DBTDL) was added to the mixture and the reaction temperature was raised to 50°C. The mixture was stirred under nitrogen for 20 hours in a jacketed reactor. After the reaction time, a 500mL shot of heptane was added to the reaction mixture and stirred for 5 minutes. The mixture was slowly poured into 5.0L of stirring heptane at room temperature. The precipitated isocyanate-terminated PEG was washed with five 1500mL portions of hexanes and dried on a Büchner funnel. The solid was then further dried under vacuum for two hours prior to the dopamine coupling step. Once dry, the isocyanate terminated polymer was transferred to a clean 5.0L jacketed reactor and dissolved in a chloroform/DMF solvent mixture - 800mL chloroform and 1650mL DMF. 39.69g (0.21mol) dopamine.HCl was added to a beaker and separately dissolved in a minimum amount of DMF. 20.20g (0.20mol) of triethylamine was added to the dopamine solution and stirred until homogeneous. The dopamine/TEA solution was then added in a one shot fashion to the jacketed reactor and stirred for 2 hours. Upon completion, the mixture was poured into 5.0L of stirring heptane. The precipitated dopamine-functionalized PEG polymer was filtered on a Büchner funnel and washed with five 1000mL portions of hexanes and dried on a Büchner funnel. The solid was then further dried under vacuum. The polymer was purified via tangential flow filtration (TFF) by dissolving 100g polymer in process water.

[0161] The polymer/water solution was passed through the TFF modules and the solvent was exchanged against a processed water for multiple solvent volume exchanges. The final water solution was freeze dried and a colorless polymer was obtained

Multi-arm molecule: Representative synthetic procedure for M240

[0162] Synthesis of three 300g batch lots of Medhesive 240 was conducted in a 5L jacketed reactor vessel. PEG20K(B-Ala)₈ (300.0 grams, 0.114 mol) was charged to the reactor vessel and dissolved in 1894mL of dichloromethane (DCM) under the flow of nitrogen at room temperature. After all of the PEG was in solution hexamethylene diisocyanate (HDI) (91.13mL, 1.138 mol) was added to the solution and allowed to stir for 10 minutes. N,N-

Diisopropylethylamine (DIPEA) (19.817mL, 0.114 mol) was added to the solution next and allowed to fully incorporate into the reaction mixture. The resulting liquid solution was allowed to stir under nitrogen at room temperature for 2 hours. Following two hours the reaction solution was poured directly into a bucket containing 6L of heptane and stirred for 10 minutes. A hazy oil formed at the bottom of the bucket. The solution was allowed to settle before the heptane was carefully decanted off, preserving the oil at the bottom. 500mL of diethyl ether was added to the hazy oil solution and stirred by overhead mixer for 10 minutes to allow the oil to become a solid. Two more 500mL amounts of diethyl ether was used to fully form a white solid from the hazy oil. The resulting solid was filtered into a Buchner funnel and washed with three 150mL portions of hexanes. The solid was placed under high vacuum and allowed to dry for 1.5 hours. Following drying, the white product solid was dissolved in 1894mL DCM in a 5L reactor vessel under nitrogen at room temperature. Once in solution 600mL of dimethylformamide (DMF) was added to the flask. In a separate beaker, 4-hydroxy-3-methoxybenzylamine (43.15g, 0.228 mol) was dissolved in 170mL DMSO. To this beaker was added DIPEA (39.63mL, 0.228 mol). The 4-hydroxy-3-methoxybenzylamine/DIPEA solution was stirred for 5 minutes prior to being placed in a dropping funnel and added to the PEG flask over the course of 30 minutes. Following complete addition of the 4-hydroxy-3-methoxybenzylamine/DIPEA solution, the reaction was allowed to stir for 1.5 hours under nitrogen at room temperature. The reaction was poured into a bucket containing 7L of heptane and stirred for 10 minutes. A hazy oil was formed at the bottom of the bucket within 10 minutes. The solution is allowed to settle prior to careful decanting of the heptane, leaving the hazy oil at the bottom of the bucket. To the hazy oil 500mL of diethyl ether was added and the solution was stirred via overhead stirring for 10-15 minutes to allow the oil to become a solid. Two more 500mL portions of diethyl ether were used to generate a white solid from the oil. The resulting solid was filtered into a Buchner funnel and washed with three 150mL portions of hexanes. The solid was placed under high vacuum and allowed to dry overnight.

[0163] The resulting material was purified using the Tangential Flow Filtration (TFF). For each TFF run the material was dissolved in process water, resulting in a 0.5% polymer solution, and stirred via a stir plate once connected to the TFF system. The polymer was diafiltered against process water as the buffer solution for multiple buffer volume exchanges. The resulting water solution for each run was the subsequently freeze dried to yield a dry polymer product.

Linear molecule

[0164] Representative synthetic procedure for Medhesive-222 (PEG_{10k}(UR-C₆H₁₂-UR-DOPA)₂).

[0165] 5.00g (1.0mmol hydroxyl group) PEG_{10k}(OH)₂ was added to a 250mL roundbottom flask, dissolved in 35mL of chloroform, and stirred under a nitrogen atmosphere using an overhead stirrer. To the PEG solution was added 0.505g (6.0mmol) of hexamethylenediisocyanate. 2-3 drops of dibutyltin dilaurate (DBTDL) was added to the mixture and the temperature was raised to 50°C. The mixture was stirred under nitrogen for 16-24 hours on a jacketed reactor. After the reaction time, the mixture was slowly poured into 1L of stirring heptane stirring at room temperature. The precipitated isocyanate-terminated PEG was washed with five 100mL portions of hexanes and dried on a Buchner funnel. The solid was then further dried under vacuum for the dopamine coupling step. Once dry, the isocyanate terminated polymer was transferred to a new 250mL roundbottom flask and dissolved in a chloroform/DMF solvent mixture - 35mL chloroform and 30mL DMF. 0.379g (2.0mmol) was added to a beaker and separately dissolved in 20mL of DMF. 0.259g (2.0mmol) of diisopropylethylamine was added to the dopamine solution and stirred until homogeneous. The dopamine solution was then added via addition funnel to the roundbottom flask over 15 min and stirred for 2-3 hours. After 2-3 hours, the mixture was poured into 1L of stirring heptane. The precipitated dopamine-functionalized PEG polymer was filtered on a Buchner funnel and washed with five 100mL portions of hexanes and dried on a Buchner funnel. The solid was then further dried under vacuum. The polymer was purified via TFF by dissolving polymer in 1600mL of a 50/50 mixture of methanol/process water. The methanol/water solution was passed through the TFF modules and the solvent was exchanged against a mildly acidic buffer (1.2 x 10⁻⁴M HCl), followed by process water for a total of 6 solvent volume exchanges (9600mL total). The final water solution was freeze dried and a colorless polymer was obtained.

