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(54) **Title:** PROCESS FOR MAKING BIODEGRADABLE AND/OR BIOABSORBABLE POLYMERS

(57) **Abstract:** A process for producing a bioabsorbable thermoplastic polyurethane tailored to a medical application is provided. The process includes identifying suitable thermoplastic polyurethane properties based on the medical application. The thermoplastic polyurethane comprises units derived from a diol chain extender, a diisocyanate, and a polyol. The thermoplastic polyurethane properties include a biodegradation rate and at least one physical property. The process can include identifying a base thermoplastic polyurethane and altering at least one parameter of the base thermoplastic polyurethane which relates to the desired thermoplastic polyurethane properties to generate a thermoplastic polyurethane.



WO 2014/004334 A1

PROCESS FOR MAKING BIODEGRADABLE AND/OR BIOABSORBABLE POLYMERS

FIELD OF INVENTION

[0001] The present embodiment relates to biodegradable and/or bioabsorbable polymers and finds particular application in connection with a process for making such compounds.

BACKGROUND

[0002] There has been an increasing interest in the use of biodegradable and/or bioabsorbable materials, rather than biostable biomaterials, in a number of applications in the biomedical field. The importance of biosafety and long-term stability of polymers used in many implants are major driving forces for this trend. The innovations in biomedical processes, such as tissue engineering, gene therapy, controlled drug release, and regenerative medicine have accelerated the use of biodegradable materials to make devices which help the body to repair and regenerate the damaged tissue so that many post or ex-plantation operations can be avoided. Exemplary of the biomedical applications of biodegradable and/or bioabsorbable materials are implants, such as screws, pins, bone plates, staples, sutures (monofilament and multifilament), drug-delivery vehicles, membranes for guided tissue regeneration, mesh and porous materials for tissue engineering, anti-adhesion barriers, tissue scaffolds, cardiovascular grafts, and wound dressings.

[0003] One of the key limitations of current biodegradable and/or bioabsorbable materials for many of the potential applications has been the lack of the proper combination of physical properties such as tensile strength, flexibility, elongation, abrasion resistance, etc. for the application. Many of these materials are brittle and are not sufficiently strong for the intended application and there has been significant research toward improving the physical and mechanical properties of these materials through various means, including varying and modifying the chemical structure and

-2-

blending of these polymers with other polymers to increase their strength, flexibility, and the like.

[0004] In addition to the desire for good physical and mechanical properties in these applications, there is a need to be able to moderate or accelerate the biodegradation rate of the materials to precisely meet the need for the application. For instance, for a wound dressing application, a biodegradation rate of days might be appropriate, while for an orthopedic application, degradation rates of months or even years in some cases might be more appropriate. Even in a given application, the rate of biodegradation that would be optimally desired might be different, depending on the individual patient. For instance, an older patient or one in poor health might benefit from a material that would degrade more slowly to match their individual rate of healing. Currently, such precise matching of the degradation rates and physical and mechanical properties of the biosorbable polymers to the specific requirements of the application or even to the needs of the individual patient has not been possible using the biosorbable polymers that are available even though it is widely known that such an ability would have significant therapeutic benefit. Accordingly, there has been much study on the ways to modify polymer structure to affect the rate of bioabsorption.

[0005] Currently available biomaterials have rather narrow ranges of combinations of these parameters and therefore, the medical industry often must choose the closest approximation to what they need from the materials that are commercially available. There have been numerous technical efforts to increase the range of properties and degradation rates of biodegradable and/or bioabsorbable polymers. See, for example, M. Florczak, J. Libiszowski, J. Mosnacek, A. Duda, S. Penczek, *Macromol. Rapid Commun.*, 28, 1385 (2007); I. Rashkov, N. Manolova, S. M. Li, J. L. Espartero, M. Vert, *Macromolecules*, 29, 50 (1996); K. Garkhal, S. Verma, S. Jonnalagadda, N. Kumar, *J. Polym. Sci. Part A, Polym. Chem.*, 45, 2755 (2007); E. Grigat, R. Koch, R. Timmermann, *Polym. Degrad. Stab.*, 59, 223 (1998); and I. Vroman, L. Tighzert, *Materials*, 2, 307 (2009). These efforts usually involve

blending of existing biodegradable and/or bioabsorbable polymers to achieve intermediate properties and/or degradation rates or preparing copolymers of the monomeric building blocks that are currently used in the biodegradable and/or bioabsorbable polymers which are in commercial use today.

[0006] There remains a need for biodegradable and/or bioabsorbable polymers to meet a variety of applications where the desired combination of physical properties and degradation rate can be chosen for the biodegradable and/or bioabsorbable polymer tailored to the specification application for which it will be used.

SUMMARY

[0007] The present invention provides processes of making a biodegradable and/or bioabsorbable thermoplastic polyurethane compound tailored for a medical application, as well as the thermoplastic polyurethane compounds themselves. As used throughout the rest of this application, the term “bioabsorbable” will be used as meaning biodegradable and/or bioabsorbable and/or biosorbable.

[0008] The processes of the invention provide the ability to independently and continuously adjust both the degradation rate and the physical properties based on an understanding of the way that the TPU physical properties and degradation rates interact with each other. These relationships include, among others, a relationship between the M_n of the polyol in the TPU and amount of phase separation and therefore physical properties, such as rebound. At the same time, however, there is a relationship between properties that affect the degradation rate, like hydrophobicity/hydrophilicity balance in the TPU. Another such relationship is the relationship between hardness and the hydrophilicity/hydrophobicity balance of the TPU. The hydrophobicity/hydrophilicity balance is one of the key properties affecting degradation rate and hardness is one of the key properties affecting the physical and mechanical properties. Therefore, an understanding of the detailed relationship between these factors is beneficial

to the design of the TPU and reduces time-consuming trial and error. These relationships enable design of TPUs which can have any combination of physical properties and degradation rate. As a result, time consuming and costly synthesis work is minimized.

[0009] Although many different biodegradable and/or bioabsorbable polymers with varying properties and degradation rates are currently commercially available, there are large gaps in properties between the commercially available materials and the degradation rate for a given material can typically not be changed without selecting a different material. The materials of disclosed herein, which offer continuously variable properties and degradation rates, make this limitation no longer a factor. Also, the ability to change the degradation rate for a material with a given set of physical properties or to change the physical properties of a material with given degradation rate by minor changes in the composition/formulation of a single class of materials has not been achievable with the materials currently available. The ability to do this sort of tailoring of properties and degradation rates to precisely match the requirements of a given application will allow the medical device producer to use a polymer which possesses exactly the combination of characteristics (degradation rate, physical properties) which are optimal for their needs. As a result of this unique combination of properties and characteristics, the materials disclosed herein can find extensive use in numerous medical applications.

[0010] The methods make use of the versatile polyurethane chemistry to prepare polymers with a wide range of physical properties. The biodegradation rates of these materials can be varied by adding to the polymeric structure units which can be readily hydrolyzed. The number of hydrolysable units in the TPU backbone per unit length is a useful parameter that can be used to control the degradation rate of the exemplary TPU materials. While degradation mechanisms have been studied previously, the ability to independently and continuously vary both the physical properties and the degradation rates has not been demonstrated. Since TPUs have been used in implanted medical devices for many years without

and significant safety issues, the exemplary materials combine the excellent toxicological aspects of the component materials used in the polymer synthesis with the opportunity to provide tailorable properties and degradation rates.

[0011] The present invention provides a process of making a bioabsorbable thermoplastic polyurethane compound tailored for a medical application, where the process includes the step of: reacting a polyisocyanate component, a diol chain extender component, and optionally a polyol component, wherein at least one of the components contains hydrolyzable units such that the resulting compound contains hydrolyzable units in its backbone, resulting in a compound with a controllable degradation rate and one or more controllable physical properties, where the degradation rate and the physical properties can be independently set.

[0012] In other words, the process of the invention provides a bioabsorbable thermoplastic polyurethane with a desired degradation rate and one or more desired physical properties, where each may be independently selected from a broad range. The present invention allows a means of selecting a desired degradation rate for a bioabsorbable thermoplastic polyurethane, in such a way that does not effectively set the physical properties of the bioabsorbable thermoplastic polyurethane, but instead allows one or more physical properties of the bioabsorbable thermoplastic polyurethane to also be selected from a wide range. In addition the present invention allows a means of selecting one or more desired physical properties for a bioabsorbable thermoplastic polyurethane, in such a way that does not effectively set the degradation rate of the bioabsorbable thermoplastic polyurethane, but instead allows the degradation rate the bioabsorbable thermoplastic polyurethane to also be selected from a wide range. This independent selection of both a degradation rate and one or more desired physical properties of a bioabsorbable thermoplastic polyurethane is the key break through the present invention represents.

[0013] The processes of the invention achieve these results by allowing both the degradation rate and the one or more physical properties of the bioabsorbable thermoplastic polyurethane to be adjusted using different parameters. In the processes of the invention, the degradation rate of the compound is set by adjusting one or more degradation rate parameters and the one or more physical properties of the compound is/are set by adjusting one or more physical property parameters, resulting in a bioabsorbable thermoplastic polyurethane compound having at least one desired physical property of the compound, and a desired degradation rate of the compound, independently set.

