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(71) Applicant: **KIMBERLY-CLARK WORLDWIDE, INC.** [US/US]; 401 N. Lake Street, Neenah, WI 54956 (US).

(72) Inventors: **HUANG, Yanbin**; 507 Belcourt Pkwy., Roswell, GA 30076 (US). **KIM, Jaeho**; 480 Elgaen Court, Roswell, GA 30075 (US).

(74) Agents: **ROBINSON, James, B.** et al.; KIMBERLY-CLARK WORLDWIDE, INC., 401 N. Lake St., Neenah, WI 54956 (US).

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(54) Title: METHODS OF MAKING FUNCTIONAL BIODEGRADABLE POLYMERS

(57) Abstract: There is provided a method to modify biodegradable polymers using the direct reaction of a biodegradable polymer in a vinyl monomer and may take place in the presence of initiators. The initiator may be free radical initiators, heat, ionic initiators, UV irradiation, ionizing irradiation and other high energy irradiation. Suitable biodegradable polymer include polycaprolactone, poly(lactic acid), poly(glycolic acid) and poly(lactic-co-glycolic acid). Suitable vinyl monomers include acrylates, methacrylates and the like.

METHODS OF MAKING FUNCTIONAL BIODEGRADABLE POLYMERS

RELATED APPLICATIONS

The present application claims priority to U.S. Provisional Application Serial No. 60/389,026, filed on June 14, 2002.

BACKGROUND OF THE INVENTION

The present invention concerns methods of making functional biodegradable materials, and their biomedical applications.

As used herein, biodegradable polymers are as polymers which are degradable in a physiologically relevant environment, either by hydrolysis, by enzymatic reactions or by other mechanisms, to produce biocompatible or non-toxic by products (see also Chih-Chang Chu, "Biodegradable Polymeric Biomaterials: An Overview", in JD Bronzino, editor-in-chief, *The Biomedical Engineering Handbook*, CRC Press, 1995; Yichun Sun et al., "Biodegradable Polymers and Their Degradation Mechanisms", *American Pharmaceutical Reviews*, 2001, 4(3), 9-18).

Typical examples of natural biodegradable polymers include proteins and polysaccharides such as gelatin, albumin, collagen, starch, detrxan, chitosan and chitin. Typical examples of synthetic biodegradable polymers include polylactic acid, polyglycolic acid, and their copolymers, and the current invention mainly concerns the functionalization of synthetic biodegradable polymers. More information on the making of synthetic biodegradable polymers can be found in Masahiko Okada, "Chemical Synthesis of Biodegradable Polymers", *Progress in Polymer Science*, 2002, 27, 87-133.

The biomedical use of biodegradable polymers is believed to have begun in the 1970s with the first biodegradable sutures prepared from copolymers poly(lactic-co-glycolic acid) (PLGA). Since then, numerous applications in the biomedical field have been made including uses such as wound closures, body implants, tissue engineering materials, and drug delivery materials.

The commonly-used biodegradable polymers such as poly(lactic-co-glycolic acid) and polycaprolactone, as linear aliphatic polyesters, don't contain functional groups such as carboxylic acid groups, hydroxyl groups and amine groups, except at the polymer chain ends. This lack of functional groups greatly limits the application of these synthetic biodegradable polymers. Functional groups containing reactive sites could, for example, bind to biologically active compounds such as peptides in order to help direct cell behavior in a tissue engineering matrix. As another example, the reactive sites could be used to bind drugs, thus making prodrugs and novel drug delivery systems. As yet another example, the incorporated functional groups make further chemical modification much easier, enabling additional properties to be added to the biodegradable polymer such as, for example, making them hydrophilic and water dispersible, and making it possible to have water-based preparation process.

Known methods for the introduction of functional groups into biodegradable polymers are: (1) incorporating special functional monomers at the beginning of the preparation of biodegradable polymers, (2) using reactions through carboxyl acid and hydroxyl groups at the chain ends and (3) using functional polymers as the ring-opening polymerization initiators in the making biodegradable polymers. Representative examples of these three approaches are:

(1) Via the incorporation of special monomers

Copolymers with pendant carboxyl groups were prepared by copolymerization of L-lactide and 3-(S)-[benzoyloxycarbonyl]-methyl]-1,4-dioxane-2,5-dione (BMD), a novel cyclic di-ester monomer consisting of both glycolate and benzyl-α-L-malate units. The copolymerization was carried out in bulk, with stannous 2-ethylhexanoate as catalyst. (see, for example, T. Yamaoka and Y. Kimura, "Biodegradable Copolymers", in JC Salamone edited *Concise Polymeric Materials Encyclopedia*, page 109-111, CRC Press, Boca Raton, 1998). The resulting polymers can only have one pendant carboxyl group for

each BMD monomer used, and the making requires a new di-ester monomer from the beginning of ring-opening polymerization and the removal of the benzoyloxy groups to display the pendant carboxyl group.

US Patents 5,399,665 and 5,654,381 and DA Barrera et al., *Macromolecules*, 1995, 28, 425-432 and JS Hrkach et al., *Macromolecules*, 1995, 28, 4736-4739 disclosed the making of biodegradable polyesters incorporated with specially-designed lysine residue monomers in the ring-opening polymerization, and also the use of the ε-amine groups in the amino acid residues of these polymers as ring-opening initiators to react with amino acid N-carboxyanhydrides (NCAs) to graft poly(amino acid) chains onto the biodegradable polymers.