[0166] Medhesive-223, PEG_{20k}(UT-C₆H₁₂-UR-DOPA)₂.

[0167] Prepared similarly to the process described for Medhesive-222.

[0168] Medhesive-224, PEG_{6k}(UT-C₆H₁₂-UR-DOPA).

[0169] Prepared similarly to the process described in Medhesive-222.

[0170] Multi-arm Medhesive-209.

[0171] 100g of PEG_{20K}(β -Ala)₈ was dissolved in 690mL of chloroform using a 3L round-bottom flask to which 1.0 equivalent of N,N-Disopropylethylamine (DIPEA) (6.5mL, 0.0375 mol) was added. In a separate flask 10.9g (0.056 mol) of *trans*-ferulic acid, 6.5mL (0.0375 mol) of DIPEA, and 7.15g (0.037 mol) of EDC were dissolved in 690mL of chloroform. Once dissolved, the ferulic acid-amine-EDC solution was added to the PEG_{20K}(β -Ala)₈ solution. The resulting mixture was allowed to stir overnight at room temperature under N₂. After 20hours, 1.45g (0.007 mol) of *trans*-ferulic acid, 1.3mL (0.007 mol) of DIPEA, and 1.43g (0.007 mol) of EDC and reaction was added to the reaction flask and allowed to stir for an additional hour at room temperature. Approximately half of the chloroform was removed via rotary evaporation and the medhesive 209 product was precipitated directly into 6L of 7:3 heptane/IPA. The resulting solid was filtered and dried via high vacuum giving 110g of crude product. The crude material was purified using two unique TFF methods. The first method incorporated an initial dilute aqueous acid wash and the second method a process water only wash. In the aqueous acid wash the pH of the process water buffer solution was reduced to 3-3.5 using concentrated HCl (0.5mL concentrated HCL in 5L of water). This acid buffer was used for one volume equivalent wash after which the buffer was replaced with normal process water. Following TFF purification the water solution containing product was freeze dried to yield a pure product.

Medhesive-161.

[0172] 250g of PEG_{20K}(β -Ala)₈ was added to a 5L round-bottom flask and dissolved in 740mL of chloroform. In a separate flask 20.96g of DOHA (0.115 mol, 1.2eq) was dissolved in 1500mL of DMF and slowly added to the flask containing PEG_{20K}(β -Ala)₈. Once dissolved, 43.63g HBTU (0.115 mol, 1.2eq) was added to the flask as a solid and allowed to dissolve. 29.40mL of triethylamine (TEA) (0.211 mol, 2.2eq) was added to the flask and the entire solution stirred overnight under N₂. After overnight stirring, the solution was precipitated directly into 7:3 heptane/IPA. To accommodate the large amount of heptane/IPA mixture needed, the precipitation was divided up into four batches. Each batch was filtered off and dried via high vacuum giving 287g of dried crude product. The crude material was purified by TFF. The polymer was diafiltered against an aqueous acid buffer (1.2x10⁻⁴M, 0.5mL concentrated HCL in 5L of water) for the first volume equivalent, after which four additional volume

equivalents were exchanged through the module using process water alone as the buffer solution. The resulting water solution containing product was freeze dried to yield pure product.

[0173] All publications and patents mentioned in the above specification are herein incorporated by reference in their entirety for all purposes. Various modifications and variations of the described compositions, methods, and uses of the technology will be apparent to those skilled in the art without departing from the scope and spirit of the technology as described. Although the technology has been described in connection with specific exemplary embodiments, it should be understood that the technology as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the technology that are obvious to those skilled in pharmacology, biochemistry, medical science, or related fields are intended to be within the scope of the following claims.

Claims

What is claimed is:

1. An ostomy device comprising a mixture comprising at least one functionalized polymer, and an active inorganic filler, and an activator; wherein the mixture, upon the addition of an amount of aqueous solvating fluid, is arranged to form a sealant material having a first form that is malleable, and sets to a second form that is an elastic hydrogel.

2. The ostomy device of claim 1, wherein the ostomy device further comprises an ostomy appliance.

3. The ostomy device of claim 1, wherein the set does not result from loss of solvating fluid from the gel.

4. The ostomy device of claim 1, wherein said at least one functionalized polymer comprises phenyl derivatives.

5. The ostomy device of claim 1, wherein said hydrogel has a strain of at least 50%.

6. The ostomy device of claim 5, wherein said hydrogel is elastic.

7. The ostomy device of claim 1, wherein said hydrogel has a strain of at least 100%.

8. The ostomy device of claim 1, wherein the burst pressure, as determined by Burst Strength Test method, of said hydrogel on wet casing is greater than 15 mm Hg.

9. The ostomy device of claim 1, wherein said hydrogel has an integrity value of greater than 80%, as determined by Integrity Testing Protocol.

10. The ostomy device of claim 1, wherein said hydrogel achieves a non-injectable point in less than 30 minutes, as determined by the Ostomy Paste Injectability Force Testing Method.

11. An ostomy device comprising a mixture comprising at least one functionalized polymer, and an active inorganic filler, and an activator; wherein the mixture, upon the addition of an amount of aqueous solvating fluid, is arranged to form a sealant material having a first form that is malleable and sets to a second form that is a hydrogel, the hydrogel being arranged to create a biocompatible seal between at least one first surface and at least one second surface.

12. The ostomy device of claim 11, wherein the ostomy device further comprises an ostomy appliance.

13. The ostomy device of claim 11, wherein the set does not result from loss of solvating fluid from the gel.

14. The ostomy device of claim 11, wherein said at least one functionalized polymer comprises phenyl derivatives.

15. The ostomy device of claim 11, wherein said hydrogel has a strain of at least 50%.

16. The ostomy device of claim 15, wherein said hydrogel is elastic.

17. The ostomy device of claim 11, wherein said hydrogel has a strain of at least 100%.

18. The ostomy device of claim 11, wherein the burst pressure, as determined by Burst Strength Test method, of said hydrogel on wet casing is greater than 15 mm Hg.