[0014] In the processes, the degradation rate parameter may include at least one of the following: (i) the quantity of bioabsorbable units in the backbone of the overall compound; (ii) the molecular weight of the polyol component; (iii) the hydrophilicity of the overall compound; (iv) the molecular weight of the overall compound; (v) the hard segment content of the overall compound; (vi) the crystallinity of the overall compound.

[0015] In the processes, the physical property may include at least one of the following: (a) the tensile strength of the overall compound; (b) the hardness of the overall compound; (c) the stiffness (flexibility) of the overall compound; (d) the resilience of the overall compound; (e) the abrasion resistance of the overall compound; (f) the water swell of the overall compound; (g) the moisture permeability of the compound; (h) the impact strength/resistance of the compound; (i) the coefficient of friction (on the surface) of the compound; (j) the creep of the compound; (k) the modulus of elasticity of the compound; and (l) the thermal transition points (T_g , T_m) of the compound.

[0016] In the processes, the physical property parameter may include at least one of the following: (i) the hard segment content of the overall compound; (ii) the molecular weight the overall compound; (iii) the stoichiometry of the overall compound; (iv) the molecular weight of a polyol component; (v) the hydrophilicity of the overall compound; (vi) the difference in polarity between the soft segments and the hard segments of the overall

compound; (vii) the difference in the degree of hydrogen bonding between the soft segments and hard segments; (viii) the molecular weight of the soft segment; and (ix) the crystallinity of the overall compound.

[0017] In some embodiments, the physical property parameter includes the stoichiometry of the overall compound, which can be adjusted by varying the molar ratio of the polyol derived component to the chain extender derived component; and/or the molar ratio of isocyanate to any active hydrogen groups, for example any hydroxyl groups, in the formulation.

[0018] In some embodiments, the physical property may include tensile strength and/or hardness and the physical property parameter includes the molecular weight of the overall compound and/or the hard segment content.

[0019] In some embodiments, the physical property may include stiffness and the physical property parameter includes the hard segment content and/or the hydrophilicity of a polyol-derived component of the thermoplastic polyurethane.

[0020] In some embodiments, the degradation rate parameter includes the quantity of bioabsorbable units in a backbone structure of the overall compound, wherein bioabsorbable units includes hydrolysable units, enzymatically cleavable units, or combinations thereof. The hydrolysable units and enzymatically cleavable units can be derived from the chain extender and/or the polyol.

[0021] The invention provides a process of preparing a bioabsorbable thermoplastic polyurethane compound by adjusting the formulation of a base thermoplastic polyurethane compound in order to generate a bioabsorbable thermoplastic polyurethane compound with the desired combination of properties, and more specifically the desired degradation rate in combination with one or more desired physical properties. In some embodiments, the base thermoplastic polyurethane is a TPU with the desired physical properties but not the desired degradation rate. In some embodiments, the base thermoplastic polyurethane is a TPU with the desired degradation rate but not the desired physical properties. In some embodiments, the base thermoplastic polyurethane is a TPU with close to the desired physical

properties but not the desired degradation rate. In some embodiments, the base thermoplastic polyurethane is a TPU with close to the desired degradation rate but not the desired physical properties. In some embodiments, the base thermoplastic polyurethane is a TPU with close to the desired degradation rate and close to the desired physical properties, in other words a readily available TPU whose properties are as close to the desired properties as possible. The processes of the present invention are then used to adjust the formulation of the TPU so that the end result is a modified TPU with the desired combination of properties.

[0022] In some embodiments of the processes, the desired degradation rate is higher than that of a base thermoplastic polyurethane compound, and the adjusting of the degradation rate of the thermoplastic polyurethane is accomplished, independent of any adjustment of one or more physical properties of the base thermoplastic polyurethane compound, by at least one of: (a) increasing the number of bioabsorbable units in the backbone structure of the base thermoplastic polyurethane compound per unit length of the backbone; (b) increasing the hydrophilicity of the base thermoplastic polyurethane compound; (c) increasing the molecular weight of the polyol-derived component; (d) decreasing the hard segment content of base thermoplastic polyurethane compound; and (e) decreasing the crystallinity of the base thermoplastic polyurethane compound. The use of one or more of these adjustors allows the process to result in a bioabsorbable thermoplastic polyurethane compound with the desired degradation rate.

[0023] In some embodiments of the processes, the desired degradation rate is lower than that of a base thermoplastic polyurethane compound, and wherein the adjusting of the degradation rate of the thermoplastic polyurethane is accomplished, independent of any adjustment of one or more physical properties of the base thermoplastic polyurethane compound, by at least one of: (a) decreasing the number of bioabsorbable units in the backbone structure of the base thermoplastic polyurethane compound per unit length of the backbone; (b) decreasing the hydrophilicity of the base thermoplastic polyurethane compound; (c) decreasing the molecular weight

of the polyol-derived component; (d) increasing the hard segment content of base thermoplastic polyurethane compound; and (e) increasing the crystallinity of the base thermoplastic polyurethane compound. The use of one or more of these adjustors allows the process to result in a bioabsorbable thermoplastic polyurethane compound with the desired degradation rate.

[0024] In some embodiments of the processes, the desired physical property of the thermoplastic polyurethane compound is higher than the physical property of a base thermoplastic polyurethane compound, and wherein the adjusting of the physical property the thermoplastic polyurethane is accomplished, independent of any adjustment of the degradation rate of the thermoplastic polyurethane, by at least one of: (a) increasing the hard segment content of the base thermoplastic polyurethane compound by altering a ratio of a polyol to a chain extender in the formulation; (b) increasing the molecular weight of the base thermoplastic polyurethane compound by varying a stoichiometric ratio of isocyanate to an amount of active hydrogen groups in the thermoplastic polyurethane compound; (c) increasing the crystallinity of the polyol-derived component; and (d) increasing the difference in polarity between hard segment components and soft segment components of the base thermoplastic polyurethane. The use of one or more of these adjustors allows the process to result in a bioabsorbable thermoplastic polyurethane compound with the desired physical property.

[0025] In some embodiments of the processes, the desired physical property of the thermoplastic polyurethane compound is lower than the physical property of a base thermoplastic polyurethane compound, and wherein the adjusting of the physical property of the thermoplastic polyurethane is accomplished, independent of any adjustment of the degradation rate of the thermoplastic polyurethane, by at least one of: (a) decreasing the hard segment content of the base thermoplastic polyurethane compound by altering the ratio of a polyol to a chain extender in the formulation; (b) decreasing the molecular weight of the base

-10-

thermoplastic polyurethane compound by varying a stoichiometric ratio of isocyanate to an amount of active hydrogen groups in the thermoplastic polyurethane compound; (c) decreasing the crystallinity of a polyol-derived component; and (d) decreasing the difference in polarity between hard segment components and soft segment components of the base thermoplastic polyurethane. The use of one or more of these adjustors allows the process to result in a bioabsorbable thermoplastic polyurethane compound with the desired physical property.

[0026] In some embodiments of the processes, the desired tensile strength of the thermoplastic polyurethane compound is higher than the tensile strength of a base thermoplastic polyurethane compound, and wherein the adjusting of the tensile strength the thermoplastic polyurethane is accomplished, independent of any adjustment of the degradation rate of the thermoplastic polyurethane, by at least one of: (a) increasing the hard segment content of the base thermoplastic polyurethane compound by altering a ratio of a polyol to a chain extender in the formulation; (b) increasing the molecular weight of the base thermoplastic polyurethane compound by varying a stoichiometric ratio of isocyanate to an amount of active hydrogen groups in the thermoplastic polyurethane compound; (c) increasing the crystallinity of the polyol-derived component; and (d) increasing the difference in polarity between hard segment components and soft segment components of the base thermoplastic polyurethane. The use of one or more of these adjustors allows the process to result in a bioabsorbable thermoplastic polyurethane compound with the desired tensile strength.

[0027] In some embodiments of the processes, the desired tensile strength of the thermoplastic polyurethane compound is lower than the tensile strength of a base thermoplastic polyurethane compound, and wherein the adjusting of the tensile strength of the thermoplastic polyurethane is accomplished, independent of any adjustment of the degradation rate of the thermoplastic polyurethane, by at least one of: (a) decreasing the hard segment content of the base thermoplastic

polyurethane compound by altering the ratio of a polyol to a chain extender in the formulation; (b) decreasing the molecular weight of the base thermoplastic polyurethane compound by varying a stoichiometric ratio of isocyanate to an amount of active hydrogen groups in the thermoplastic polyurethane compound; (c) decreasing the crystallinity of a polyol-derived component; and (d) decreasing the difference in polarity between hard segment components and soft segment components of the base thermoplastic polyurethane. The use of one or more of these adjustors allows the process to result in a bioabsorbable thermoplastic polyurethane compound with the desired tensile strength.

[0028] In some embodiments of the processes, the hardness of the thermoplastic polyurethane compound is higher than the hardness of a base thermoplastic polyurethane compound, and wherein the adjusting of the hardness the thermoplastic polyurethane is accomplished, independent of any adjustment of the degradation rate of the thermoplastic polyurethane, by at least one of: (a) increasing the hard segment content of the base thermoplastic polyurethane compound by altering a ratio of a polyol to a chain extender in the formulation; (b) decreasing the molecular weight of the polyol component used to prepare the base thermoplastic polyurethane compound; and (c) increasing the crystallinity of the polyol-derived component. The use of one or more of these adjustors allows the process to result in a bioabsorbable thermoplastic polyurethane compound with the desired hardness.