(2) Via reaction at the chain end:

EB Lavik et al. in *Journal of Biomedical Materials Research Applied Biomaterials*, 2001, 58, 291-294, disclosed the making of block copolymer of PLGA (poly(lactic-co-glycolic acid)) and polylysine by direct coupling of protected polylysine (poly-ε-carbobenzoic-lysine) with carboxylic-acid-ending PLGA polymer, followed by the removal of the protection groups from the polylysine blocks.

WO 00/60956 (C.-Y. Won et al.) and Y. Zhang et al., *Journal of Polymer Science A: Polymer Chemistry*, 1999, 37, 4554-4569 disclose the modification of PLGA polymers by first adding vinyl groups at their chain ends, and then reacting the modified polymers with vinyl-group-incorporated polysaccharides such as dextran. The resulting network then has both hydrophilic and hydrophobic components.

M. Furch et al. in *Polymer*, 1998, 39, 1977-1982 describes the synthesis of copolymers of polyglycolide and methyl acrylate (PMA-g-PGA), by firstly making vinyl-group-ending polyglycolide macromonomers, which in turn was made by HEMA (2-hydroxylethyl methacrylate)-initiated ring-opening polymerization of glycolide. In the same paper, they mentioned that copolymers of polylactide with vinyl pyrrolidone and N, N'-

dimethyl-acrylamide co-monomers. H. Shinoda and K. Matyjaszewski in *Macromolecules*, 2001, 34, 6243-6248 describe the making of poly(methyl methacrylate)-g-poly(lactic acid) (PMMA-g-PLA) by a similar procedure but through the atom transfer radical polymerization.

(3) Via the use of polyols as the polymerization initiators:

Block copolymers of PLGA and poly(ethylene glycol) (PEG) have been discussed in the literature by JL Hill-West et al., in the *Proceeding of National Academy of Science USA*, 1994, 91, 5967-5971; by JL West et al., *Proceeding of National Academy of Science USA*, 1996, 93, 13188-13193; by B. Jeong et al., *Nature*, 1997, 388, 860-862; by B Jeong et al., *Macromolecules*, 1999, 32, 7064-7069; by T. Riley et al., *Langmuir*, 2001, 17, 3168-3174; and by T. Kissel et al., *Advanced Drug Delivery Reviews*, 2002, 54, 99-134. These copolymers include PLGA-PEG, PLGA-PEG-PLGA and PEG-PLGA-PEG types, and are mainly made by PEG-initiated ring-opening polymerization of cyclic esters.

B. Jeong et al., in *Macromolecules*, 2000, 33, 8317-8322, also discloses the making of graft copolymers PEG-g-PLGA with PEG as the backbone chains and PLGA as the side chains. The grafting reaction was made possible by first incorporate pendant-hydroxyl-group-bearing units in the backbone chains and later used these modified PEG chains to ring-opening polymerize lactide and glycolide monomers.

The use of poly(propylene glycol) (PPG) instead of PEG as the initiators for ring-opening polymerize lactide resulted in polylactide-PPG-polylactide tri-block copolymers, was disclosed by T. Yamaoka and Y. Kimura in "Biodegradable Copolymers", in *Concise Polymeric Materials Encyclopedia*, page 109-111, CRC Press, Boca Raton, 1998. It should be noted that the use of PEG and PPG as polymer initiators, though it may change the hydrophilicity of the final polymers, doesn't introduce functional groups in the biodegradable polymers.

US Patent 5,929,196, Y. Li et al. in *Polymer*, 1997, 38, 6197-6206; Y. Li et al. in *Polymer*, 1998, 39, 3087-3097; and A. Breitenbach et al., in *Polymer*, 2000, 41, 4781-4792

describe the making of graft copolymers with PLGA as side chains and polyols as the backbone chains. Their polyols include both neutral polymers such as poly(vinyl alcohol)s and polyelectrolytes such as dextran sulfate sodium, diethylaminoethyl dextran chloride, and also copolymers of poly(vinyl alcohol) and poly(β-methacrylic acid). The copolymers were made by ring-opening polymerization of cyclic ester monomers, with the hydroxyl groups in the polyol backbone chains as the initiators.

An exception to the above-mentioned approaches can be found in US Patent 5,610,241, which discloses the modification of biodegradable polymers such as Poly-DL-lactic acid with side chains of amino acid groups such as L-lysine, where the starting biodegradable polymers have repeating units consisting of carbonyl groups and hydrogen atoms on the carbon on the α position to the carbonyl group. The modification was done first by reacting the starting biodegradable polymers with a base such as alkali metal alkoxides, to form carbon ions on the α-carbon of the carbonyl groups in the repeating units (-CHR-C(=O)- to -C⁻R-C(=O)-); and then react the carbon-ion-bearing polymers with protected reactive amino acids, followed by the de-protection of side chain groups. The formation of carbon ions in the biodegradable polymers involves low temperature such as -78° C.

As is apparent to those skilled in the art, the known methods to functionalize biodegradable polymers use complicated chemistry and chemical processes. They either use specially designed monomers or multi-step reactions, or extreme reaction conditions. There is a great need to develop a simple and versatile method to make functional biodegradable polymers.

SUMMARY OF THE INVENTION

In response to the discussed problems encountered in the prior art, a new, simple and versatile method has been developed to functionalize biodegradable polymers by direct reaction of the biodegradable polymers in the medium of functional monomers, particularly vinyl monomers. An important point relevant to the current invention is that the commonly-used biodegradable polymers are soluble or dispersible in functional vinyl monomers.