19. The ostomy device of claim 11, wherein said hydrogel has an integrity value of greater than 80%, as determined by Integrity Testing Protocol.

20. The ostomy device of claim 11, wherein said hydrogel achieves a non-injectable point in less than 30 minutes, as determined by the Ostomy Paste Injectability Force Testing Method.

21. The ostomy device of claim 11, wherein the activator is soluble in aqueous solvating fluid.

22. The ostomy device of claim 14, where said phenyl derivatives are one of: catechol, guaiacol, syringol, diamine phenyl derivative.

23. The ostomy device of claim 11, wherein said at least one surface comprises at least one tissue.

24. The ostomy device of claim 11, wherein the at least one second surface comprises an ostomy appliance.

25. The ostomy device of claim 11, wherein the mixture further comprises a pH modulator.

26. The ostomy device of claim 11, wherein said mixture further comprises a second filler.

27. The ostomy device of claim 26, wherein said second filler comprises at least one of: organic filler, inorganic filler, pH modulator, biologically active agents, odor absorption, pain reducers, vitamins, soothing agents, deodorants, anti-perspirants and combinations thereof.

28. The ostomy device of claim 11, wherein the aqueous solvating fluid comprises a solution, suspension or slurry.

29. The ostomy device of claim 28, wherein said aqueous solvating fluid further comprises salts, clays, starch,

30. The ostomy device of claim 11, wherein the inorganic filler modulates pH.

31. The ostomy device of claim 11, wherein the activator comprises an oxidant.

32. The ostomy device of claim 11, activator is one or more of activator is selected from the group consisting of NaIO_4 , tetra-alkyl ammonium periodates (TPAP, tetrabutylammonium periodate), AgNO_3 , Ag_2CO_3 , tetrabutylammonium permanganate, tetrabutylammonium dichromate, iron(III) acetonlactenoate, iron(III)nitrate, potassium ferrate, di-tert-butyl peroxide, cumene hydroperoxide, 2-butanone peroxide.

33. An ostomy device comprising an ostomy appliance comprising a plate comprising a sealant comprising a mixture of at least one functionalized polymer, and an activator; wherein the mixture, upon the addition of an amount of aqueous solvating fluid, said at least one functionalized polymer and said activator chemically react to form a hydrogel, the hydrogel being arranged to create a biocompatible seal between at least one first surface and at least one second surface.

34. The ostomy device of claim 33, wherein said chemical reaction creates covalent bonds between said functionalized polymers and further between said functionalized polymers and said surfaces.

35. The ostomy device of claim 33, wherein said ostomy device further comprises at least one of: an ostomy containment, and an ostomy adhesive.

36. The ostomy device of claim 35, wherein said ostomy plate is affixed to said ostomy containment.

37. The ostomy device of claim 33, wherein said ostomy sealant is applied as a layer adjacent to said ostomy adhesive.

38. The ostomy device of claim 33, wherein the mixture further comprises an active inorganic filler.

39. The ostomy device of claim 33, wherein the mixture further comprises a second functionalized polymer.

40. The ostomy device of claim 39, wherein the second functionalized polymer comprises an average molecular weight that is greater than the average molecular weight of said at least one functionalized polymer.

41. The ostomy device of claim 33, wherein the mixture further comprises at least one additive.

42. The ostomy device of claim 41, wherein said at least one additive is a polymer, biologically active agent, drug,

43. The ostomy device of claim 1, 11, or 33, wherein said sealant is used to adhere said ostomy medical device to tissue that is mucosal or dermal tissue.

44. The ostomy paste device of claim 33, wherein the inorganic material comprises a ceramic.

45. The ostomy paste device of claim 33, wherein the inorganic material comprises at least one of calcium carbonates, magnesium carbonates, silicates, silicic acids, aluminum hydrates, calcium sulfates, calcium phosphates, hydroxyapatite, alumina silicate (is this necessarily Zeolite, put in broader term), bioglasses, and silica, and combinations thereof.

46. The ostomy paste device of claim 45, wherein the calcium phosphate comprises at least one of tri-calcium phosphate, dicalcium phosphate, monocalcium phosphate and combinations thereof;

47. The ostomy paste device of claims 33, wherein the aqueous compatible adhesive comprises at least one of a catecholate adhesive, a guaiacolate adhesive, a syringol adhesive, a di-amino phenyl derivative adhesive; and combinations thereof

48. The ostomy paste device of claims 33, wherein the activator comprises an oxidant.

49. The ostomy paste device of claims 33, wherein the activator is selected from the group consisting of NaIO_4 , tetra-alkyl ammonium periodates (TPAP, tetrabutylammonium periodate), AgNO_3 , Ag_2CO_3 , tetrabutylammonium permanganate, tetrabutylammonium dichromate, iron(III) acetonylactenoate, iron(III)nitrate, potassium ferrate, di-tert-butyl peroxide, cumene hydroperoxide, 2-butanone peroxide.

50. The ostomy paste device of claim 11, wherein the mixture comprises less than 50% of said functionalized polymer, and greater than 50% filler material.

51. The ostomy paste device of claim 50, the mixture comprising less than 25 % functionalized polymer.

52. The ostomy paste device of claim 50, mixture comprising less than 10% functionalized polymer.

53. The ostomy paste device of claim 50, the mixture comprising less than 5% functionalized polymer.

54. The ostomy paste device of claim 50, the mixture comprising greater than 75% filler material.

55. The ostomy paste device of claim 51, the mixture comprising greater than 90% filler material.

56. The ostomy paste device of claim 50, the mixture comprising greater than 95% filler material.

57. The ostomy paste device of claim 40, wherein the functionalized polymer comprises a Polyalkylene.

58. The ostomy paste device of claim 57, the functionalized polymer comprises a Polyethyleneglycol.

59. An ostomy appliance comprising a sealant material for sealing the appliance to at least one of the peristomal area tissues and stoma tissues, the appliance further comprising a body waste collector component, wherein the sealant component comprises a mixture comprising a functionalized polymer, and an active inorganic filler, and an activator; wherein the mixture, upon the addition of an amount of aqueous solvating fluid, is arranged to form a sealant material having a first form that is malleable, and sets to a second form that is a hydrogel, the hydrogel being arranged to create a biocompatible seal between said body waste collector component and said tissues.