[0029] In some embodiments of the processes, the desired hardness of the base thermoplastic polyurethane compound is lower than the hardness of a base thermoplastic polyurethane compound, and wherein the adjusting of the hardness of the thermoplastic polyurethane is accomplished, independent of any adjustment of the degradation rate of the thermoplastic polyurethane, by at least one of: (a) decreasing the hard segment content of the base thermoplastic polyurethane compound by altering a ratio of a polyol to a chain extender in the formulation; (b) increasing the molecular weight of the polyol component used to prepare the base thermoplastic polyurethane

compound; and (c) decreasing the crystallinity of the polyol-derived component. The use of one or more of these adjustors allows the process to result in a bioabsorbable thermoplastic polyurethane compound with the desired hardness.

[0030] In some embodiments of the processes, the desired moisture permeability of the thermoplastic polyurethane compound is higher than the moisture permeability of a base thermoplastic polyurethane compound, and wherein the adjusting of the moisture permeability the thermoplastic polyurethane is accomplished, independent of any adjustment of the degradation rate of the thermoplastic polyurethane, by at least one of: (a) decreasing the hard segment content of the base thermoplastic polyurethane compound by altering a ratio of a polyol to a chain extender in the formulation; (b) decreasing the molecular weight of the polyol component used to prepare the base thermoplastic polyurethane compound; (c) increasing the crystallinity of the polyol-derived component; and (d) increasing the hydrophilicity of the polyol component used to prepare the base thermoplastic polyurethane. The use of one or more of these adjustors allows the process to result in a bioabsorbable thermoplastic polyurethane compound with the desired moisture permeability.

[0031] In some embodiments of the processes, the desired moisture permeability of the thermoplastic polyurethane compound is lower than the moisture permeability of a base thermoplastic polyurethane compound, and wherein the adjusting of the moisture permeability of the thermoplastic polyurethane is accomplished, independent of any adjustment of the degradation rate of the thermoplastic polyurethane, by at least one of: (a) increasing the hard segment content of the base thermoplastic polyurethane compound by altering a ratio of a polyol to a chain extender in the formulation; (b) increasing the molecular weight of the polyol component used to prepare the base thermoplastic polyurethane compound; (c) decreasing the crystallinity of the polyol-derived component; and (d) decreasing the hydrophilicity of the polyol component used to prepare the base thermoplastic polyurethane. The use of one or more of these adjustors

allows the process to result in a bioabsorbable thermoplastic polyurethane compound with the desired moisture permeability.

[0032] In all of the processes described above, it is important to note that many, if not all, of the variables described as impacting the degradation rate and/or one or more physical properties of the thermoplastic polyurethane may in actually cause a multitude of effects, some of which change the described property in the direction as noted, and some of which change the described property in a different direction or even no direction at all. The direction of change listed for each variable is considered to be direction of change resulting from the overall combination of effects caused by the variable and/or the direction of change for the primary effect caused by the variable. The impact of these variables, and the means to balance their effects to achieve the desired goal, may require some iteration and/or experimentation, but in view of the teachings of this invention such experimentation would not be lengthy or undue in nature, and would allow the user to reach the goal (the desired combination of properties) quickly and efficiently.

[0033] In some embodiments, the degradation rate is expressed as a function of at least one of: a change in molecular weight with time, a change in tensile strength with time, and a change in weight of the polymer with time.

[0034] In some embodiments, the polyisocyanate comprises an aliphatic diisocyanate, the polyol is selected from the group consisting of polyester polyols, polyether polyols, and combinations and derivatives thereof, and the chain extender is selected from the group consisting of diols, diamines, and combinations thereof.

[0035] In some embodiments, the isocyanate is selected from the group consisting of 4,4'-methylene dicyclohexyl diisocyanate (HMDI), 1,6-hexane diisocyanate (HDI), 1,4-butane diisocyanate (BDI), L-lysine diisocyanate (LDI), 2,4,4-trimethylhexamethylenediisocyanate, and combinations thereof. In some embodiments, the polyol is selected from the group consisting of poly lactic acid (PLA), polyglycolic acid (PGA), polybutylene adipate,

polybutylene succinate, poly-1,3-propylene succinate, polycaprolactone, poly(lactide-co-caprolactone), copolymers of two or more thereof, and mixtures thereof. In some embodiments, the chain extender is selected from the group consisting of 1,4-butanediol, 2-ethyl-1,3-hexanediol (EHD), 2,2,4-trimethyl pentane-1,3-diol (TMPD), 1,6-hexanediol, 1,4-cyclohexane dimethanol, 1,3-propanediol, diethylene glycol, dipropylene glycol, and combinations thereof.

[0036] The bioabsorbable unit of the polyol may be derived from lactic acid, glycolic acid, caprolactone, or a combination thereof.

[0037] The present invention also provides for a bioabsorbable thermoplastic polyurethane compound, tailored for a medical application, where the compound comprises the reaction product of a polyisocyanate component, a diol chain extender component, and optionally a polyol component, wherein at least one of the components contains hydrolyzable units such that the resulting compound contains hydrolyzable units in its backbone. The degradation rate of the compound is set by adjusting one or more degradation rate parameters and at least one physical property of the compound is set by adjusting one or more physical property parameters. The bioabsorbable thermoplastic polyurethane compound thus has at least one physical property and a degradation rate which are independently set.

[0038] The bioabsorbable thermoplastic polyurethane compound of the invention may be a bioabsorbable thermoplastic polyurethane compound with a degradation rate higher than that of a base thermoplastic polyurethane compound on which the bioabsorbable thermoplastic polyurethane compound is based. The degradation rate of the base thermoplastic polyurethane compound can be adjusted to the higher rate of the bioabsorbable thermoplastic polyurethane compound, independent of any adjustment of one or more physical properties of the base thermoplastic polyurethane compound, by at least one of: (a) increasing the number of bioabsorbable units in the backbone structure of the base thermoplastic polyurethane compound per unit length of the backbone; (b) increasing the hydrophilicity of the base thermoplastic polyurethane compound; (c)

increasing the molecular weight of the polyol-derived component; (d) decreasing the hard segment content of base thermoplastic polyurethane compound; and (e) decreasing the crystallinity of the base thermoplastic polyurethane compound.

[0039] The bioabsorbable thermoplastic polyurethane compound of the invention may be a bioabsorbable thermoplastic polyurethane compound with a degradation rate lower than that of a base thermoplastic polyurethane compound on which the bioabsorbable thermoplastic polyurethane compound is based. The degradation rate of the base thermoplastic polyurethane compound can be adjusted to the lower rate of the bioabsorbable thermoplastic polyurethane compound, independent of any adjustment of one or more physical properties of the base thermoplastic polyurethane compound, by at least one of: (a) decreasing the number of bioabsorbable units in the backbone structure of the base thermoplastic polyurethane compound per unit length of the backbone; (b) decreasing the hydrophilicity of the base thermoplastic polyurethane compound; (c) decreasing the molecular weight of the polyol-derived component; (d) increasing the hard segment content of base thermoplastic polyurethane compound; and (e) increasing the crystallinity of the base thermoplastic polyurethane compound.

[0040] The bioabsorbable thermoplastic polyurethane compound of the invention may be a bioabsorbable thermoplastic polyurethane compound with one or more physical properties, for example tensile strength, higher than those of a base thermoplastic polyurethane compound on which the bioabsorbable thermoplastic polyurethane compound is based. The physical property, such as the tensile strength of the base thermoplastic polyurethane compound, can be adjusted to the higher tensile strength of the bioabsorbable thermoplastic polyurethane compound, independent of any adjustment of the degradation rate of the thermoplastic polyurethane, by at least one of: (a) increasing the hard segment content of the base thermoplastic polyurethane compound by altering a ratio of a polyol to a chain extender in the formulation; (b) increasing the molecular weight of the

base thermoplastic polyurethane compound by varying a stoichiometric ratio of isocyanate to an amount of active hydrogen groups in the thermoplastic polyurethane compound; (c) increasing the crystallinity of the polyol-derived component; and (d) increasing the hydrogen bonding between hard segment components and soft segment components of the base thermoplastic polyurethane.

[0041] The bioabsorbable thermoplastic polyurethane compound of the invention may be a bioabsorbable thermoplastic polyurethane compound with one or more physical properties, for example, tensile strength, lower than those of a base thermoplastic polyurethane compound on which the bioabsorbable thermoplastic polyurethane compound is based. The physical property, such as the tensile strength of the base thermoplastic polyurethane compound, can be adjusted to the lower tensile strength of the bioabsorbable thermoplastic polyurethane compound, independent of any adjustment of the degradation rate of the thermoplastic polyurethane, by at least one of: (a) decreasing the hard segment content of the base thermoplastic polyurethane compound by altering the ratio of a polyol to a chain extender in the formulation; (b) decreasing the molecular weight of the base thermoplastic polyurethane compound by varying a stoichiometric ratio of isocyanate to an amount of active hydrogen groups in the thermoplastic polyurethane compound; (c) decreasing the crystallinity of a polyol-derived component; and (d) decreasing the difference in polarity between hard segment components and soft segment components of the base thermoplastic polyurethane.

[0042] In some embodiments, the bioabsorbable thermoplastic polyurethane compound is prepared from an aliphatic diisocyanate; a polyol selected from the group consisting of polyester polyols, polyether polyols, and combinations and derivatives thereof; a chain extender selected from the group consisting of diols, diamines, and combinations thereof.