The method to modify biodegradable polymers uses the direct reaction of a biodegradable polymer with at least one vinyl monomer and may take place in the presence of an initiator. The initiator may be free radical initiators, heat, ionic initiators, UV irradiation, ionizing irradiation and other high energy irradiation.

The vinyl monomer may contain functional groups which may be chosen from carboxylic acid groups, hydroxyl groups, amine groups, chloride groups, sulfonic groups, phosphoric groups, aldehyde groups, oxirane groups, mercaptan groups, isocyanate groups, sulfide groups, activated amide groups, activated ester groups, and combinations thereof.

The biodegradable polymers may be chosen from aliphatic polyesters, copolymers of linear aliphatic polyesters and their copolymers, polyanhydrides, polyorthoesters, poly(ester-ether), polyamines, phosphorus-based polymers and combinations thereof. An aliphatic polyester may be chosen from polylactic acid, polyglycolic acid, poly(lactic-co-glycolic acid), polycaprolactone, their copolymers and combinations thereof.

The biodegradable polymer may be dissolved or dispersed in the vinyl monomers. The method may also include a solvent.

Particularly notable combinations of biodegradable polymer and vinyl monomer include poly(lactic-co- glycolic acid) and acrylic acid, polycaprolactone and acrylic acid and poly(lactic-co-glycolic acid) and 2-hydroxylethyl methacrylate.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1 and 2 are 1H-and 13C-NMR graphs of the reaction product of Example 1.

Figure 3 is a depiction of three possible structures for PLGA-g-PAA (Figure 3 A, B and C).

Figure 4 is a depiction of the structure of PAA-g-PLA.

DETAILED DESCRIPTION OF THE INVENTION

In contrast with the known methods, the present invention is directed to a new, simple and versatile method to functionalize biodegradable polymers. The method is made possible because the commonly-used biodegradable polymers such as poly(lactic-co-glycolic acid) and polycaprolactone are soluble in functional monomers such as acrylic acid and hydroxylethyl methacrylate. The chemical modification of these biodegradable polymers can be done, therefore, by direct reaction of biodegradable polymers in the medium of functional monomers. This is accomplished by starting with the biodegradable polymer, dissolving or dispersing it into the media of functional monomers with the help of suitable initiators or with irradiation and under suitable temperature, forming reactive spots along the biodegradable polymer chains, and thereby grafting monomers onto them.

More information on the uses of functionalized biodegradable compositions may be found in US provisional patent application 60/389,022, attorney docket 17716, filed June 14th, 2002 using express mail number EL 471213251 US, by the same inventors, and commonly assigned. This application teaches bioadhesive polymers incorporated with biodegradable components. The bioadhesive components used are polycarboxylic acids, particularly poly(acrylic acid), poly(methacrylic acid), and their copolymers, while the biodegradable components can be any synthetic degradable polymer, particularly biodegradable polyesters whose degradation products are low molecular weight acids. Examples of biodegradable components include poly(lactic acid), poly(glycolic acid), poly(lactic-co-glycolic acid), and so on.

The two polymer components may be covalently bound to each other forming graft, block or random copolymers. Examples include poly(acrylic acid)-graft-poly(lactic acid) (PAA-g-PLA) and poly(lactic-co-glycolic acid)-g-poly(acrylic acid) (PLGA-g-PAA), the making of which are described in the examples below. Possible structures for PLGA-g-PAA are given in Figure 3 A, B and C. The structure of PAA-g-PLA is given in Figure 4. The two components may also be incorporated into one material by forming a non-covalent interpolymer complex via, for example, hydrogen bonding, ionic bonding or hydrophobic bonding. Typical examples in this category include the hydrogen bonding interpolymer complex formed between poly(methacrylic acid) and poly(lactic acid)-b-poly(ethylene glycol)-b-poly(lactic acid) tri-block copolymers, or more generally, complexes formed between polycarboxylic acids and PEG-PLGA copolymers or PVA-PLGA copolymers.

The 17716 materials may be used without including a treatment agent, to provide a lasting acidic pH environment. In this embodiment, the bioadhesive property enables the material to adhere strongly to biological surfaces, while the degradation of the biodegradable polyesters releases non-toxic low molecular weight acids. An acidic pH is very important to maintain or to establish a healthy body cavity environment such as, for example, in the vaginal cavity.

The 17716 materials may also be used as a treatment agent delivery system and the treating agent may be an agents for treating menstruation disorders and infections, agent for treating cardiovascular conditions, agents for treating internal conditions, agents for treating mental health conditions, anti-inflammatory agents, chemotherapeutic agents, cardiac tonics, expectorants, oral antiseptics, enzymes, birth control agents, opthalmic treating agents and combinations thereof. The 17716 materials can be either used without loading active agents as bioadhesive systems slowly releasing low molecular weight acids, or loaded with active agents as bioadhesive drug delivery systems.