60. The ostomy paste device of claim 59, wherein said sealant component is adhesive.

61. An medical device comprising a mixture comprising at least one functionalized polymer, and an active inorganic filler, and an activator; wherein the mixture, upon the addition of an amount of aqueous solvating fluid, is arranged to form a sealant material having a first form that is malleable, and sets to a second form that is an elastic hydrogel.

62. The medical device of claim 61, wherein said medical device is externally applied to a living being.

63. A device composed of a polymer comprising a partially soluble region and a soluble region, wherein the polymer when exposed to a solvent, and mixed results in air trapped in the polymer/solvent combination that forms a stable suspension of bubbles within the partially solvated material, wherein said bubbles are prevented from coalescing into with other bubbles, and wherein the polymer oxidatively reacts to set as a foam.

64. The device of claim 63, wherein prior to setting as a foam the combination of partially solvated material and bubbles forms a foam paste.

65. The device of claim 63, wherein the foam is one of a tissue sealant, tissue adhesive, tissue void filler, and medical device adhesive.

66. The device of claim 63, wherein said mixing occurs within one of a reciprocating syringe, or static mixing tip.

67. The device of claim 64 wherein said foam paste is sprayed onto a tissue prior to setting into a foam.

68. The device of claim 64, wherein said foam paste is applied over a mesh that is in contact with a tissue prior to setting into a foam.

69. The device of claim 63 wherein the foam contains a drug, biologic, ceramic, bioactive glass or combination thereof.

70. The device of claim 63, wherein the foam has an elongation at break of at least 100%.

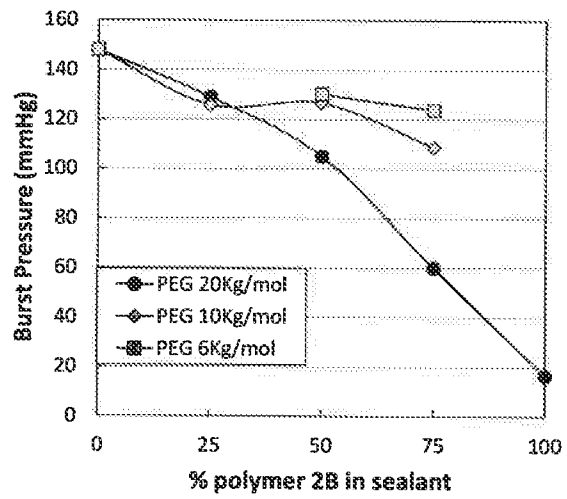


Figure 1. Burst Pressure of cured hydrogel vs. % polymer 2B.

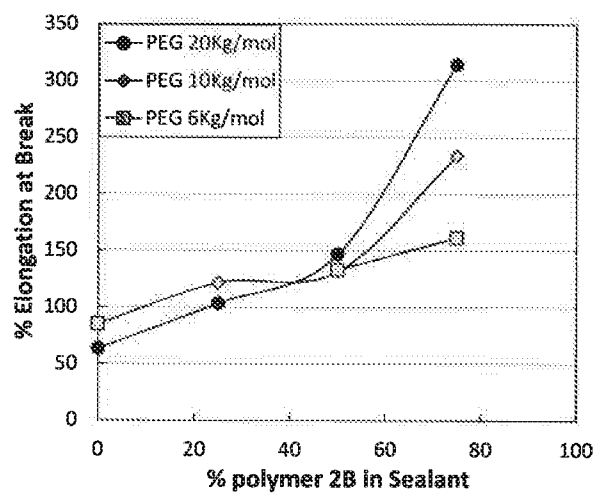


Figure 2. % Elongation at break of cured hydrogel vs. % polymer 2B.



Figure 3. Delivery syringe with static mixer

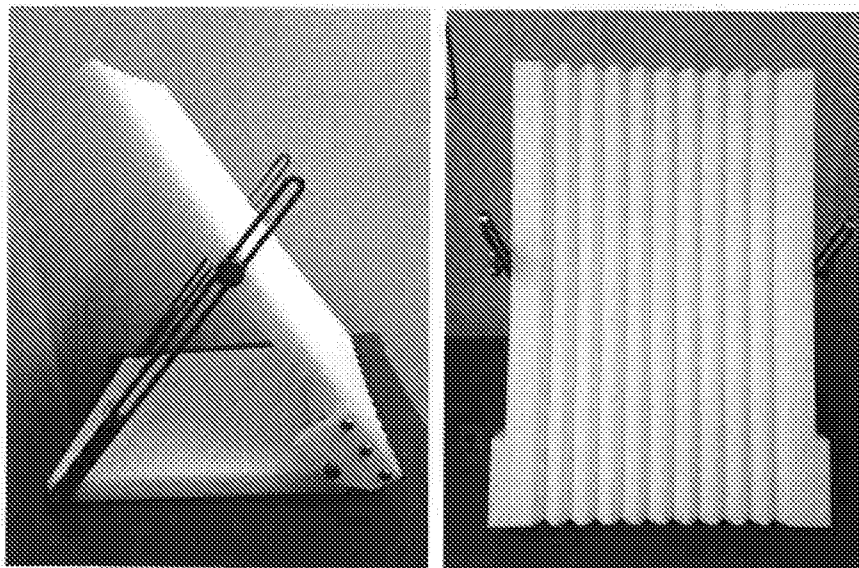


Figure 4. 60 degree ramp for testing sealant flow.