[0043] In some embodiments, the bioabsorbable thermoplastic polyurethane compound is prepared from a isocyanate selected from the group consisting of 4,4'-methylene dicyclohexyl diisocyanate (HMDI), 1,6-

hexane diisocyanate (HDI), 1,4-butane diisocyanate (BDI), L-lysine diisocyanate (LDI), 2,4,4-trimethylhexamethylene diisocyanate, and combinations thereof; a polyol selected from the group consisting of poly lactic acid (PLA), polyglycolic acid (PGA), polybutylene adipate, polybutylene succinate, poly-1,3-propylene succinate, polycaprolactone, poly(lactide-co-caprolactone), copolymers of two or more thereof, and mixtures thereof; and a chain extender is selected from the group consisting of 1,4-butanediol, 2-ethyl-1,3-hexanediol (EHD), 2,2,4-trimethyl pentane-1,3-diol (TMPD), 1,6-hexanediol, 1,4-cyclohexane dimethanol, 1,3-propanediol, diethylene glycol, dipropylene glycol, and combinations thereof.

[0044] In some embodiments, the bioabsorbable thermoplastic polyurethane compound contains bioabsorbable units derived from lactic acid, glycolic acid, caprolactone, or a combination thereof, where such units may have been present in the polyol and/or the chain extender used to prepare the bioabsorbable thermoplastic polyurethane compound.

[0045] It is noted that while the processes of the invention provide the ability to independently and continuously adjust both the degradation rate and the physical properties of a TPU composition based on an understanding of the way that the TPU physical properties and degradation rates interact with each other, each of the variables identified for adjusting the degradation rate and the physical properties of a TPU are very often interrelated with one another and can have an impact on physical properties and degradation rates. That is, changing any one of these identified variables may impact the physical properties and degradation rates of a TPU, but the process of the invention, through coordinated adjustment of two or more of these variables allow for the physical properties and degradation rates of the TPU to be independently set.

[0046] While some similar TPU materials which contain similar structures and which are claimed to be biosorbable have been reported in the literature, there are nowhere in the literature reported materials of this type wherein the degradation rate and the physical properties can be independently and continuously adjusted to specifically match the

-18-

requirements of the medical application or even the requirements of the individual patient. This capability, although widely recognized by the medical community as highly desirable for their therapeutic usefulness has never before been reported. Our disclosure of such materials as well as a process for producing such a highly useful and novel class of materials, which contains an essentially infinite number of materials differing in properties and degradation rates and which fill in the gaps where materials which have previously been describe are not currently available is, therefore, surprising and of high value in the biomedical device industry.

DETAILED DESCRIPTION

[0047] Aspects of the invention relate to a process for the preparation of bioabsorbable polymers which may be prepared to have physical properties and degradation rates chosen and independently set. The invention allows both the physical and mechanical properties and the biodegradation rates of polymers to be independently modified to precisely match the needs of the application or to fit a particular patient profile. The described bioabsorbable polymers, through minor variations of ratios and/or specific identifies of ingredients used, allow significant differences in bioabsorption rate and physical properties to be achieved independently of one another.

[0048] As used herein, a bioabsorbable polymer is a polymer which when placed into the body of a human or animal subject is degraded and/or absorbed by the body, for example, by hydrolyzation and/or enzymatic cleavage. The bioabsorption properties of the polymer are simulated through measurable biodegradation properties. A bioabsorbable polymer thus has one or more biodegradation properties, such as a change in molecular weight with time, a change in tensile strength with time, a change in weight of the polymer with time, or a combination thereof when placed in the body. The biodegradation property can be estimated, for example, through *in vitro* measurements in conditions which simulate the conditions to which the bioabsorbable polymer is expected to be exposed in the body. The measured change in the biodegradation property, under such test

conditions is generally no less than 10% over the course of a year. However, a wide variation in the biodegradation properties of the exemplary polymers is provided in order to enable candidate polymers to be identified which cover a range of the biodegradation property.

[0049] The bioabsorbable polymers of the invention include bioabsorbable thermoplastic polyurethane compounds. A thermoplastic polyurethane is a polyurethane which includes hard segments and soft segments. The hard segments are generally derived from an isocyanate and a chain extender. The soft segments are derived from a polyol. The term “polyurethane” as used herein includes polyureas and compounds with both urethane and urea linkages.

[0050] The soft segment provides some or all of the biodegradation properties of the polymer, although in some embodiments, at least some of the degradation properties are influenced and/or provided by the chain extender.

[0051] The thermoplastic polyurethane compound (TPU) can thus be a multi-block copolymer which is the reaction product of a) at least one polyol, b) at least one chain extender, c) at least one isocyanate, and d) optionally at least one catalyst, and e) optionally at least one additive, other than the components a), b), c) and d).

[0052] Component (a) provides the soft segment of the final TPU material. Suitable polyols include OH-terminated oligomeric glycols, such as polyether polyols, polyester polyols, and mixtures and derivatives thereof. Exemplary polyether polyols include polyethylene glycol (PEG), and poly(trimethylene oxide) glycol (PTMEG). Exemplary polyester polyols include aliphatic polyester polyols, such as copolymers of a cyclic lactone (such as lactide, glycolide, acetolactone, beta-propiolactone, caprolactone, valerolactone, butyrolactone, pivalolactone, or decalactone) and an α -hydroxy acid or ester thereof (such as lactic acid or glycolic acid), and polymer blends thereof. Examples of such polyester polyols include poly(lactide-co-caprolactone), and poly(glycolide-co-caprolactone). Other exemplary polyester polyols include polylactic acid, polyalkylene adipates

(such as poly(butylene adipate), poly(ethylene adipate), poly(hexamethylene adipate), poly(tetramethylene-co-hexamethylene adipate)), succinates (such as poly(butylene succinate), poly-(1,3-propylene succinate)), polycarbonate polyols (such as poly(hexamethylene carbonate), poly(pentamethylene carbonate), poly(trimethylene carbonate)), copolymers of two or more thereof, and mixtures thereof. Component (a) can also be the condensation product of a short (e.g., MW (400 – 1000Mn)) polyester glycol and an α -hydroxy acid, such as lactic acid, glycolic acid, or a mixture thereof. Component (a) can also be the condensation product of an α -hydroxy acid, an alkylene diacid (such as one or more of adipic acid, succinic acid, sebacic acid, azelaic acid), and an alkylene diol (such as one or more of ethylene glycol, propylene glycol, butanediol, hexanediol). Component (a) can also be an alpha, omega-hydroxy telechelic random copolymer of at least one of a cyclic lactone, a carbonate, and an ester monomer, such as D-lactide, L-lactide, meso-lactide, glycolide, dioxanone, trimethyl carbonate, acetolactone, propiolactone, butyrolactone, valerolactone, and caprolactone. One particularly suitable polyol includes poly(lactide-co-caprolactone) or a derivative thereof.

[0053] In some embodiments, the polyol component may also include a diamine, including any of the diamines described herein, as well as any similarly active-hydrogen compounds that are reactive with isocyanate groups. The hydroxyl groups of the polyols described above being one of the most suitable examples.

[0054] The mole ratio of cyclic lactone (e.g., caprolactone) to α -hydroxy acid (e.g., lactic acid) in the copolymer can be about 95:5 to about 30:70, such as from 45:55 to 30:70 or from about 95:5 to about 5:95.

[0055] The polyester/polyether polyols can be random, block, segmented, tapered blocks, graft, tri-block, etc., having a linear, branched, or star structure.

[0056] The weight average molecular weight of component (a) (polyol) within the exemplary polymer can be up to 20,000, and in one embodiment, up to 10,000, such as in the range of 500 – 5000. A glass transition

temperature of component a) can be lower than ambient temperature (e.g., lower than 25°C) and in one embodiment, lower than 0°, or lower than -15°C.

[0057] The chemical composition of component (a) can be chosen so that it is sufficiently different in polarity, has the ability to hydrogen-bond, and other such properties known to those skilled in the art so that it will effectively phase separate from the hard segment of the multi-block copolymer that is formed on reaction of the various components. Lack of phase separation can result in the properties of the final product being compromised, although for some applications, such lack of phase separation may be acceptable or even useful.

[0058] Component (b) is generally a low molecular weight diol or diamine chain extender. Suitable chain extenders include diols, diamines, and combinations thereof. Exemplary chain extenders include alkane diols of from 1-30 carbon atoms, ethylene glycol, 1,3-propanediol, 1,2-propanediol, 1,4-butanediol, pentanediol, hexamethylenediol, heptanediol, nonanediol, dodecanediol, 2-ethyl-1,3-hexanediol (EHD), 2,2,4-trimethyl pentane-1,3-diol (TMPD), 1,6-hexanediol, 1,4-cyclohexane dimethanol, diethylene glycol, dipropylene glycol, and combinations thereof. Suitable diamine chain extenders can be aliphatic or aromatic in nature, such as alkylenediamines of from 1-30 carbon atoms (e.g., ethylenediamine, butanediamine, hexamethylenediamine). Component (b) can also be synthesized by condensation of an alpha-hydroxy acid, such as lactic acid, glycolic acid, or a mixture thereof, with a small alkylenediol and/or hydroxyl amine molecule of from 1-20 carbon atoms, such as ethylene glycol, butanediol, hexamethylenediol, ethanolamine, aminobutanol, or a mixture thereof. Component (b) can also be synthesized by condensation of an alpha-amino acid such as glycine, lysine or similar amino acids with a small alkylene diol molecule of from 1-20 carbon atoms such as ethylene glycol, butane diol, hexamethylene diol or a mixture of thereof.

