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(54) **THERMOPLASTIC POLYURETHANE ADMIXTURES**

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(57) **ABSTRACT**

The invention relates to admixtures of thermoplastic polyurethane base polymers that resist surface dulling and fluorinated additives and their use in the manufacture of articles, such as medical devices. For example, the admixtures of the invention are useful in the manufacture of blood dwelling medical devices, such as catheters.

FIG. 1A

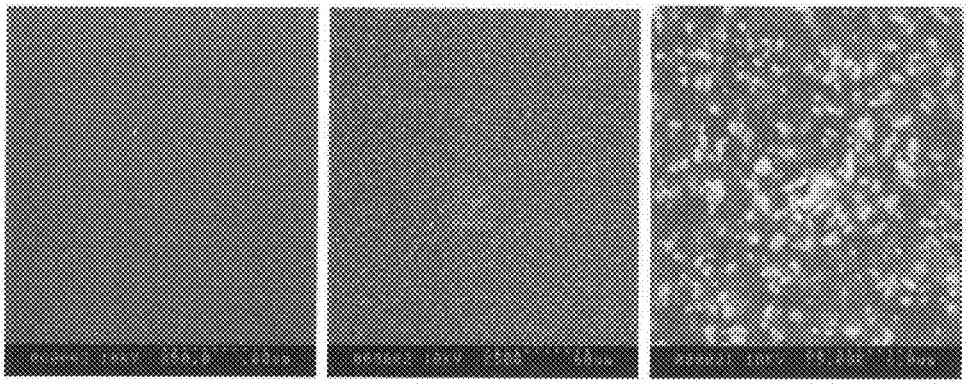


FIG. 1B

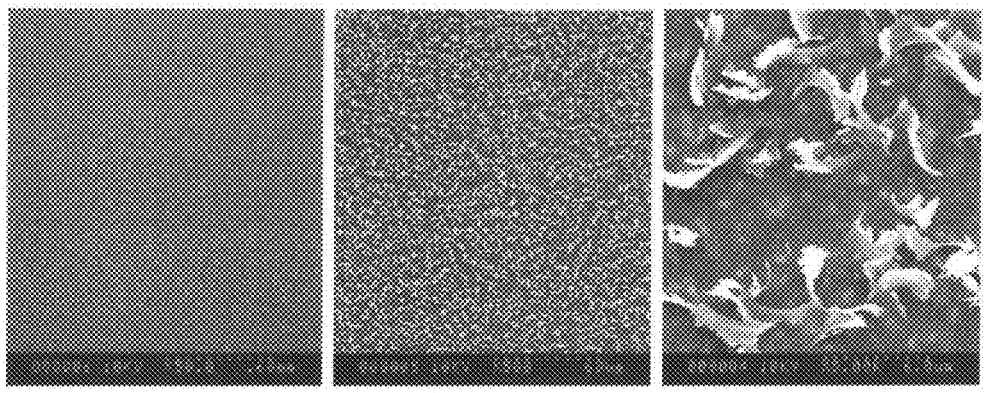
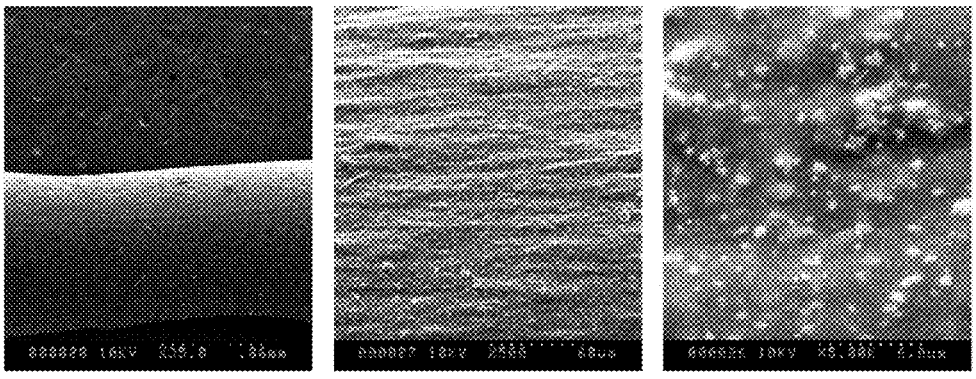


FIG. 1C



THERMOPLASTIC POLYURETHANE ADMIXTURES

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims benefit from U.S. Provisional Application No. 61/793,691, filed Mar. 15, 2013.