Biodegradable Polymers

In addition to synthetic polymers made from bio-related monomers such as amino acids, sugar units and nucleotides, examples of synthetic biodegradable polymers include: (1) linear aliphatic polyesters such as polylactic acid, polyglycolic acid, polycaprolactone, polyhydroxybutyrate, polyhydroxyvalerate and their copolymers within the aliphatic polyester family such as poly(lactic-co-glycolic acid) and poly(glycolic acid-co-caprolactone); (2) copolymers of linear aliphatic polyesters and other polymers such as poly(glycolic acid-co-trimethylene carbonate) copolymers, poly(lactic acid-co-lysine) copolymers, tyrosine-based polyarylates or polyiminocarbonates or polycarbonates, poly(lactide-urethane) and poly(ester-amide) polymers; (3) polyanhydrides such as poly(sebacic anhydride); (4) polyorthoesters such as 3,9-diethyldiene-2,4,8,10-tetraoxaspiro-5,5-undecane based polymers; (5) poly(ester-ether) such as poly-p-dioxanone; (6) polyamides, poly(amide-enamines) and poly(amido amine) dendrimers; and (7) phosphorus-based polymers such as polyphosphazene and poly[bis(carboxy-lactophenoxy) phosphazene.

It should also be noted that biodegradable polymers having unsaturated bonds groups are quite useful for the present invention, since it's believed that it may be easier to generate reactive sites at these groups. These unsaturated bonds may be in the main or side chains. Examples of these biodegradable polymers include those wherein at least one of the monomers is maleic acid.

It should also be noted by those skilled in the art that the biodegradable polymers include the copolymers of the above-described biodegradable polymers and non-biodegradable polymers. Examples include the block copolymers of poly(lactic-co-glycolic acid) and poly(ethylene glycol) as described in US Patent 6,117,949 and 6,201,072.

Functional Vinyl Monomers

The vinyl monomers useful in the present invention can be any compounds with a vinyl group, particularly vinyl monomers with functional groups, and more particularly functional monomers with carboxylic acid, hydroxyl and amine groups. The monomers may have more than one vinyl group and hence act as cross-linkers.

The functional vinyl monomers include those with functional groups such as carboxylic acid groups, carboxylic acid chlorides, sulfonic groups, phosphoric groups, amine groups, aldehyde groups, oxirane groups, hydroxyl groups, mercaptan groups, isocyanate groups, sulfide groups, activated amide groups and activated ester groups.

Examples of vinyl monomers containing carboxylic acid groups include acrylic acid, methacrylic acid, butane dicarboxyl acid, 3-butene-1,2,3-tricarboxylic acid, and crotonic acid. Examples of vinyl monomers containing carboxylic acid chloride groups include acryloyl chloride and methacryloyl chloride. Examples of vinyl monomers containing sulfonic acid groups include 2-propene-1-sulfonic acid, 2-sulfoethyl methacrylate, 3-sulfopropyldimethyl-3-methacrylamidopropyl ammonium, and 3-sulfopropyl methacrylate; examples of vinyl monomers with phosphoric acid groups include bis(2-methacryloxyethyl) phosphate and monoacryloxyethyl phosphate.

Examples of vinyl monomers containing primary amine groups include 2-aminoethyl methacrylate hydrochloride and N-(3-aminopropyl) methacrylamide hydrochloride; examples of vinyl monomers containing secondary amine groups include 2-(tert-butylamino)ethyl methacrylate, diallylamine, and 2-(iso-propylamino) ethylstyrene; examples of vinyl monomers containing tertiary amine groups include 2-(N,N-diethylamino)ethyl methacrylate, 2-(diethylamino)ethyl styrene, 2-(N,N-dimethylamino) ethyl acrylate, N-[2-(N,N,-dimethylamino)ethyl] methacrylamide, 2-(N,N-dimethylamino) ethyl methacrylate, N-[3-(N,N-dimethylamino)propyl] acrylamide, N-[3-(N,N-dimethylamino)propyl] methacrylamide, and 4-vinylpyridine; examples of vinyl monomers

containing quaternary amine groups include 2-acryloxyethyltrimethylammonium chloride, diallyldimethylammonium chloride, and 2-methacryloxyethyltrimethyl ammonium chloride.

Examples of vinyl monomers containing aldehyde groups include acrolein. Examples of vinyl monomers containing oxirane groups include allyl glycidyl ether, glycidyl acrylate, and glycidyl methacrylate. Examples of vinyl monomers containing hydroxyl groups include glycerol monomethacrylate, 4-hydroxybutyl methacrylate, 2-hydroxyl acrylate, 2-hydroxyethyl methacrylate, N-(2-hydroxypropyl) methacrylamide, and hydroxypropyl methacrylate. Examples of vinyl monomers containing mercaptan groups include N,N'-cyctaminebisacrylamide. Examples of vinyl monomers containing isocyanate groups include dimethyl-3-isopropenylbenzyl isocyanate. Examples of vinyl monomers containing sulfide groups include 2-(ethylthio)ethyl methacrylate. Examples of vinyl monomers containing methylolamide groups include N-methylolacrylamide. Examples of vinyl monomers containing activated ester groups include N-acryloxysuccnimide.

The Direct Reaction of Biodegradable Polymers in Functional Monomers

One of the methods of making graft copolymers is via the formation of reactive centers on the polymer chain backbone in the presence of the monomers that will be grafted onto it. In the present invention, the backbones are the biodegradable polymers while the monomers used for grafting are vinyl monomers.

The creation of reactive centers along the biodegradable polymers can be made by free radical initiators such as peroxides, persulfates, or azo-compounds, by heat, by UV or other ionizing irradiation or other high energy irradiation methods, or by cationic or anionic (i.e. ionic) initiators. More and specific examples of these initiation methods can be found in "Principles of Polymerization" by G. Odian, McGraw-Hill Inc., New York, 1970.