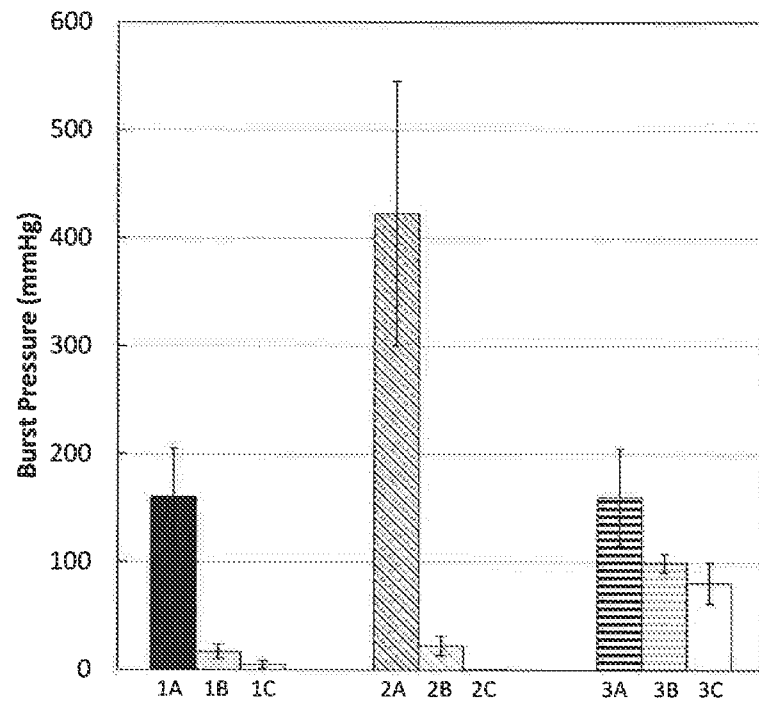


Figure 5. Effective burst pressure under conditions with increasing moisture. Product 1: Brava ostomy ring. Product 2: Coloplast Bag wafer. Product 3: Eakin ostomy ring. Condition A: Accessory on dry mylar (PET). Condition B: Accessory on dry collagen casing. Condition C: Accessory on pre-moistened collagen.

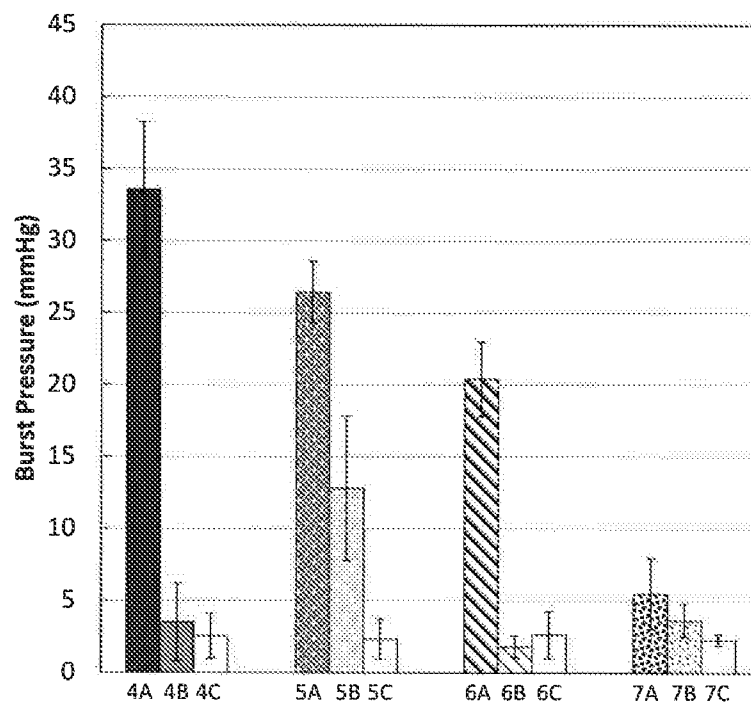


Figure 6. Effective burst pressure under conditions with increasing moisture. Product 4: Coloplast ostomy paste. Product 5: Stomahesive ostomy paste. Product 6: Adapt ostomy paste. Product 7: NuHope ostomy paste. Condition A: Paste on dry mylar (PET). Condition B: Paste on dry collagen casing. Condition C: Paste on pre-moistened collagen.

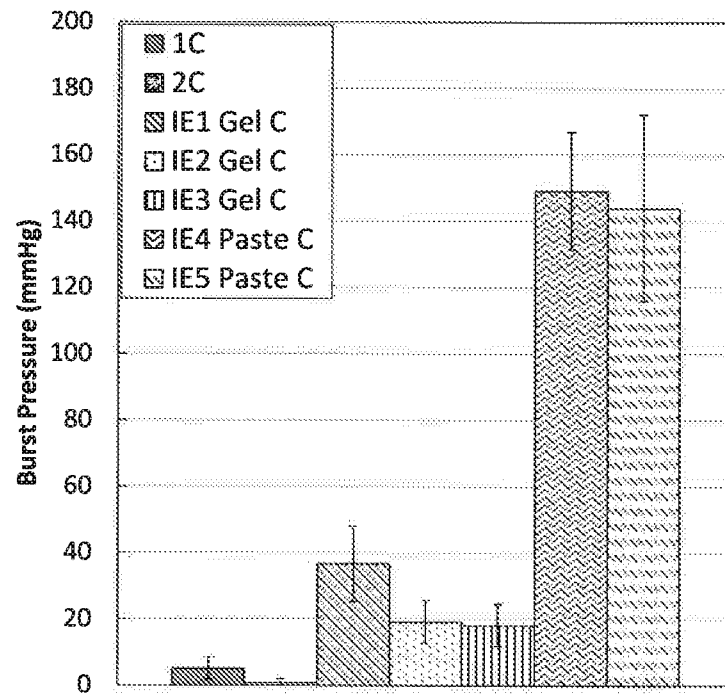


Figure 7. Effective burst pressure of sealant on pre-moistened collagen (condition C).

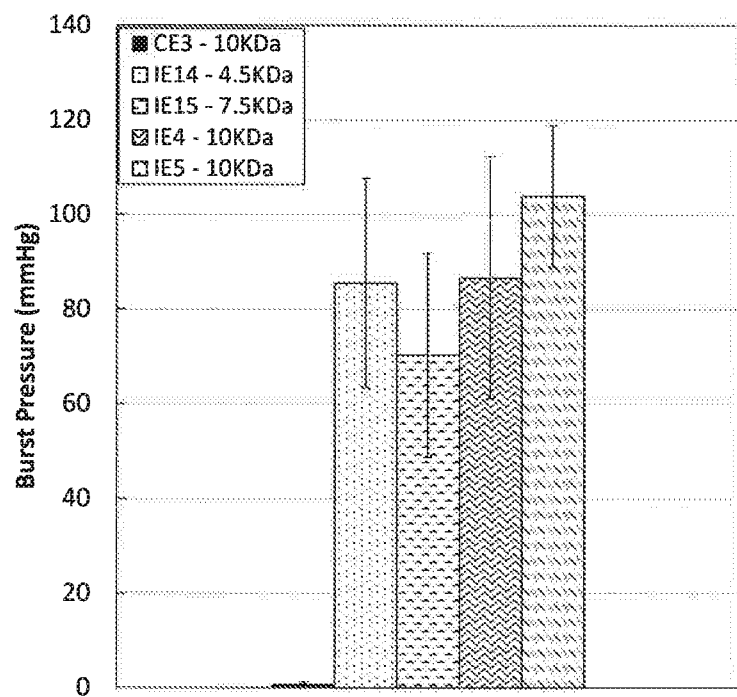


Figure 8. Effective burst pressure of Medhesive sealant on pre-moistened collagen (condition C) containing polymer with molecular weights ranging from 4.5KDa to 10KDa.