BACKGROUND OF THE INVENTION

[0002] The invention relates to admixtures of thermoplastic polyurethane base polymers and fluorinated additives that resist surface dulling and their use in the manufacture of articles, such as implantable medical devices.

[0003] Various fluorochemicals have been used to impart water and oil repellency, as well as soil resistance, to a variety of substrates. These fluorochemicals have most often been applied topically (for example, by spraying, padding, or finish bath immersion). The resulting repellent substrates have found use in numerous applications where water and/or oil repellency (as well as soil resistance) characteristics are valued, such as in protective garments for medical technicians and laboratory workers.

[0004] Certain low molecular weight fluorinated additives have been used in admixture with base polymers to impart water and oil repellency and/or hemocompatibility. When admixed with a base polymer, the fluorinated additives are sized accordingly to permit migration within, and blooming to the surface of, the base polymer. The advantage of this technical approach is that the surface properties of a polymer can be modified without significantly compromising the properties (e.g., elasticity or tensile strength) of the underlying base polymer. For the fluorinated additives to bloom to the surface of a base polymer, they are manufactured to be relatively small (e.g., typically less than 10,000 Daltons, depending upon the composition of the fluorinated additive and composition of the base polymer).

[0005] For particular applications, such as blood dwelling medical devices, it is desirable that the fluorinated additive be modified to avoid compromising the esthetically unpleasing appearance and dulling appearance of the product. We have discovered that this dulling can be controlled by reducing the amount of a specific species called trimer.

SUMMARY OF THE INVENTION

[0006] The invention features an admixture including a thermoplastic polyurethane base polymer and a fluorinated additive. These admixtures are useful in the manufacture of implantable devices.

[0007] In a first aspect, the invention features an admixture including a thermoplastic polyurethane base polymer having a Shore durometer hardness of between 60 A and 85 D and a fluorinated additive mixture, wherein the fluorinated additive mixture includes compounds of formula (I):

$$G\text{-}[B\text{-}A]_n\text{-}B\text{-}G \quad (I),$$

and less than 10% (w/w) trimer of formula (II):

$$G\text{-}B\text{-}G \quad (II),$$

wherein A is a soft segment including polypropylene oxide, polyethylene oxide, or polytetramethylene oxide, hydrogenated polybutadiene (HLBH), poly (2,2 dimethyl-1-3-propyl carbonate) (PCN), poly(hexamethylene carbonate)diol, hydroxyl terminated polydimethylsiloxanes (PrO-PDMS-PrO) block copolymer, hydrogenated-hydroxyl terminated polyisoprene, poly(ethyleneglycol)-block-poly(propyleneglycol))-block-poly(ethylene glycol), 1,12-dodecanediol, hydrogenated polyisoprene (HHTPI), poly(hexamethylene carbonate), or poly(2-butyl-2-ethyl-1,3-propyl carbonate); B is a hard segment including terminal urethane linkages; G is an polyfluoroalkyl group; and n is an integer from 1 to 15. In particular embodiments, the fluorinated additive mixture includes between 0% and 5% (w/w) (e.g., from 0% to 1.5%, 0% to 2%, 0.1% to 2.2%, 0.3% to 3%, or 0.5% to 5% (w/w)) trimer of formula (II). The polyfluoroalkyl group can be selected from radicals of the general formula $CF_3(CF_2)_rCH_2CH_2$— wherein r is 2-20, and $CF_3(CF_2)_s(CH_2CH_2O)_\chi$ wherein χ is 1-10 and s is 1-20.

[0008] In particular embodiments, the fluorinated additive mixture is formed by a process that includes (i) reacting a hard segment diisocyanate with a soft segment diol to form a prepolymer, and (ii) reacting the prepolymer with a polyfluoroalkyl alcohol to form a mixture of compounds of formula (I).

