

prise an anionic graft polymer comprising an anionic polymer backbone, referenced herein as backbone polymer with pendent carboxylic acid groups, and pendent chains comprising amphipathic or hydrophilic polymers, referenced herein as pendent chain polymers covalently bonded to a portion of said pendent carboxylic acid groups.

[0042] Suitable backbone polymers include, but are not limited to, polyanhydrides, poly(acrylic acids), poly(alkylacrylic acids), anionic polysaccharides such as carboxymethylcellulose, anionic polypeptides such as polyglutamic acid and polyaspartic acid, and vinyl copolymers comprised of monomers such as alkyl acrylates, alkyl methacrylates, acrylamidomethylpropane sulfonic acid (AMPS), vinyl alcohol, and vinyl acetate, or combinations thereof. Preferably, the backbone polymer comprises poly(alkyl acrylic acid), most preferably poly(methacrylic acid) or poly(propylacrylic acid).

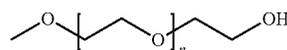
[0043] The term “hydrophilic polymer,” as used herein, means any macromolecule (molecular weight of 200 daltons and greater) which exhibits an affinity for or attraction to water molecules and which comprises multiple instances of an identical subunit (“monomer”) connected to each other in chained and/or branched structures. The hydrophilic polymer component can be a synthetic or naturally occurring hydrophilic polymer.

[0044] Naturally occurring hydrophilic polymers include, but are not limited to: polypeptides and proteins such as collagen and derivatives thereof, fibronectin, albumins, globulins, fibrinogen, and fibrin, with collagen particularly preferred; carboxylated polysaccharides such as polymannuronic acid and polygalacturonic acid; aminated polysaccharides, particularly the glycosaminoglycans, e.g., hyaluronic acid, chitin, chondroitin sulfate A, B, or C, keratin sulfate, keratosulfate and heparin; and activated polysaccharides such as dextran and starch derivatives.

[0045] Useful synthetic hydrophilic polymers include, but are not limited to: poly(alkylene oxides), particularly poly(ethylene glycol) and poly(ethylene oxide)-poly(propylene oxide) copolymers, including block and random copolymers; polyols such as glycerol, polyglycerol (in particular, highly branched polyglycerol), propylene glycol and trimethylene glycol substituted with one or more poly(alkylene oxides), e.g., mono-, di- and tri-polyoxyethylated glycerol, mono- and di-polyoxyethylated propylene glycol, and mono- and di-polyoxyethylated trimethylene glycol; polyoxyethylated sorbitol, polyoxyethylated glucose; acrylic acid polymers and analogs and copolymers thereof, such as poly(acrylic acid) per se, poly(methacrylic acid), poly(hydroxyethylmethacrylate), poly(hydroxyethylacrylate), poly(methylalkylsulfoxide methacrylate), poly(methylalkyl-sulfoxide acrylate) and copolymers of any of the foregoing, and/or with additional acrylate species such as aminoethyl acrylate and mono-2-(acryloxy)-ethyl succinate; polymaleic acid; poly(acrylamides) such as polyacrylamide per se, poly(methacrylamide), poly(dimethylacrylamide), and poly(N-isopropylacrylamide); poly(olefinic alcohols) such as poly(vinyl alcohol); poly(N-vinyl lactams) such as poly(vinyl pyrrolidone), poly(N-vinyl caprolactam), and copolymers thereof; polyoxazolines, including poly(methyloxazoline) and poly(ethyloxazoline); and polyvinylamines.

[0046] Preferred embodiments utilize poly(ethylene glycol) (PEG), also known as poly(ethylene oxide) (PEO), hav-

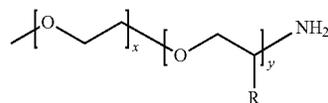
ing a molecular weight of from about 1 kDa to about 10 kDa, more preferably from about 2 kDa to about 5 kDa, and a general formula (II).



(II)

[0047] The term “amphipathic polymer,” as used herein, refers to any macromolecule (molecular weight of 200 daltons and greater) which have both polar substructures and non-polar substructures. The polar substructures evidence an affinity for or attraction to other polar molecular structures such as water (hydrophilic), while the nonpolar substructures exhibit an affinity or attraction for nonpolar molecules such as lipids, oils, greases, fats, etc. (lipophilic). Suitable amphipathic polymers include, but are not limited to, polyether and polyetherester copolymers such as poly(ethylene glycol) and poly(butylene terephthalate) copolymers, poly(ethylene oxide) and poly(propylene oxide) copolymers, poly(ethylene oxide) and poly(propylene oxide) block copolymers.

[0048] The amphipathic polymers also include polyetheramines such as those known commercially as JEFFAMINE®. These polyetheramines contain primary amino groups attached to the end of a polyether backbone which is typically based on propylene oxide (PO), ethylene oxide (EO), or a mixture thereof. The JEFFAMINE® family includes monamines, diamines, triamines and secondary amines. JEFFAMINE® is available from Huntsman Corporation, The Woodlands, Tex. By way of non-limiting example, certain embodiments can employ a JEFFAMINE® Monoamine having a molecular weight of about 2 kDa, PO/EO ratio of 10/31 and a general formula (III):



(III)

wherein R is H for EO or CH₃ for PO.

[0049] The instant graft polymers can be synthesized by reacting carboxylic acid groups of the backbone polymer with the end group of the pendent chain polymers. In general, a backbone polymer can be added to a polar aprotic solvent, such as dimethylsulfoxide (DMSO), along with a catalyst, such as 4-(dimethylamino)pyridinium p-toluenesulfonate (DPTs) or 1-hydroxybenzotriazole (HOBt) and a pendent chain polymer. The amount of graft chain polymer can be in a slight molar excess required to achieve the desired amount of the graft chain polymer attached to the backbone. A carboxyl activating agent, such as 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide (EDCI), can be added to the mixture after stirring the mixture for a short period of time. The reaction is then allowed to proceed and is driven to completion with subsequent additions of the carboxyl activating agent. The mixture can then be dialyzed against deionized water before converting the polymer into a form suitable for storage, such as by lyophilizing the dialyzed solution.

[0050] The term “graft density,” as used herein, refers to the average percent on a molar basis of pendent carboxyl groups on the backbone of the graft polymer which react with the end