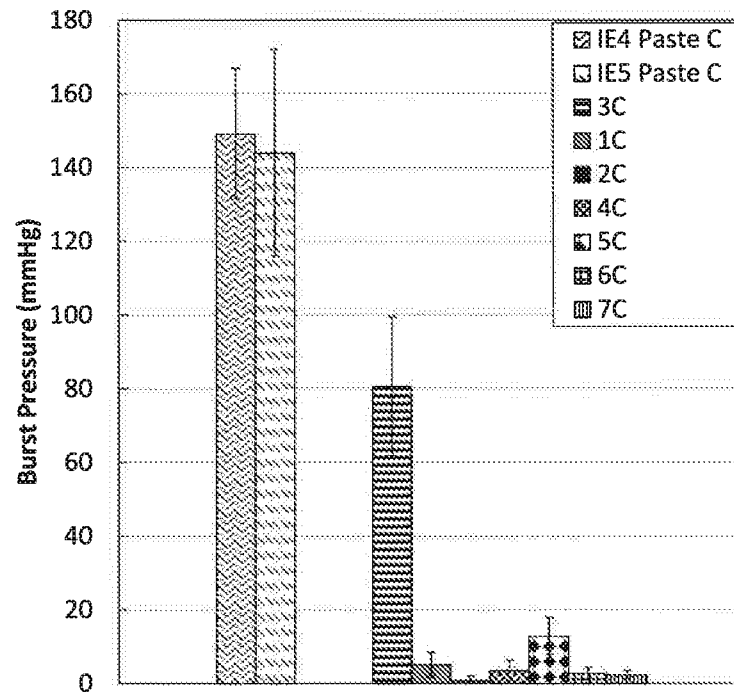


Figure 9. Effective burst pressure of ostomy sealants on pre-moistened collagen (condition C).

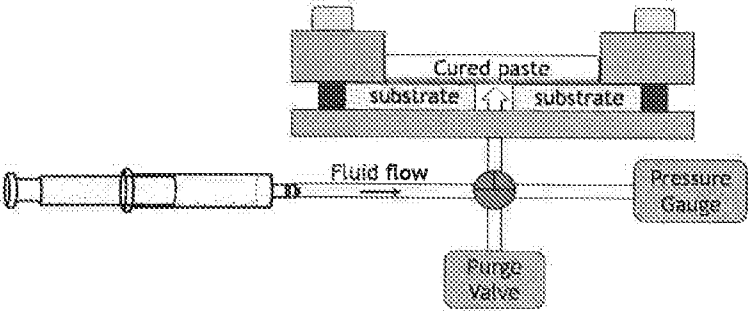


Figure 10. Schematic diagram for Burst Pressure Test.

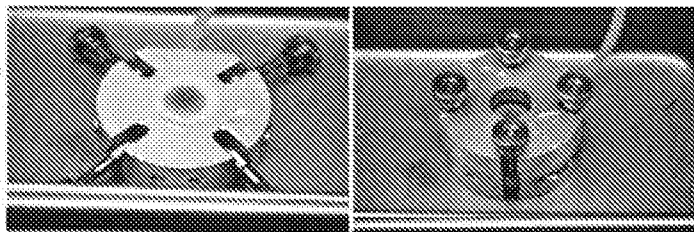


Figure 11. Photos of burst pressure test fixture containing a cured paste on casing test sample.

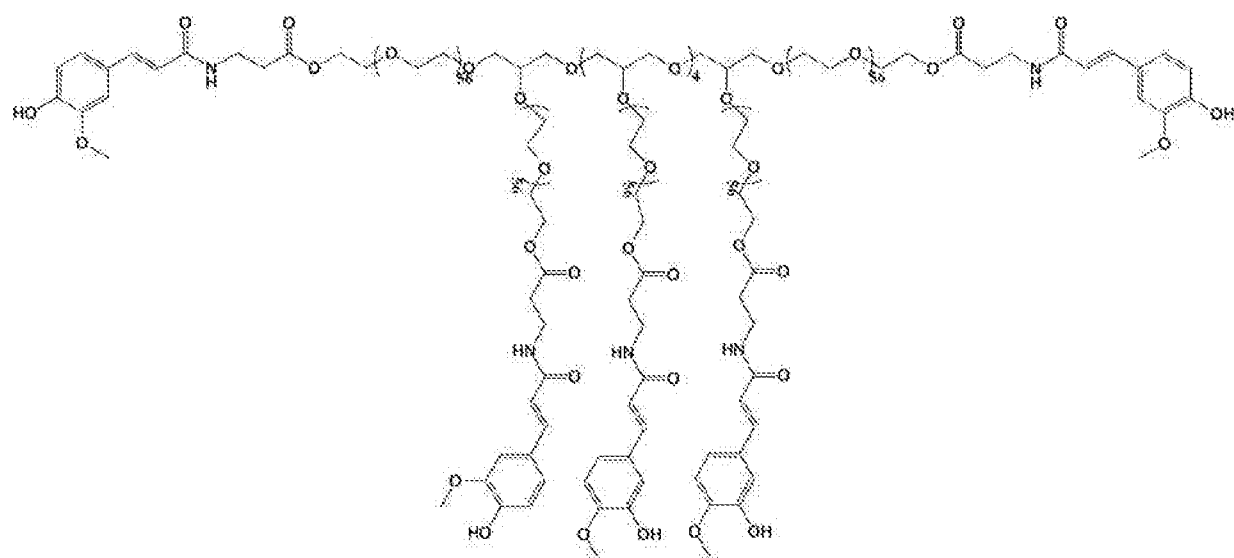
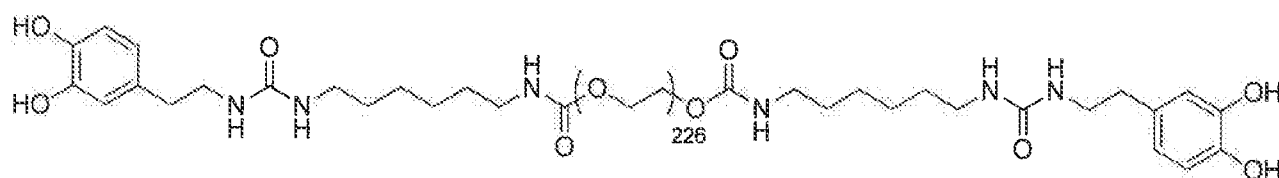
**Medhesive-209**PEG_{20k}-(γ -Ala-FA)₈