[0009] The soft segment diol can have a theoretical molecular weight of from 400 to 3,000 Daltons (e.g., 400 to 1,200, 800 to 1,600, or 1,200 to 3,000 Da). The diisocyanate can be selected from 2,4 toluene diisocyanate, 2,6 toluene diisocyanate, methylene bis(p-phenyl) diisocyanate, 1,5 naphtanene diisocyanate, 3,3' bitoluene diisocyanate, methylene bis (p-cyclohexyl isocyanate), 1,6 hexane diisocyanate, 1,12 dodecane diisocyanate, isophorone diisocyanate, cyclohexyl diisocyanate, lysine diisocyanate, and trimethyl-1,6 diisocyanatohexane. The soft segment diol can be selected from polyalkylene oxide diols, polycarbonate diols, polyester diols, and lactone diols. For example, the soft segment diol can be a polyalkylene oxide diol selected from polyethylene oxide diol, polypropylene oxide diol, and polytetramethylene oxide diol. In particular embodiments, the soft segment diol has a theoretical molecular weight of from 400 to 3,000 Daltons (e.g., 400 to 1,200, 800 to 1,600, or 1,200 to 3,000 Da). In certain embodiments, the diisocyanate is 1,6 hexane diisocyanate. The fluorinated additive mixture can formed by a process that includes (i) reacting about 1 equivalent of the soft segment diol with about 1.4 to 1.8 equivalents (e.g., 1.4 to 1.5, 1.5 to 1.6, 1.6 to 1.7, or 1.7 to 1.8 equivalents) of diisocyanate to form a prepolymer and (ii) reacting the prepolymer with a polyfluoroalkyl alcohol to form the fluorinated additive mixture. In particular embodiments, the fluorinated additive mixture is formed by a process that includes (i) reacting about 1 equivalent of polyalkylene oxide diol with about 1.4 to 1.8 equivalents (e.g., 1.4 to 1.5, 1.5 to 1.6, 1.6 to 1.7, or 1.7 to 1.8 equivalents) of 1,6-hexamethylene diisocyanate to form a prepolymer; and (ii) reacting the prepolymer with a polyfluoroalkyl alcohol to form the fluorinated additive mixture. Optionally, the fluorinated additive mixture is formed by a process that includes an extraction step (e.g., with a hydrocarbon, such as hexane) for removing some or all of the trimer of formula (II). Alternatively, trimer can be removed by dialysis or chromatographic methods. In particular embodiments, the polyfluoroalkyl alcohol is selected from 1H,1H,2H,2H-perfluoro-1-decanol; 1H,1H,2H,2H-per-

[0010] In any of the above admixtures, the fluorinated additive mixture can have a polystyrene equivalent weight average molar mass, M_w, of from 2,000 to 26,000 g/mole (e.g., 6,000±4,000, 8,000±4,000, 10,000±4,000, 12,000±4,000, 18,000±4,000, 20,000±4,000, 22,000±4,000, or 24,000±2,000 g/mole).

[0011] In any of the above admixtures, the fluorinated additive mixture can have a polystyrene equivalent number average molar mass, M_n, of from 2,000 to 18,000 g/mole (e.g., 6,000±4,000, 8,000±4,000, 10,000±4,000, 13,000±2,000, 14,000±2,000, 15,000±2,000, or 16,000±2,000 g/mole).

[0012] In any of the above admixtures, the fluorinated additive mixture can have a polystyrene equivalent molecular weight at highest peak, M_p, of from 16,000 to 26,000 g/mole (e.g., 20,000±4,000, 22,000±4,000, or 24,000±2,000 g/mole).

[0013] In any of the above admixtures, the fluorinated additive mixture can have a polydispersity index of between 1.0 and 2.0 (e.g., a polydispersity of 1.1 to 1.4, 1.3 to 1.6, 1.35 to 1.55, 1.5 to 1.7, or 1.6 to 1.9).

[0014] In any of the above admixtures, the fluorinated additive mixture has a polystyrene equivalent weight average molar mass, M_w, of from 2,000 to 14,000 g/mole (e.g., 6,000±4,000, 8,000±4,000, or 12,000±2,000 g/mole), and/or a polystyrene equivalent number average molar mass, M_n, of from 2,000 to 12,000 g/mole (e.g., 6,000±4,000, 8,000±4,000, or 10,000±2,000 g/mole), and comprises between 0% and 3% (w/w) (e.g., from 0% to 1.5%, 0% to 2%, 0.1% to 2%, 0.1% to 2.2%, 0.3% to 2.2%, or 0.5% to 2.5% (w/w)) trimer of formula (II).

[0015] In any of the above admixtures, the fluorinated additive mixture has a polystyrene equivalent weight average molar mass, M_w, of from 14,000 to 26,000 g/mole (e.g., 18,000±4,000, 20,000±4,000, or 22,000±4,000 g/mole), and/or a polystyrene equivalent number average molar mass, M_n, of from 10,000 to 16,000 g/mole (e.g., 12,000±2,000 or 14,000±2,000 g/mole), and comprises between 0% and 3% (w/w) (e.g., from 0% to 1.5%, 0% to 2%, 0.1% to 2%, 0.1% to 2.2%, 0.3% to 2.2%, or 0.5% to 2.5% (w/w)) trimer of formula (II).