As another method, the reactive centers may be first created on the biodegradable polymer chains, and the reactive biodegradable polymers can then be dissolved into the

vinyl monomers. This method may be an effective way to minimize the homopolymerization of the vinyl monomers and hence improve the grafting efficiency.

Still another method involves activation of the biodegradable polymers in the presence of oxygen to form peroxide and hydroperoxide groups along the chains, which are then thermally decomposed to polymer radicals in the presence of the vinyl monomers.

Without being limited to any particular theory for the chain transfer method of grafting, it's believed that the efficiency of the grafting reaction, i.e., the amount of graft polymerization relative to homopolymerization, is dependent on the tendency of a radical to chain transfer relative to its tendency to propagate. One can make a reasonable estimate of the grafting efficiency for a particular monomer/polymer combination from the values of the propagation rate constant for the monomers and the transfer constants for the degradable polymers. For the irradiation methods, it's believed that the grafting efficiency depends on the relative rates of reactive center formation in the degradable polymers and the vinyl monomers, which usually corresponds at least qualitatively to the transfer constants for the degradable polymers and the vinyl monomers, or to the bond energies of the weakest bonds of the polymers and the monomers.

According to the *Polymer Data Handbook*, edited by J. E. Mark (Oxford University Press, New York, 1999), the solvents for polylactic acid include benzene, chloroform, ethyl acetate, acetone, bromobenzene, m-cresol, dichloroacetic acid, dichloromethane, dioxane, dimethylformamide, isoamyl alcohol, N-methyl pyrrolidones, toluene, tetrahydrofuran, trichloromethane, p-xylene (p 627-633); the solvents for polyglycolic acid are hexafluroisopropanol at room temperature, glycolide and phenol/trichlorophenol at high temperature according to (p 566-569); and the solvents for polycaprolactone include dimethylacetamide, benxzene and chloroform (p 361-362).

It's believed that one of the reasons the literature teaches away from trying to dissolve degradable polymers like poly(lactic-co-glycolic acid) (PLGA) into functional

monomers like acrylic acid might be the belief that PLGA degrades very quickly in acidic or basic solutions. As shown in the following examples, however, the direct reaction involved in the present invention would most likely only need a few minutes. Even if the degradation of PLGA in acrylic acid occurs, the degradation should not have a significant effect on the reaction.

Although not intended to be bound to a particular mode of operation, it's believed that the creation of reactive centers on the biodegradable polymer chains likely involves the hydrogen atom abstraction from the backbone chains, caused by irradiation, by hydrogen transfer to the initiator, or by hydrogen transfer to the propagating monomer. The chain transfer and irradiation methods are both likely to yield a mixture of products including the graft copolymer, backbone polymers and homopolymers of the monomer. The relative amount of the three products depends on the monomer/polymer combinations and the reaction conditions.

In the practice of the invention generally, vinyl monomers (such as acrylic acid and HEMA) are polymerized in the presence of a biodegradable polymer (such as PLGA and PLA), with or without the presence of a solvent. The ratio of the monomer to biodegradable polymer may be from 10:90 to 90:10. More particularly, the ratio may be from 30:70 to 70:30 and still more particularly the ratio may be from 40:60 to 60:40.

The consideration on the choice of solvent is solubility of the reagents (monomer and biodegradable polymer) and possible interference with the polymerization process. For example, biodegradable polymers (such as PLA and PLGA) can be polymerized with vinyl monomers (such as acrylic acid and HEMA) in acetone. When the biodegradable polymer is soluble in the vinyl monomer, no solvent is needed for the latter to be polymerized in the presence of the former. Thus, both acrylic acid and HEMA were polymerized in the presence of PLA or PLGA without a solvent in the Examples below.

Polymerizations can be initiated by a free radical, ionic, cationic or an organometallic monomer. Depending on the nature of the initiator, polymerization may be

initiated thermally or by radiation, at elevated or room temperatures. An example of a free radical initiator useful for polymerizing vinyl monomers is 2, 2'-azobisisobutyronitrile (AIBN; 98%, from Aldrich Chem., catalog no. 44, 109-0, CAS 78-67-1). When AIBN is used as an initiator, heating the mixture to >50° C will initiate the polymerization. Typically, 0.01 - 2 weight percent of the initiator, relative to the monomer, may be used.

Alternatively, the monomers may be polymerized thermally or by radiation without the presence of an initiator.

The following examples illustrate the method of this invention in greater detail:

Example 1: PLGA/AA Systems:

Two sets of experiments were done to prove firstly that PLGA is soluble in acrylic acid. (1) 1 g of PLGA from Alkermes, Cambridge, MA (Medisorb® PLGA DL 5050 1A) was mixed with 1 g acrylic acid from Aldrich Chemical Company of Milwaukee, Wisconsin, (catalog no. 14723-0, vacuum distilled to remove inhibitors) and stirred for 40 minutes, the final mixture was homogeneous; (2) 1 g PLGA was dissolved in 1g acetone. Then, 40 ml of acrylic acid was added to the solution, and resulted in a homogeneous and clear solution. The whole solution was poured into 800 mL water and white precipitation was observed.

As a test, 5.7 g PLGA was dissolved in 5.7 g acrylic acid with stirring. After the dissolution, 0.014 g 2, 2'-azobisisobutyronitrile (AIBN) 98%, from Aldrich Chem. (catalog no. 44, 109-0, cas no. 78-67-1) was added into the solution, and the whole system was transferred into a 70 °C oil bath. After 5 minutes, there was a self-acceleration effect observed and the whole system solidified. The mixture was put into a vacuum oven to remove the unreacted monomers.