[0059] The chain extender can have a number-average molecular weight M_n of up to 2000 and in some embodiments, up to 1000, such as for example, 100 to 700.

[0060] Component (c) can be a diisocyanate. Suitable isocyanates include aliphatic diisocyanates, such as 4,4'-methylene dicyclohexyl diisocyanate (HMDI), 1,6-hexane diisocyanate (HDI), 1,4-butane diisocyanate (BDI), L-lysine diisocyanate (LDI), 2,4,4-trimethylhexamethylenediisocyanate, other similar diisocyanate, and mixtures thereof. Other diisocyanates which can be used include aromatic diisocyanates such as toluene diisocyanate (TDI), 2,4'-methylene diphenyl diisocyanate, and 4,4'-methylene diphenyl diisocyanate, and mixtures thereof.

[0061] Component (c) can be used in an approximately stoichiometrically equivalent amount to the total amount of hydroxyls and amine groups (where present) in the formulation (i.e., in components a) and b)) such that the number of moles of isocyanate groups is equal to the number of moles of hydroxyl and amine groups. This favors high MW TPUs with material properties suited to many biomedical applications. By adjusting this ratio slightly, the molecular weight of the TPU can be controlled to within a desired range. In one embodiment, a molar ratio of isocyanate groups to hydroxyl plus amine groups is in a range of 0.8-1.2. Alternatively or additionally, a monofunctional alcohol, amine, or isocyanate molecule can be utilized in combination with the diisocyanate for controlling the final TPU MW.

[0062] Component (d) can be any suitable urethane polymerization catalyst. Some specific examples include metal alkyls, chlorides, esters, and carboxylates, and mixture thereof. Amines, such as tri(m)ethylamine, triethylenediamine, N-(m)ethylmorpholine, dimethylcyclohexylamine, N,N'-dimethylpiperazine, dimethylaniline, N,N,N',N'-tetramethylethylenediamine, 1,8-diazobicyclo[5,4,0]undec-7-ene, and tri(dimethylaminomethyl)phenol, can also be used as catalysts. In some cases, a catalyst is not needed. For example, it can be dispensed with when the polymerization kinetics are

sufficiently fast to produce a high MW TPU in a reasonable amount of time. A weight ratio of catalyst (d) to components (a)+(b)+(c) can be from 0:1 to 0.1:1, e.g., at least 0.0001:1.

[0063] Component (e) is also an optional ingredient and can include one or more performance additives such as process aids, antioxidants, UV-stabilizers, light stabilizers, lubricants, mineral and/or inert fillers, colorants, opacifying pigments, and mixtures thereof. A weight ratio of component (e) to components (a)+(b)+(c)+(d) can be from 0:1 to 10:1, e.g., 0.001:1 to 1:1.

[0064] The hard segment content (%HS) of the copolymer (i.e., the combined content of the components derived from the chain extender and isocyanate, expressed by weight percentage) can range from 2-100 wt. %, 2-95 wt%, and in one embodiment, is at least 5 wt. % or at least 10 wt. %, for at least one of the polymers forming the set of the bioabsorbable polymers. In one embodiment, the set of polymers includes at least one polymer in each of two or more, or at least three, or at least four non-overlapping ranges, such as selected from the following ranges:

i) up 10 %HS; ii) 10-15 %HS, iii) 15-20 %HS, iv) 20-30 %HS; v) 30-40 %HS; vi) 40-50 %HS; vii) 50-60 %HS; viii) 60-70 %HS; ix) >70 %HS, and even x) 100%HS (where the hard segment is based on amino acid based chain extenders, and no soft segment derived from a polyol is present in the TPU).

[0065] The soft segment content (%SS) of the copolymer (i.e., the percentage by weight of the components derived from the polyol) can range from 5-95%, and in one embodiment, is at least 25% or at least 40%, for at least one of the polymers forming the set of the bioabsorbable polymers. In one embodiment, the set of polymers includes at least one polymer in each of two or more, or at least three, or at least four non-overlapping ranges, such as selected from the following ranges:

i) up 20 %SS; ii) 20-30 %SS; iii) 30-40 %SS; iv) 40-50 %SS; v) 50-60 %SS; vi) 60-70 %SS; vii) 70-80 %SS; viii) 80-90 %SS; and ix) >90 %SS.

[0066] The soft segment content can be determined by subtracting the hard segment content from 100%.

[0067] The bioabsorbable polymers include at least one bioabsorbable unit. A bioabsorbable unit is one which undergoes hydrolysis and/or enzymatic cleavage under conditions similar to those which the polymer is expected to be exposed in the body. In general, the polyol includes at least one bioabsorbable unit. In one embodiment, the bioabsorbable unit is derived from an α -hydroxy acid, such as poly lactic acid (PLA) in the soft segment. In other embodiments, at least some of the bioabsorbable units are in the hard segment, e.g., derived from the chain extender.

[0068] The bioabsorbable unit content (e.g., α -hydroxy acid content) of the soft segment of the copolymer, expressed as a percentage by weight % (% PLA) can range from 2-70 wt. %. In one embodiment, the set of polymers includes at least one polymer in each of two or more, or at least three, or at least four non-overlapping ranges, such as selected from the following ranges:

i) up 5 % PLA; ii) 5-10 % PLA; iii) 10-15 % PLA; iv) 15-20 % PLA; v) 20-30 % PLA; vi) 30-40 % PLA; vii) 40-50 % PLA; viii) 50-60 % PLA; >60 % PLA.

[0069] The exemplary polymers are useful for a wide variety of biomedical applications. The polymers can be readily tailored to provide selected biodegradation properties and physical and mechanical properties that are suited for a specific application/patient.

[0070] As will be appreciated, the steps of the method need not all proceed in the order illustrated and fewer, more, or different steps.

Physical Property

[0071] The physical property described above can be selected from a finite set of physical properties. By way of example, the selectable physical properties may include one or more of the following: tensile strength, hardness, stiffness (flexibility), resilience, abrasion resistance, impact resistance, coefficient of friction (on the surface of the TPU), creep, modulus of elasticity, thermal transition points (T_g , T_m), water absorption, moisture permeability, contact angle, electrostatic properties such as surface and volume resistivity and conductivity, and combinations thereof.

[0072] Methods for determining some of these properties and the units in which they can be expressed are given by way of example.

[0073] Tensile strength: This can be determined according to ASTM D638 - 10 Standard Test Method for Tensile Properties of Plastics. Exemplary polymers have initial tensile strengths, according to this test method, in the range of 5 – 80 MPa, such as 35-70MPa. Percentage change in tensile strength can be used as a degradation property, as noted below. The set of polymers contemplated by the invention may include polymers which are adjusted in their tensile strength by at least 5 MPa, or at least 10 MPa, or at least 20 MPa, or vary by at least 10%, or at least 20%, or at least 30%.

[0074] Hardness: This can be determined according to ASTM D2240-05(2010) Standard Test Method for Rubber Property—Durometer Hardness, DOI: 10.1520/D2240-05R10. Exemplary polymers have a hardness, according to this test method in the range of 60 Shore A – 85 Shore D, e.g., 65-95 Shore A or even 65-75 Shore A. The set of polymers contemplated by the invention may include polymers which are adjusted in their hardness by at least 5 Shore A, or at least 10 Shore A, or at least 20 Shore A, or vary by at least 10%, or at least 20%.

[0075] Stiffness (flexibility): This can be determined according to ASTM D790-10 Standard Test Methods for Flexural Properties of Unreinforced and Reinforced Plastics and Electrical Insulating Materials, DOI: 10.1520/D0790-10. Exemplary polymers have a stiffness, according to this test method, in the range of 5–15000 MPa. The set of polymers contemplated by the invention may include polymers which are adjusted in their stiffness by at least 5 MPa, or at least 20 MPa, or at least 1000 MPa, or vary by at least 10%, or at least 20%, or at least 30%.

[0076] Resilience (rebound): This can be determined according to ASTM D2632-01(2008) Standard Test Method for Rubber Property—Resilience by Vertical Rebound, DOI: 10.1520/D2632-01R08. Exemplary polymers have a resilience, according to this test method, in the range of 1-95%, such as 30-80%. The set of polymers contemplated by the invention may include

polymers which are adjusted in their resilience by at least 5%, or at least 10%, or at least 20%.

[0077] Abrasion resistance: This can be determined according to ASTM D3389-10 Standard Test Method for Coated Fabrics Abrasion Resistance (Rotary Platform Abrader); DOI: 10.1520/D3389-10 (Taber, H18 wheel, 1000g). Exemplary polymers have an abrasion resistance, according to this test method, in the range of 2 – 400 mg/1000 cycles, such as 2 – 100 mg/1000 cycles. The set of polymers contemplated by the invention may include polymers which are adjusted in their abrasion resistance by at least 5 mg, or at least 10 mg, or at least 20 mg, or vary by at least 10%, or at least 20%, or at least 30%.