[0016] In certain embodiments, the thermoplastic polyurethane base polymer is a poly(carbonate urethane) base polymer. For example, the thermoplastic polyurethane base polymer can be a poly(carbonate urethane) base polymer including poly(hexamethylene carbonate) and 4,4'-methylene bis(cyclohexyl urethane). In still other embodiments, the poly (carbonate urethane) base polymer has a Shore durometer hardness of between 60 A and 85 D (e.g., 60 A to 95 A, 75 A to 90 A, 85 A to 100 A, 5 D to 50 D, or 25 D to 85 D).

[0017] In particular embodiments, the admixture includes from 1% to 8% (w/w) (e.g., 1% to 6%, 1% to 5%, 2% to 6%, or 3% to 6% (w/w)) fluorinated additive mixture. The admixture can include less than 1%, 0.5%, 0.3%, 0.2%, or 0.1% (w/w) trimer of formula (II) (e.g., from 0 to 1%, 0 to 0.5%, 0 to 0.3%, 0 to 0.2%, or 0.001% to 0.2% (w/w) trimer).

[0018] The admixtures of the invention can include other materials, such as radiopaque materials (e.g., as powders or other particulates). Suitable radiopaque additives include bismuth subcarbonate, bismuth oxychloride, bismuth trioxide, the present invention include colorants such as pigments, dyes, or other suitable colorant materials.

[0019] In a related aspect, the invention features a medical device having a surface including an admixture of the invention. The medical device can be a blood dwelling device, such as a catheter (e.g., a central venous catheter, dialysis catheter, implanted port, or peripherally inserted central catheter).

[0020] The admixtures of the invention can be used to impart hemo compatibility to a surface. For example, the admixtures can be used to provide a surface for a blood dwelling device having reduced thrombogenicity.

[0021] As used herein, the terms "polystyrene equivalent weight average molecular weight" (M_w), "polystyrene equivalent number average molecular weight" (M_n), and "polystyrene equivalent molecular weight of the highest peak" (M_p) refer to polystyrene equivalent values determined by gel permeation chromatography as described in Example 8.

[0022] The percentage by weight of trimer in the fluorinated additive mixture is calculated based upon the mass of fluorinated components in the mixture (e.g., excluded from the calculation are the mass of solvents and other non-fluorinated materials that might be included as carriers or other components (e.g., opacifying agents, colorants, antioxidants, etc.) that may be also included in the admixture).

[0023] Other features and advantages of the invention will be apparent from the Detailed Description, the drawings, and the claims.

DRAWINGS

[0024] FIG. **1**A is an SEM image of a Carbothane™ (Shore Hardness 95 A, with barium sulfate radiopaque filler) film without fluorinated additive at magnifications of 50×, 500×, and 5000×.

[0025] FIG. **1**B is an SEM image of a Carbothane™ (Shore Hardness 95 A, with barium sulfate radiopaque filler) film with formulation 1 at magnifications of 50×, 500×, and 5000×. At 5000× magnification, a residue is visible for the admixture with formulation 1.

[0026] FIG. **1**C is an SEM image of a Carbothane™ (Shore Hardness 95 A, with barium sulfate radiopaque filler) film with formulation 7 at magnifications of 50×, 500×, and 5000×. In contrast to FIG. **1**B, no residue is observed for the admixture with formulation 7.

DETAILED DESCRIPTION

[0027] The methods and compositions of the invention feature admixtures of thermoplastic polyurethane base polymers and fluorinated additive mixtures that resist dulling. The admixtures of the invention are useful in the manufacture of blood dwelling medical devices, such as catheters (i.e., central venous catheter or peripherally inserted central catheter). The medical devices can be fabricated using various processes, including injection molding and extrusion processes resulting from compounded admixture materials.

[0028] Applicants have discovered that for admixtures formed from thermoplastic polyurethane base polymers the molecular weight of the fluorinated additive mixture must be (i) low enough to permit migration within, and blooming to the surface of, the base polymer, and (ii) with reduced trimer

ciated with dulling of the surface leading to esthetically unpleasing product. Admixtures with reduced trimer content can be prepared as described in the examples.

[0029] Thermoplastic Polyurethane Base Polymers

[0030] Thermoplastic polyurethanes encompass many different types of materials as well as materials of different durometers. Initial selection of a polyurethane may be based on the performance of the material. Thermoplastic polyurethanes are available with Shore Durometers of from 60 A to 85 D. Thermoplastic polyurethanes come in a variety of different chemical structures, which are selected based upon how the base polymer is being used, and for how long.