The ^{1}H- and ^{13}C-NMR spectra of the product polymer are shown in Figure 1 and 2, respectively. Both PLGA and PAA groups have been identified.

The solution structure of the product polymer was also tested using a Coulter tester. The pH was adjusted with NaOH. In pH 9.6 solution, PLGA-g-PAA formed a milky solution with average particle size of 2 micron. The particle aggregation and precipitation became significant after one day of preparation. Further increasing pH to 13.7 resulted in a clear solution of PLGA-g-PAA with average particle size of 347 nm.

Example 2: Polycaprolactone in acrylic acid

This example illustrates that polycaprolactone is also soluble in acrylic acid, and hence it also may be functionalized by direct reaction in acrylic acid.

First, 1 g of polycaprolactone from Aldrich (catalog no. 44075-2, MW 10,000) was mixed with 5 g acrylic acid from Aldrich (catalog no. 14723-0). After 50 minutes of stirring, the mixture became a clear and homogeneous solution. The solution was then poured into100 ml of water, and formed white precipitate.

As a second test, 2 g polycaprolactone was dissolved in 2 g chloroform, a known solvent for it. The solution was then poured into 30 mL of acrylic acid, resulting a clear solution. This solution was then poured into 800 mL water, and a white precipitate was observed, followed by phase separation of chloroform/water.

As a third test, 2 g polycaprolactone was stirred and mixed with 2 g acrylic acid. After 2 hours, a homogeneous mixture was formed.

Example 3: PLGA in HEMA

This example is to show that PLGA is also soluble in another biocompatible and functional monomer, 2-hydroxylethyl methacrylate (HEMA). 1 g of PLGA (Medisorb® PLGA DL 5050 1A) was mixed with 5 g HEMA from Aldrich (catalog no. 12863-5) with stirring. It was found that PLGA was easily dissolved. Then, 4 g more PLGA was added to the solution, and it was also easily dissolved. To the above formed solution, 0.01 g AIBN

was added and dissolved. The new solution was transferred to a 65-75 °C oil bath. After 5 minutes, the mixture became milky and solidified, i.e., the solution reacted.

Many variations of this method will be apparent to those who are skilled in the art, and are contemplated to be within the scope of the present The biodegradable polymers, for example, can be used in mixtures of several polymers, and the monomer medium can comprise more than one type of monomer. Furthermore, the use of a solvent as mentioned above, other than vinyl monomer, is considered within the scope of the present invention. Such solvents might be useful to help the dissolution or dispersion of biodegradable polymers in the vinyl monomers. Also known to those skilled in the art, however, is that the presence of other solvents might decrease the grafting efficiency. Again without being limited to a particular theory, it's believed that the solvents other than vinyl monomers may compete with the biodegradable polymers for chain transfer reaction.

CLAIMS:

What is claimed is:

1) A method to modify biodegradable polymers comprising direct reaction of a biodegradable polymer with at least one vinyl monomer.

2) The method of claim 1 wherein said reaction occurs at room temperature.

3) The method of claim 1 wherein said reaction occurs in the absence of a solvent.

4) The method of claim 1 further comprising an initiator wherein said initiator is selected from the group consisting of free radical initiators, heat, ionic initiators and UV irradiation, ionizing irradiation and other high energy irradiation

5) The method of modifying biodegradable polymers of claim 1 wherein said vinyl monomer contains at least one functional group selected from the group consisting of carboxylic acid groups, hydroxy groups, carboxylic acid chloride groups, sulfonic groups, phosphoric groups, aldehyde groups, oxirane groups, mercaptan groups, isocyanate groups, sulfide groups, amine groups, activated amide groups, activated ester groups, and combinations thereof.

6) The method of modifying biodegradable polymers of claim 1 wherein said biodegradable polymers are selected from the group consisting of aliphatic polyesters, copolymers of linear aliphatic polyesters and their copolymers, polyanhydrides, polyorthoesters, poly(ester-ether), polyamines, phosphorus-based polymers and combinations thereof.

7) The method of claim 5 wherein said biodegradable polymer is an aliphatic polyester and said aliphatic polyester is selected from the group consisting of polylactic acid, polyglycolic acid, poly(lactic-co-glycolic acid), polycaprolactone, their copolymers and combinations thereof.

8) The method of claim 1 wherein said biodegradable polymer is dissolved or dispersed in said vinyl monomers.

9) The method of claim 5 wherein said biodegradable polymer comprises unsaturated bonds.

10) A method to modify biodegradable polymers comprising direct reaction of a biodegradable polymer in a vinyl monomer, in the presence of initiator selected from the group consisting of free radical initiators, heat, ionic initiators, UV irradiation, ionizing irradiation and other high energy irradiation wherein said biodegradable polymer is poly(lactic-co-glycolic acid) and said vinyl monomer is acrylic acid.

11) The method of claim 10 wherein said reaction occurs at room temperature.

12) The method of claim 11 wherein said reaction occurs in the absence of a solvent.

13) A method to modify biodegradable polymers comprising direct reaction of a biodegradable polymer in a vinyl monomer, in the presence of initiator selected from the group consisting of free radical initiators, heat, ionic initiators, UV irradiation, ionizing irradiation and other high energy irradiation wherein said biodegradable polymer is polycaprolactone and said vinyl monomer is acrylic acid.

14) The method of claim 13 wherein said reaction occurs at room temperature.