Figure 12

**Medhesive-222**

PEG_{10K}(UT-C₆H₁₂-UR-DOPA)₂

Figure 13

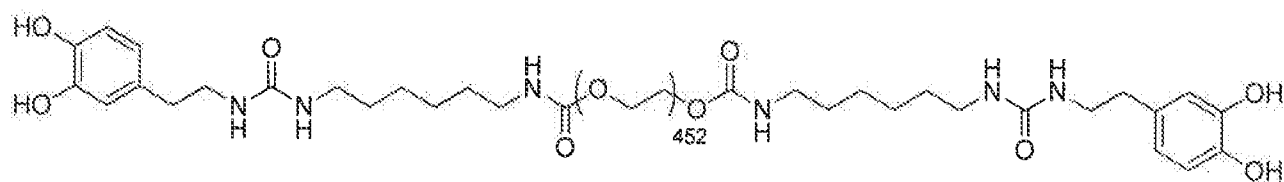
**Medhesive-223**PEG_{20K}(UT-C₆H₁₂-UR-DOPA)₂

Figure 14

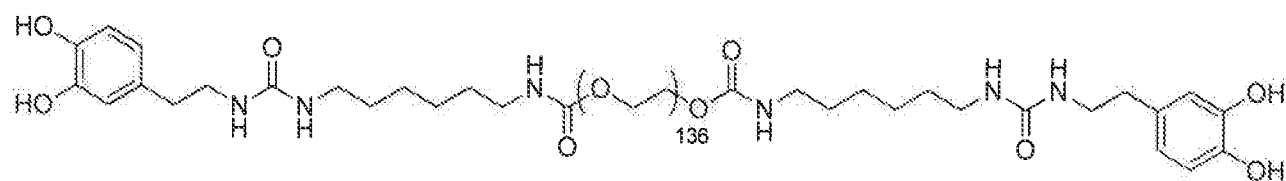
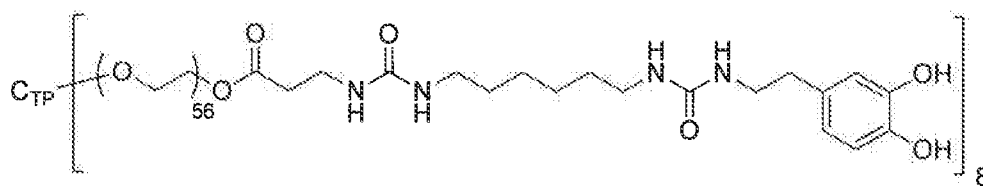
**Medhesive-224** $\text{PEG}_{6k}(\text{UT-C}_6\text{H}_4\text{-UR-DOPA})_2$

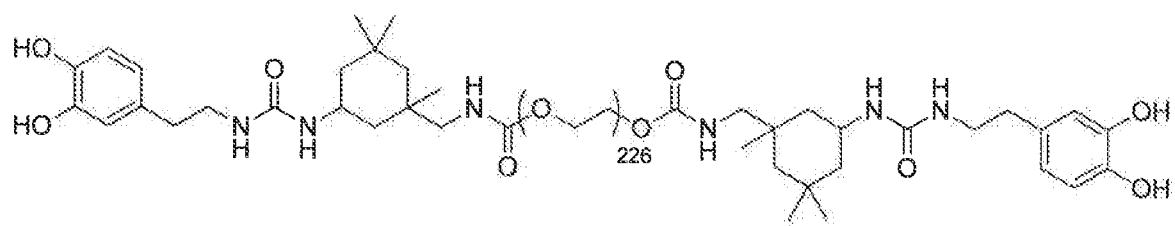
Figure 15

**Medhesive-225**

PEG_{20K}(L-Ala-UR-C₆H₁₂-UR-DOPA)₈

C_{TP} = Tripentaerythritol Core

Figure 16

**Medhesive-231**

PEG_{10K}(UT-isophorone-UR-DOPA)₂

Figure 17

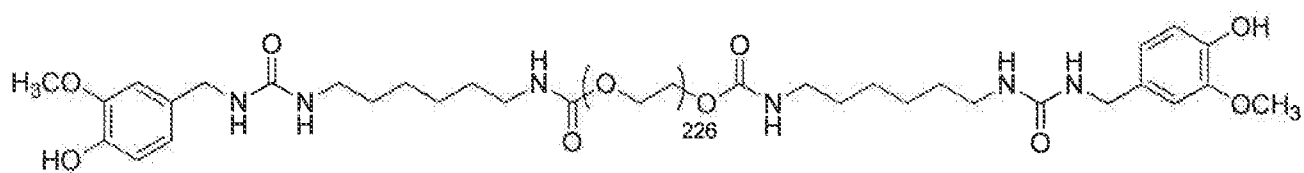
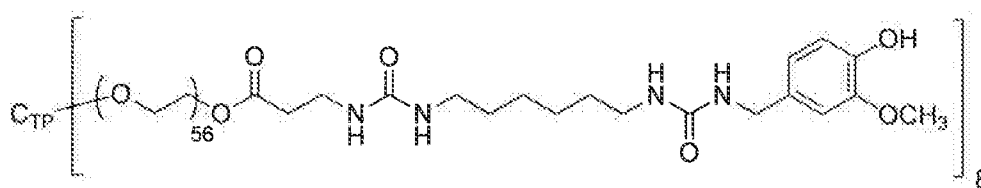
**Medhesive-239**PEG_{10K}(UT-C₆H₁₂-UR-BzGu)₂