[0078] Impact Resistance (Izod): This can be determined according to ASTM D256-10 Standard Test Methods for Determining the Izod Pendulum Impact Resistance of Plastics; DOI: 10.1520/D0256-10. Exemplary polymers have an impact resistance, according to this test method, in the range of No failure - 10 ft-lb/in, such as No failure - 2 ft-lb/in. Percentage change in impact resistance can be used as a degradation property, as noted below. The set of polymers contemplated by the invention may include polymers which are adjusted in their impact resistance by at least 1 ft-lb/in or at least 2 ft-lb/in, or vary by at least 10%, or at least 20%.

[0079] Coefficient of friction (on the surface of the TPU): This can be determined according to ASTM D1894-11e1 Standard Test Method for Static and Kinetic Coefficients of Friction of Plastic Film and Sheeting, DOI: 10.1520/D1894-11E01. Exemplary polymers have a coefficient of friction, according to this test method, in the range of 0.5 - 10. The set of polymers contemplated by the invention may include polymers which are adjusted in their coefficient of friction by at least 0.5, or at least 1.0, or vary by at least 5%, or at least 10%, or at least 20%.

[0080] Creep: This can be determined according to ASTM D2990-09 Standard Test Methods for Tensile, Compressive, and Flexural Creep and Creep-Rupture of Plastics, DOI: 10.1520/D2990-09. Exemplary polymers have creep, according to this test method, in the range of 5-95%, or 50-40%.

-27-

The set of polymers contemplated by the invention may include polymers which are adjusted in their creep by at least 5%, or at least 10%, or at least 20%.

[0081] Modulus of elasticity: This can be determined according to ASTM F1635-11. Exemplary polymers have a modulus of elasticity, according to this test method, in the range of 10 – 2000 MPa. The set of polymers contemplated by the invention may include polymers which are adjusted in their modulus of elasticity by at least 10 MPa, or at least 20 MPa, or at least 100 MPa, or vary by at least 5%, or at least 10%, or at least 20%.

[0082] Thermal transition points: (glass transition temperature, T_g , melting point T_m): These can be determined according to ASTM D3418 - 08 Standard Test Method for Transition Temperatures and Enthalpies of Fusion and Crystallization of Polymers by Differential Scanning Calorimetry; DOI: 10.1520/D3418-08. Exemplary polymers have a T_g , according to this test method, in the range of -60 – 50°C, e.g., -60 – 0°C, and a T_m of 80 - 200°C. The set of polymers contemplated by the invention may include polymers which are adjusted in their T_g or T_m by at least 10°C, or at least 20°C, or at least 100°C.

[0083] Water absorption: This can be determined according to ASTM D570 - 98(2010)e1 Standard Test Method for Water Absorption of Plastics; DOI: 10.1520/D0570-98R10E01. Exemplary polymers have a water absorption, according to this test method, in the range of 0.5 – 1000%, e.g., 5 – 600%. The set of polymers contemplated by the invention may include polymers which are adjusted in their water absorption by at least 10%, or at least 50%, or at least 100%.

[0084] Water Vapor Transmission (Moisture permeability): This can be determined according to ASTM E96/E96M-10 Standard Test Methods for Water Vapor Transmission of Materials, DOI: 10.1520/E0096_E0096M-10 (Upright cup, 23°C, 50%RH). Exemplary polymers have a moisture permeability, according to this test method, in the range of 0 - 900 g/m²*24h. The set of polymers contemplated by the invention may include polymers

-28-

which are adjusted in their moisture permeability by at least $10 \text{ g/m}^2 \cdot 24\text{h}$, or at least $100 \text{ g/m}^2 \cdot 24\text{h}$, or at least $500 \text{ g/m}^2 \cdot 24\text{h}$.

[0085] Of these properties, tensile strength and hardness are particularly useful.

Physical Property Parameter

[0086] Following are examples of the physical property parameters which are modifiable to reduce a difference between the desired physical property and the measured physical property, and suitable methods which can be used to measure them.

[0087] The first parameter can be selected from a predefined set of first parameters. These can include one or more of hard segment content of the thermoplastic polyurethane, molecular weight of the thermoplastic polyurethane, stoichiometry of the thermoplastic polyurethane; a molecular weight of a polyol-derived component of the thermoplastic polyurethane, a hydrophilicity of the overall component and/or the hydrophilicity of a polyol-derived component of the thermoplastic polyurethane, a difference in polarity between the soft segments and the hard segments, a difference in the degree of hydrogen bonding between the soft segments and hard segments, a molecular weight of the soft segment, a polarity of the soft segments, a crystallinity of the overall compound and/or the crystallinity of the soft segments, and combinations thereof.

[0088] These can be determined as follows:

[0089] Hard segment content of the thermoplastic polyurethane: %HS, as described above. This can be adjusted by changing a ratio of polyol to chain extender.

[0090] Molecular weight of the thermoplastic polyurethane: this can be the weight average molecular weight M_w or the number average molecular weight M_n .

[0091] Stoichiometry of the thermoplastic polyurethane. This can be described in terms of a molar ratio of the polyol derived component to the chain extender derived component in the formulation and/or by a molar ratio of isocyanate to hydroxyl groups in the formulation.

[0092] Molecular weight of a polyol-derived component of the thermoplastic polyurethane: this value may be determined by GPC, according to ASTM F1635-11, or by hydroxyl number determination. Exemplary polymers may have a molecular weight of 80-250 KDa, e.g., 100-200 KDa.

[0093] A hydrophilicity of the overall compound and/or the hydrophilicity of a polyol-derived component of the thermoplastic polyurethane. This can be estimated by measuring the contact angle of water with the polymer surface or by water swell.

[0094] A difference in polarity between the soft segments and the hard segments.

[0095] A difference in the degree of hydrogen bonding between the soft segments and hard segments.

[0096] A polarity of the soft segments.

[0097] A crystallinity of the soft segments and/or hard segments.

[0098] For example, when the physical property includes tensile strength, the first parameter can include molecular weight of the thermoplastic polyurethane and optionally also hard segment content. As another example, when the physical property includes hardness, the first parameter can include hard segment content. As another example, when the physical property includes stiffness, the first parameter can include the hard segment content %HS and the optionally hydrophilicity of the polyol-derived component of the thermoplastic polyurethane.

Degradation Rate Parameter

[0099] The degradation rates of the exemplary TPUs depend on a number of factors, which may be referred to as the degradation rate parameter. First is the number of hydrolysable units in the TPU's backbone. Generally, the higher the number of hydrolysable units in the polymer's backbone, the more rapid is the degradation rate, everything else being equal. This, however, is not the only factor that impacts degradation rate. The hydrophilicity of the TPU is also a significant contributor to the degradation rate. For a polymer to hydrolyze, it must come into contact with water and if a polymer is very

-30-

hydrophobic, the rate of degradation will be significantly lower for a given percentage of hydrolysable polymer backbone units when compared with a polymer that is more hydrophilic. This tends to be related to the HS% since the HS is significantly more hydrophobic than the soft segment and also sometimes is crystalline which makes permeation of water into the TPU less facile.

[0100] Another factor that impacts the degradation rate is the degree of crystallinity of the polymer. Since the exemplary materials are primarily for use in the body are based on aliphatic isocyanates and this type of TPU does not have crystalline hard segments like aromatic TPUs, the main contributor to crystallinity is the soft segment crystallinity. As the lactic acid content increases, the concentration of hydrolytically labile ester groups increases. Formulations based on amorphous poly(lactide-co-caprolactone) polyols with higher number of ester linkages for a given hard segment content therefore are expected to degrade faster. Lower lactic acid content based formulations are expected to degrade slower due to crystalline (more hydrophobic) nature and lower number of ester linkages.

[0101] Phase mixing, which is related to a number of factors including polyol molecular weight and overall TPU Mw, can also affect the rate of degradation. As the more hydrophobic hard phases are more phase-mixed into the hydrolysable soft segments, the overall hydrophobicity of the soft phase will increase and the degradation rate will, as a result, decrease.

[0102] In the exemplary embodiment, therefore, the degradation rate parameter, can include one or more of a finite set of parameters, such as one or more of a parameter based on a quantity of bioabsorbable units in a backbone structure of the thermoplastic polyurethane compound, the hydrophilicity of the overall compound and/or the hydrophilicity of the polyol-derived component of the thermoplastic polyurethane compound, a molecular weight of the polyol-derived component, and combinations thereof.

[0103] The parameter based on a quantity (e.g., number average, molar ratio, or the like) of bioabsorbable units in a backbone structure of the

thermoplastic polyurethane compound: this can include one or both of a quantity of hydrolysable units and a quantity of enzymatically cleavable units. This can be the %PLA in the polyol which may also contain other units which are less liable to hydrolyze, as described above, i.e., the bioabsorbable units in the soft segment. However, other components that contribute segments to the backbone of the bioabsorbable polymer, including the chain extender, may also include bioabsorbable units and these may be included in the overall quantity of bioabsorbable units.

[0104] It will be noted that some of the degradation rate parameters described above are also physical property parameters. In some embodiments, the invention includes the proviso that the one or more degradation rate parameters used in the process are each different from the one or more physical property parameters used in the process and in some cases more than one parameter must be adjusted to maintain the degradation rate while adjusting one or more physical properties to the desired level, while in other cases more than one parameter must be adjusted to maintain one or more physical properties, while adjusting the degradation rate to the desired level.