15) The method of claim 14 wherein said reaction occurs in the absence of a solvent.

16) A method to modify biodegradable polymers comprising direct reaction of a biodegradable polymer in a vinyl monomer, in the presence of a free radical initiator selected from the group consisting of heat, UV irradiation, ionic initiators, ionizing irradiation and other high energy irradiation wherein said biodegradable polymer is poly(lactic-co-glycolic acid) and said vinyl monomer is 2-hydroxylethyl methacrylate.

17) The method of claim 16 wherein said reaction occurs at room temperature.

18) The method of claim 17 wherein said reaction occurs in the absence of a solvent.

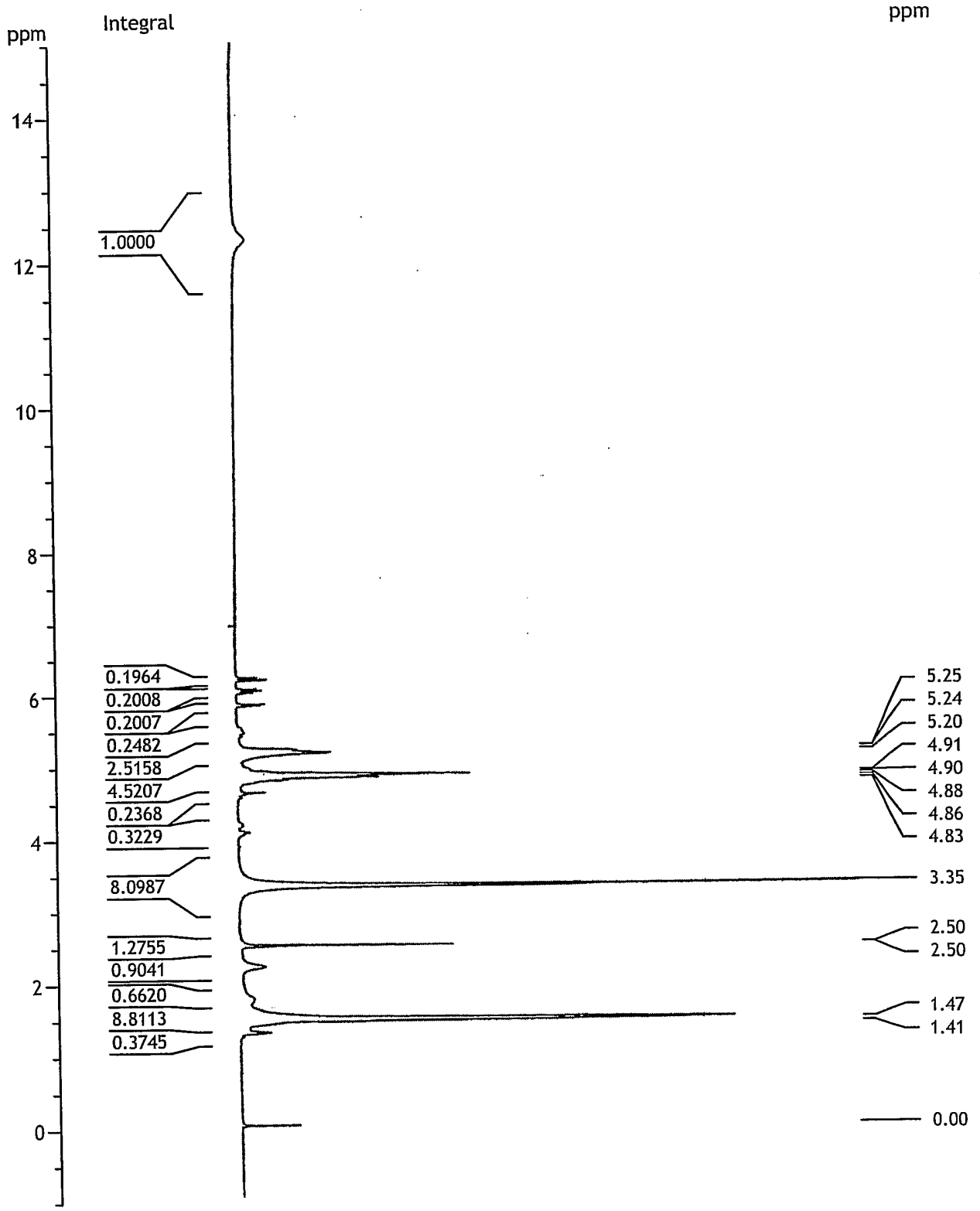

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FIG. 1

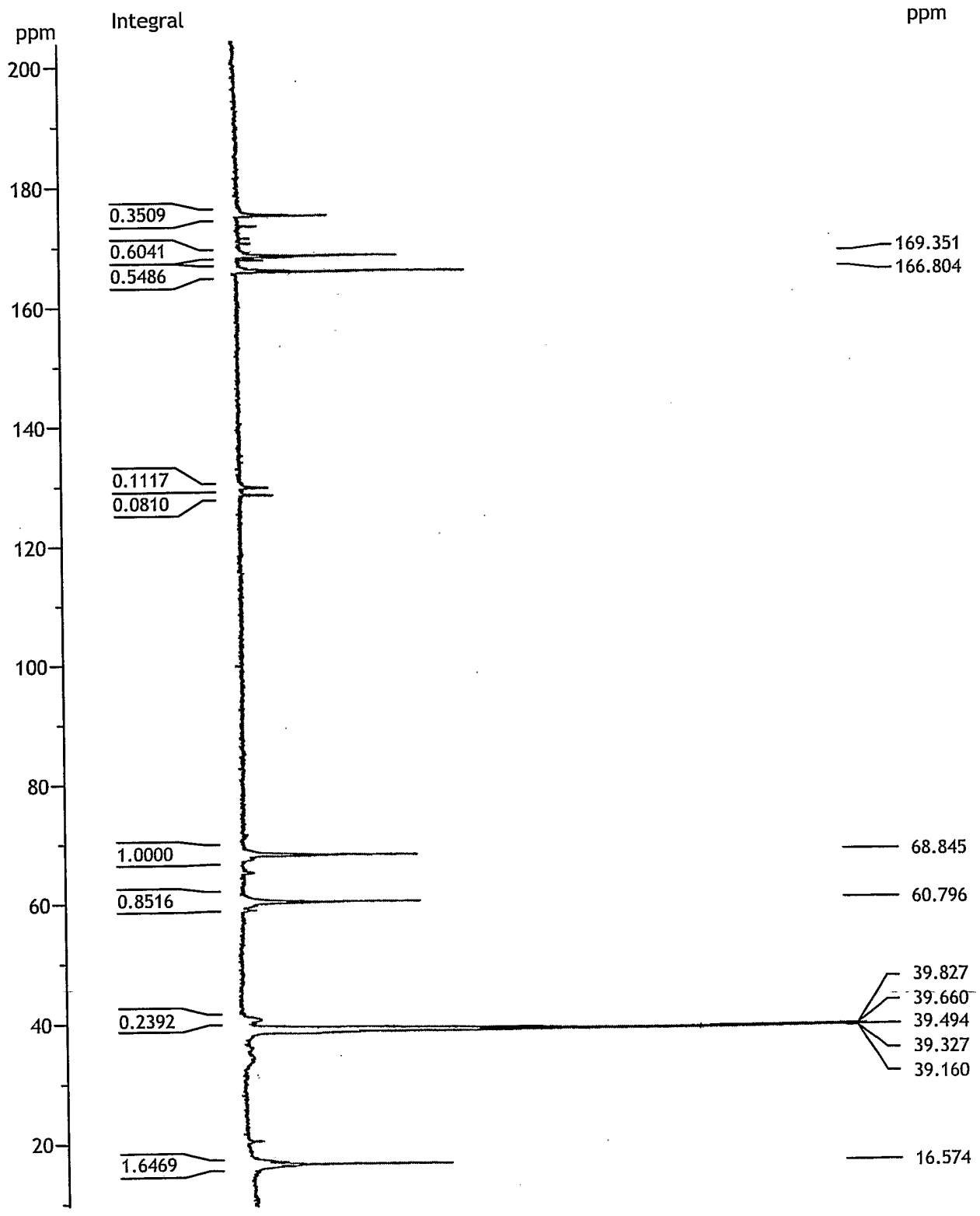
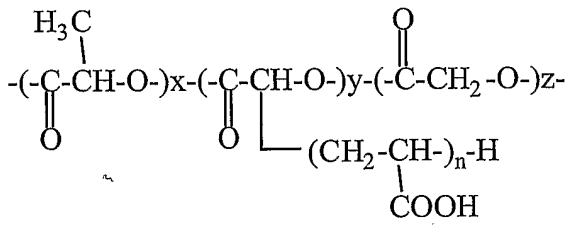
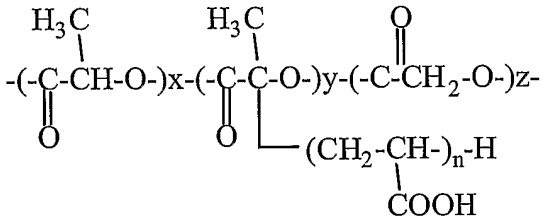

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FIG. 2

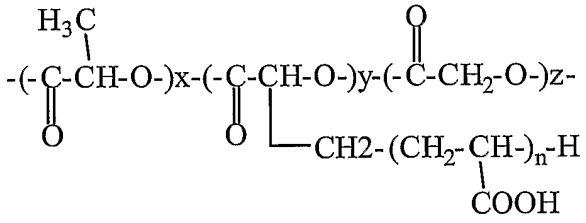
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A



B



C

FIG. 3

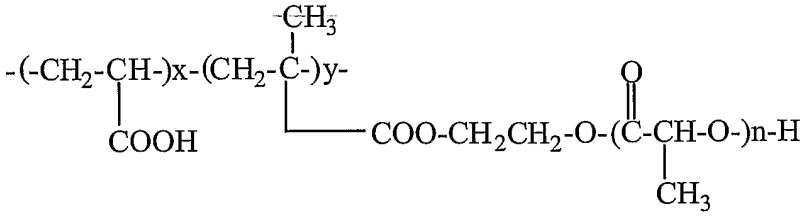


FIG. 4

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/15956

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C08F283/02 C08F283/00

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 7 C08F

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 47670 A (UNIV MINNESOTA) 18 December 1997 (1997-12-18) page 9, line 18 - page 12, line 24	1,3-8
X	EP 0 429 307 A (ROHM & HAAS) 29 May 1991 (1991-05-29) page 3, line 23 - page 4, line 34	1,3-5
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X	WO 98 55147 A (BATTELLE MEMORIAL INSTITUTE) 10 December 1998 (1998-12-10) claims 36-39	1

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 October 2003	14/10/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Meulemans, R.

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INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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