Figure 18

**Medhesive-240**

PEG_{20K}(C_{TP} -Ala-UR-C₆H₁₂-UR-BzGu)₈

C_{TP} = Tripentaerythritol Core

Figure 19

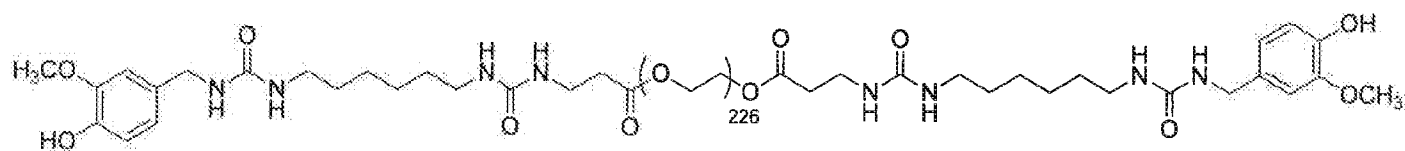
**Medhesive-243**PEG_{10K}($\square$ -Ala-UR-C₆H₁₂-UR-BzGu)₂

Figure 20

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 16/51168

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C08F 22/40, C08F 12/30 (2016.01)

CPC - A61L27/52; A61K9/0024; A61L2400/18; A61L24/0031

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)

IPC(8): C08F 22/40, C08F 12/30 (2016.01)

CPC: A61L27/52; A61K9/0024; A61L2400/18; A61L24/0031

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

CPC: C08F22/40; C08F12/30; C08F222/40; A61L2400/00; A61L24/00

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

Pat Base (AU BE BR CA CH CN DE DK EP ES FI FR GB IN JP KR SE TH TW US WO), Google Patent, Google Scholar; Search terms: seal adhesive ostomy functionalized polymer inorganic filler activator hydrogel solvent elastic malleable plate ceramic strain diamino phenyl burst pressure strength integrity value test protocol paste injectability force pH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 8,784,893 B2 (DANILOFF et al.) 22 July 2014 (22.07.2014)	1-9, 11-19 and 21-62
---	col 2, ln 36-46; col 3, ln 4-11; col 6, ln 31-34; col 11, ln 1-8; col 12, ln 29-32; col 13, ln 22-24; col 22, ln 51-53; col 41, ln 31-34; col 42, ln 65-66; col 43, ln 4-11; col 46, ln 25-56; col 47, ln 1-5; col 50, ln 16-25; col 53, ln 53-65; col 57, ln 6-28 and ln 40-42; claims 1, 3, 7 and 18	10 and 20
A		
Y	US 2009/0118831 A1 (TRIEU) 07 May 2009 (07.05.2009)	1-9, 11-19, 21-32, 50-56 and 59-62
---	para [0002], [0027], [0028], [0051], [0063]; claims 1-2	
A		10 and 20
Y	US 5,722,965 A (KUCZYNSKI) 03 March 1998 (03.03.1998)	33-49 and 57-58
	col 1, ln 58-67; col 2, ln 19-23; col 4, ln 41-43; col 7, ln 13-27; figure 2; claim 1	
Y	US 4,689,378 A (CHAUDHARI et al.) 25 August 1987 (25.08.1987)	4, 14, 22 and 47
	col 1, ln 31-34; col 5, ln 29-33 and ln 57-62; abstract	
Y	US 2005/0008705 A1 (PENNINGES et al.) 13 January 2005 (13.01.2005)	5-7 and 15-17
	para [0007], [0011], [0058], [0071]	
Y	US 2010/0016886 A1 (LU et al.) 21 January 2010 (21.01.2010)	8 and 18
	(para [0158]-[0163]; table 4	
Y	US 2013/0252932 A1 (SEWARD) 26 September 2013 (26.09.2013)	25-27 and 30
	para [0027]; abstract; claim 17 and 21	
Y	US 2014/0219973 A1 (BOYES et al.) 07 August 2014 (07.08.2014)	29
	para [0004], [0015]	

☒ Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

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

"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

"&" document member of the same patent family

Date of the actual completion of the international search

12 January 2017

Date of mailing of the international search report

26 JAN 2017

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:

Lee W. Young

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 16/51168

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.:
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.

Group I: Claims 1-62, directed a method of forming a sealant using a functionalized polymer, an activator and aqueous solvating fluid.

Group II: Claims 63-70, directed a device composed of a polymer comprising a partially soluble region and a soluble region.

****please see the continuation at the end of this form****

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.:
1-62

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.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 16/51168

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4,569,976 A (ZIMMERMAN et al.) 11 February 1986 (11.02.1986) col 2, ln 4-6; col 5, ln 42-58; col 7, ln 7-18	32 and 49
Y	US 6,406,498 B1 (TORMALA et al.) 18 June 2002 (18.06.2002) col 2, ln 8-19; col 5, ln 52-58	44
Y	US 2003/0014023 A1 (KANBARA) 16 January 2003 (16.01.2003) para [0002], [0008]	59-60
A	WO 1998/025653 A2 (REPROGENESIS, INC.) 18 June 1998 (18.06.1998) abstract	10 and 20

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 16/51168

****Continuation of Box III (Lack of Unity)****

The inventions listed as Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:
Special Technical Features:

Group I requires a mixture comprising at least one functionalized polymer and an activator and an amount of aqueous solvating fluid; and forming hydrogel, not required by group II.

Group II requires a polymer comprising a partially soluble region and a soluble region, wherein the polymer when exposed to a solvent, and mixed results in air trapped in the polymer/solvent combination that forms a stable suspension of bubbles within the partially solvated material, wherein said bubbles are prevented from coalescing into with other bubbles, and wherein the polymer oxidatively reacts to set as a foam, not required by Group I.

Common Technical Features:

Groups I and II share the technical feature of a device; mixing a polymer and solvent/ solvating-fluid. However, these shared technical features do not represent a contribution over prior art, because the shared technical feature is anticipated by US 2014/0196748 A1 to Phelps et al. (hereinafter Phelps). Phelps teaches a device (para [0019]; devices and methods are described to perform cleaning with a cleaning polymer); mixing a polymer and solvent/ solvating-fluid (claim 1; para [0019]; mixing a polymer and a solvent in a desired ratio).

As the shared technical features were known in the art at the time of the invention, they cannot be considered common technical features that would otherwise unify the groups. Therefore, Groups I-II lack unity under PCT Rule 13.