Degradation Rate

[0105] The degradation property (which may be referred to as the degradation rate) can be expressed as a function of at least one of: a change in molecular weight of the polymer with time, a change in tensile strength of the polymer with time, a change in impact resistance of the polymer with time, and a change in weight of the polymer with time. These values can be determined *in vitro*, in a suitable test environment, such as a liquid, with properties of the TPU being measured at intervals, such as days, weeks, or months. In the exemplary embodiment, these degradation properties are measured according to ASTM 1635-11.

[0106] The change in tensile strength (or impact resistance) can be expressed as a percentage of the initial value, where the initial and subsequent values are measured according to ASTM 1635-11, as described above. In some embodiments, the present invention may allow a base

thermoplastic polyurethane to be modified such that its initial tensile strength is adjusted by at least 20%, or at least 40%, or at least 60% upward, and in other embodiments by at least 20%, or at least 40%, or at least 60% downward. In still other embodiments, the adjustment may be to the tensile strength as measured 8 weeks after being inserted into the environment where the material is expected/desired to degrade (i.e., a patient's body), where the same adjustments are possible.

[0107] Weight loss: The change in weight can be measured according to ASTM 1635-11, expressed as a percentage of the initial value. The set of polymers contemplated by the invention may include polymers which are adjusted in their % change in weight over eight weeks by at least 20%, or at least 40%, or at least 60%.

[0108] Molecular Weight loss: The change in molecular weight can be measured according to ASTM 1635-11, expressed as in KDa. The set of polymers contemplated by the invention may include polymers which are adjusted in their % change in molecular weight over eight weeks by at least 20%, or at least 40%, or at least 60%.

[0109] In the Examples below, the degradation property is measured according to ASTM F1635-11 (Standard test method for *in vitro* degradation testing of hydrolytically degradable polymer resins and fabricated forms for surgical implants). This test method is specified for use with polymers that are known to degrade primarily by hydrolysis, such as homopolymers and copolymers of *L*-lactide, *D*-lactide, *D,L*-lactide glycolide, caprolactone, and *p*-dioxanone. In this test, the samples are placed in a phosphate buffered saline (PBS) solution, where the pH is maintained at 7.4+/-0.2 at 37+/-2°C. After each time period, one sample is taken out and tested for tensile strength, elongation, molecular weight, and weight loss, using the test methods described above.

[0110] The degradation property can be computed, based on these measurements, and can be expressed as, for example, a loss in the property over a specified time interval, either from the start of the immersion, or starting at a specified time thereafter. The degradation property can be

expressed in other ways, such as, for example, the time to reach a specified loss in the property such as a specified weight loss or specified percentage change in weight (e.g., a 50% weight loss), or the like.

Example Modifications

[0111] The properties of the exemplary TPU's tend to be highly dependent on the polymer's molecular weight (Mw), hard segment content (HS%), polyol chemical identity and the degree of phase separation (PS) of the TPU. The design of the polymer typically takes place by adjusting the factors (HS%, Mw, PS, polyol chemical identity, etc.) to achieve a TPU which is expected to have the approximate properties required. In order for a polymer to have a certain HS%, the ratio of polyol to chain extender can be adjusted. This would be a primary factor controlling the stiffness (flex modulus) of the polymer. The Mw of the polymer can be controlled by varying the stoichiometry (ratio of isocyanate to hydroxyl groups) or by the addition of a monofunctional hydroxyl containing component. This is a significant factor that controls the tensile strength of the polymer although hardness (HS%), phase separation and various other parameters have an effect on this as well but their effect is of a lesser extent. There are other parameters that impact the properties, which include the chemical identity and molecular weight of the polyol used to for the TPU. The chemical identity determines the hydrophilicity/hydrophobicity balance of the TPU formed (which affects water absorption and moisture permeability of the material) and some of the thermal properties of the polymer along with various other properties such as toughness and abrasion resistance. The balancing of each of these requirements for a given application can often only be an approximation, as there are numerous tradeoffs as one property is maximized others are lowered (see Table 1 below).

TABLE 1

Physical Property	Increase HS%	Increase TPU Mw	Increase Polyol mol. wt.	Increase polyol hydrophilicity
Tensile strength	Increases	Increases	Variable*	Typically decreases
Hardness	Increases	No effect	Variable*	No effect
Hydrophobicity	Variable*	Increases	Variable*	Decreases
Abrasion resistance	Increases	Increases	Increases	Typically decreases
Flexibility	Decreases	No effect	Slightly decreases	Increases
Resilience	Decreases	Increases	Increases	Decreases

**: Varies depending on the morphology (crystalline vs. amorphous) of the polyol and/or the chemical nature (polarity) of the polyol, and/or on the overall balance of effects caused by the change.*

[0112] The balancing of each of the parameters which impact degradation to give a TPU with a desired degradation rate is also an approximation, since there are numerous tradeoffs in that many of these parameters affect the degradation rate in opposite directions (see Table 2 below).

TABLE 2

Degradation Rate Parameter	Degradation rate
Increase Polyol hydrophilicity	Increases
Increase polyol mol. Wt.	Increases
Increase TPU Mw	Decreases
Increase HS%	Decreases
Increased Crystallinity	Decreases
Decrease number of hydrolysable units in polyol backbone	Decreases

[0113] The design of a bioresorbable TPU with a specified degradation rate and set of physical properties can thus involve an iterative process whereby the major controllable parameters which affect the physical properties, such as HS%, Mw, polyol molecular weight and chemical identity, stoichiometry, etc., are selected along with the parameters which affect the degradation rate such as number of hydrolysable units in the

backbone and the hydrophilicity of the polyol and the polyol molecular weight are chosen. Some parameters, such as hard segment content, may affect both the degradation rate and one or more physical properties of the bioresorbable TPU, and so in some embodiments a second, or even a third parameter is also adjusted along with the first, in order to arrive at a TPU with the desired combination of properties, that is the desired degradation rate and one or more physical properties.

[0114] This initial set of parameters is used to prepare a base TPU which and the properties and degradation rate of this material are measured. Based on the results of these initial measurements, a number of additional TPUs are produced, by varying the parameters in such a way that is designed to produce a material that more closely matches the requirements of the application. For example, to produce a material that has the same physical properties as the initial TPU but with a faster degradation rate, then the next set of materials could be prepared using a polyol that has a higher number of hydrolysable units in its backbone or which has a higher hydrophilic character compared to the first polymer.

[0115] As an example, when the desired degradation rate is higher (or respectively, lower) than that of the base thermoplastic polyurethane compound, the adjustment by the modification component can include at least one of: (a) increasing (or decreasing) a number of bioabsorbable units in a backbone structure of the base thermoplastic polyurethane compound per unit length of the backbone; (b) increasing (or decreasing) a hydrophilicity of a polyol-derived component of the thermoplastic polyurethane compound; (c) increasing (or decreasing) a molecular weight of the polyol-derived component; (d) decreasing (or increasing) a molecular weight of the thermoplastic polyurethane compound; (e) decreasing (or increasing) a hard segment content of the thermoplastic polyurethane compound; and (f) decreasing (or increasing) a crystallinity of the thermoplastic polyurethane compound.

[0116] As another example, when the desired physical property includes a tensile strength property, and the base thermoplastic polyurethane

-36-

compound has a lower (or respectively, higher) tensile strength than the desired tensile strength, the computing of the at least one thermoplastic polyurethane compound includes at least one of: (a) increasing (or decreasing) a hard segment content of the base thermoplastic polyurethane compound by altering a ratio of a polyol to a chain extender in the formulation; (b) increasing (or decreasing) a molecular weight of the base thermoplastic polyurethane compound by varying a stoichiometric ratio of isocyanate to an amount of hydroxyl groups in the thermoplastic polyurethane compound; (c) increasing (or decreasing) the crystallinity of a polyol-derived component; and (d) increasing (or decreasing) a difference in polarity between hard segment components (isocyanate and chain extender) and soft segment components (polyol) of the polymer.

Hypothetical Example:

[0117] TPU 1 has tensile strength of X, hardness of Y, and biodegradation rate of Z. If the customer seeks TPU 2 with the following:

Hardness: >Y

Tensile strength: =X

Biodegradation rate : <Z

[0118] The process may include: (1) Increasing the hard segment of TPU to increase the hardness; and/or (2) Decreasing the MW of the soft segment to compensate the tensile strength increase with increasing the hard segment; (3) Increasing the hydrolysable units in the soft segment to increase the degradation rate; or (4) Increasing the hard segment content and incorporating hydrolysable units in the hard segment and change the soft segment MW to keep the tensile strength the same.

Forming the Bioabsorbable thermoplastic polyurethane compound

[0119] Any suitable methods can be used for forming the exemplary bioabsorbable copolymers. The exemplary polyols, such as poly(lactide-co-caprolactone) polyols, are solids at room temperature and may be liquefied by heating prior to blending with the hard segment components. The polyol

may be analyzed for hydroxyl number, acid number, and moisture content, and this information can be used to allow a user to adjust the stoichiometry of the components used to prepare the TPU, for example, to obtain a TPU with a higher MW, thus adjusting one or more physical properties and/or the degradation rate of the TPU in the desired direction. By way of example only, a blend can be prepared by premixing the polyol(s) and chain extender(s) or by adding these directly to a reaction vessel. This blend can be heated to a suitable reaction temperature prior to combining with the isocyanate, with stirring, followed by addition of catalyst, if any. The temperature of the reaction can be monitored. Prior to setting or gelling, the polymer can be placed in a suitably shaped mold and cured for a suitable time at a curing temperature of, for example, 100-200°C.