[0031] Tecoflex medical grade thermoplastic polyurethanes (Grades EG-80A, EG-93A and EG-60D) are a group of aliphatic, polyether based resins that have established credentials for implants including having passed the following standard screening tests: MEM Elution, Hemolysis, USP Class VI, 30 Day Implant, and Ames Mutagenicity.

[0032] Tecoflex EG-80A is a medical-grade, aliphatic, polyether-based thermoplastic polyurethane elastomer with a durometer value of 72 A. Tecoflex EG-85A is a medical-grade, aliphatic, polyether-based thermoplastic polyurethane elastomer with a durometer value of 77 A. Carbothane PC-3575A is a medical-grade, aliphatic, polycarbonate-based thermoplastic polyurethane elastomer with a durometer value of 73 A. Carbothane PC-3585A is a medical-grade, aliphatic, polycarbonate-based thermoplastic polyurethane elastomer with a durometer value of 84 A.

[0033] Bionate thermoplastic polycarbonate polyurethanes are a family of thermoplastic elastomers formed as a reaction product of a hydroxyl terminated polycarbonate, an aromatic diisocyanate and a low molecular weight glycol to form the soft segment.

[0034] These base polymers can be useful in the admixtures of the invention. It is possible that the elastomeric nature of the base polymers renders them both, ideal for use in catheters, but susceptible to dulling when used in combination with fluorinated additive mixtures having high trimer content.

[0035] Exemplary poly(carbonate urethanes) that may be included in the admixtures of the invention include, without limitation, CARBOTHANE®, CHRONOFLEX® AL (aliphatic), CHRONOFLEX® AR (aromatic), CHRONOFLEX® C (aromatic), and BIONATE® (aromatic), in a variety of durometers 80 A, 85 A, 90 A, 95 A, 55 D, and 75 D.

[0036] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how the methods and compounds claimed herein are performed, made, and evaluated, and are intended to be purely exemplary of the invention and are not intended to limit the scope of what the inventors regard as their invention.

of the reaction conditions (as described in the examples below). These include, but are not limited to, the component reagents mentioned below.

[0038] Reagents

[0039] HDI=hexamethylene diisocyanate

[0040] PTMO=poly(tetramethylene oxide) diol

[0041] FOH C8=$(CF_3)(CF_2)_5CH_2CH_2OH$ (1H,1H,2H,2H Perfluorooctanol)

EXAMPLE 1

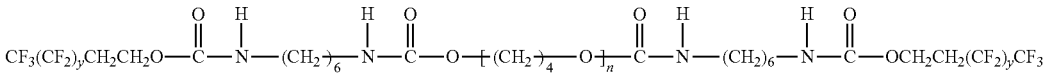
Formulation 1

[0042] To dry reactor glassware was added 1 molar ratio of of degassed polytetramethylene oxide diol (M_w 1000) and dimethyl acetamide (DMAC). To the solution was added 2 molar ratio of hexamethylene diisocyanate, and the reaction flask was placed in a water bath. 0 5 mL of dibutyltin dilaurate(DBTDL)was added to the system. The reaction mixture was stirred for 4 hours at 65° C. to produce the desired HDI-PTMO prepolymer.

[0043] Once the prepolymer reaction is complete, the reactor contents was cooled to 45° C. and degassed FOH C8 was added to the reactor at a molar ratio of 2.3 to end-cap the pre-polymer. A syringe was used to add ca 1.0 mL dibutyltin dilaurate(DBTDL). The reaction mixture was stirred overnight at 45° C. to produce the desired fluorinated polymers.

[0044] The polymer was precipitated in deionized water under constant stirring. The volume of water used for the precipitation should be approximately 3.3 times the volume of the DMAc solvent in the solution.

[0045] The polymer was purified by dissolution in boiling isopropanol, followed by cooling to 50-60° C., and precipitation by slow addition of hexane. The precipitatead polymer was collected on a filter and washed with hexane. The purified polymer was dried in a convection oven at 50° C. for at least 48 hours to produce Formulation 1 (general formula depicted below).



EXAMPLE 2

Formulations 2 and 3

[0046] Formulation 1 was dissolved in tetrahydrofuran and processed through a GPC prep column. Exiting fractions were collected at 0-31 minutes and 31-43 minutes, corresponding to a high molecular weight fraction (Formulation 2) and low molecular weight fraction (Formulation 3), respectively. A rotary evaporator was used to remove the tetrahydrofuran, and the fractions dried under vacuum overnight. About 550 mg of Formulation 2 and about 250 mg of Formulation 3 were isolated from 1 gram of Formulation 1.

EXAMPLE 4

Formulation 4

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

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With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

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Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.