[0120] Physical and degradation properties of the cured bioabsorbable polymer can then be measured and the impact of the adjusted parameters can be assessed, allowing for more accurate adjustments as needed.

[0121] Poly(lactide-co-caprolactone) polyols can be made by ring opening copolymerization of lactide and caprolactone monomers. This results in a random distribution of lactide-derived units and caprolactone-derived units in the polyol, which can be verified by NMR.

[0122] The exemplary method provides the ability to independently and continuously adjust both the degradation rate and the physical properties based on an understanding of the way that the TPU physical properties and degradation rates interact with each other. These relationships include, among others, a relationship between the M_n of the polyol in the TPU and amount of phase separation and therefore physical properties, such as rebound. At the same time, however, there is a relationship between properties that affect the degradation rate, like hydrophobicity/hydrophilicity balance in the TPU. Another such relationship is the relationship between hardness and the hydrophilicity/hydrophobicity balance of the TPU. The hydrophobicity/hydrophilicity balance is one of the key properties affecting degradation rate and hardness is one of the key properties affecting the physical and mechanical properties. Therefore, an understanding of the

detailed relationship between these factors is beneficial to the design of the TPU and reduces time-consuming trial and error. These relationships enable design of TPUs which can have any combination of physical properties and degradation rate. As a result, time consuming and costly synthesis work is minimized.

[0123] Although many different bioresorbable polymers with varying properties and degradation rates are currently commercially available, there are large gaps in properties between the commercially available materials and the degradation rate for a given material can typically not be changed without selecting a different material. The materials disclosed herein, which offer continuously variable properties and degradation rates, make this limitation no longer a factor. Also, the ability to change the degradation rate for a material with a given set of physical properties or to change the physical properties of a material with given degradation rate by minor changes in the composition/formulation of a single class of materials has not been achievable with the materials currently available. The ability to do this sort of tailoring of properties and degradation rates to precisely match the requirements of a given application will allow the medical device producer to use a polymer which possesses exactly the combination of characteristics (degradation rate, physical properties) which are optimal for their needs. As a result of this unique combination of properties and characteristics, the materials disclosed herein can find extensive use in numerous medical applications.

[0124] The method makes use of the versatile polyurethane chemistry to prepare polymers with a wide range of physical properties. The biodegradation rates of these materials can be varied by adding to the polymeric structure units which can be readily hydrolyzed. The number of hydrolysable units in the TPU backbone per unit length is a useful parameter that can be used to control the degradation rate of the exemplary TPU materials. While degradation mechanisms have been studied previously, the ability to independently and continuously vary both the physical properties and the degradation rates has not been demonstrated or

disclosed in the literature. Since TPUs have been used in implanted medical devices for many years without any significant safety issues, the exemplary materials combine the excellent toxicological aspects of the component materials used in the polymer synthesis with the opportunity to provide tailorable properties and degradation rates.

EXAMPLES

[0125] Poly(lactide-co-caprolactone) polyols with varying monomer ratios were converted to TPU using 4,4'-methylene dicyclohexyl diisocyanate-1,4-butanediol as the hard segment at 30-60 wt.% hard segment concentrations. The poly(lactide-co-caprolactone) polyols used include materials such as Perstorp's Capa™ 600422, consisting of a 2k molecular weight polyol with a composition of 88 caprolactone:12 lactide, on a molar basis. The initial synthesis, characterization and 8 week *in vitro* bioabsorption data is reported for exemplary bioabsorbable TPUs. The data provides initial results which indicate that independently controlling the physical and biodegradation properties with these materials is readily achievable.

Materials

[0126] Biodegradable copolymers poly(lactide-co-caprolactone) polyols ($M_n \sim 2000$) composed of caprolactone and lactic acid units at varying ratios were used. These were random polymers, as verified by NMR. However, no stereocenter dyad analysis was made. Poly(lactide-co-caprolactone) polyols with 12.5 and 25.0% lactide are crystalline and those with 30.0 and 50.0% lactide contents are amorphous. HMDI, butanediol, and an aliphatic diisocyanate (Desmodur W) are used as well. Cotin 430 was employed as the reaction catalyst at 100ppm.

Synthesis

[0127] The TPU's were synthesized using typical aliphatic TPU lab polymerization procedures as follows:

[0128] Most polyols are solids at room temperature and so are first liquefied in an oven. Polyols were thoroughly melted and vigorously shaken, prior to blending. If the polyol had not yet been analyzed, a 4 ounce sample

-40-

of it was submitted for hydroxyl number, acid number, and moisture content. Blends were prepared by premixing the ingredients (polyol(s) and chain extender(s)) in an appropriately sized glass jar or by weighing the ingredients directly into a reactor can. If premixing was used, then all of the blend ingredients were weighed into a glass jar, the lid was tightened, and the contents were vigorously shaken to homogenize the blend. The required amount of polyol blend was poured into the reactor tin can (the reaction can). If weighing directly into a reactor can is the preferred procedure, then all of the blend ingredients were weighed into an appropriately sized reactor cans (a quart size tin can for 400-gram). The blend was placed in the oven to equilibrate at the temperature required for the reaction. The curing pans (Teflon® coated) were preheated to the temperature required for aging. The amount of aliphatic diisocyanate (Desmodur WTM) plus an estimated amount of drain residue was weighed into an appropriately sized can, and it was placed in the oven to equilibrate at the temperature required.

[0129] As soon as the starting temperature(s) were reached, the reactor cans were removed from the oven(s) and place in the fume hood. A firmly mounted, air driven agitator was positioned approximately ¼ inch from the bottom of the reactor can. With slow stirring to avoid splashing, the appropriate amount of diisocyanate was rapidly poured into the reaction can containing the polyol blend. A short time was allowed for the diisocyanate to drain out of the can. The catalyst was added and the start temperature was recorded. The exotherm temperature was monitored every 30 to 60 seconds. Before final product began to set up or gel, the preheated Teflon® coated pan were taken from the oven, the mixer was stopped and the reaction product was poured into the preheated pan. The reaction product temperature was monitored every 30 to 60 seconds until product began to set up or gel. The product was then placed in the oven at 125°C for 5 hours. After the polymer had cured, the covered pan was removed from the oven and placed in the fume hood to cool.

Characterization:

[0130] The biodegradation test for all samples is performed using the ASTM F1635 (Standard test method for *in vitro* degradation testing of hydrolytically degradable polymer resins and fabricated forms for surgical implants), as described above. After each time period (here 2 days, 1 week, 2, 4, 8, 12, 20, 28, 36 ... weeks) one sample is taken out and tested for tensile strength, elongation, molecular weight and weight loss. Only 8 weeks data (molecular weight, tensile and elongation data) for the samples based on poly(lactide-co-caprolactone) polyols is reported here. Thermal characterization of these materials using DSC is also reported.

[0131] Physical properties are measured according to the methods described above.

[0132] The DSC curves (not reported here) exhibit endotherms right after the low temperature T_g which is usually attributed to enthalpic relaxation due to left over stress in these polymers. While not wishing to be bound by theory, this is somewhat expected with these materials because the thermodynamic incompatibility of the poly(lactide-co-caprolactone) polyols and the non-crystalline hard segment is reduced by incorporation of lactic acid units which may decrease the degree of phase separation and phase separation kinetics in these materials. This trend can also be deduced from the increase of the soft or mixed segment glass transition temperature as the lactic acid content is increased. Broad transitions (over 50°C) are observed for these materials and this range increased as the hard segment content is increased. This is also another manifestation of poor phase separation or high degree of phase mixing present in these materials. This amorphous morphology generated high modulus materials, however a very slight hint of yielding is observed for the high hard segment (60%) formulations. Melting endotherms are observed for the 30 and 45% hard segment formulations probably due to disruption of an ordered non-crystalline segments which do not crystallize or pack rapidly at least not in the time frame of the DSC measurements so no melting transitions during

the second heat or crystallization exotherms during the cooling cycles are observed

Results

[0133] Poly(lactide-co-caprolactone) polyols are classified by the lactic acid contents. The general chemical structure for the TPUs based on these materials is shown below in Structure 1. A number of different polymers were prepared. The polymers synthesized and their thermal characterization (by DSC) are shown in Tables 2, 3, and 4. The results are categorized according to the amount of hard segment; 30, 45, 60%. Control formulations based on PCL (2000Mn) at 30 and 60% hard segment are also made and being tested. The thermal and biodegradation results for each set of materials are given in Tables. Not all the samples were tested for “hardness” so this property is reported whenever it is available, otherwise it is left blank. PLA content (%) is the polylactide content of the poly(lactide-co-caprolactone) polyol used in the formulation.

[0134] Table 3 shows the PLA content (%) of various poly(lactide-co-caprolactone) polyols used in the Examples. The poly(lactide-co-caprolactone) polyols are identified by the (approximate) PLA content.

TABLE 3: Polyol IDs and PLA contents

Polyol ID	PLA Content (%)
POLYOL 12	12.5
POLYOL 25	25.0
POLYOL 30	30.0
POLYOL 50	50.0

[0135] The initial analysis of polymers in this study is shown in Table 4. The TPU IDs reference the amounts of polyol PLA wt. % (1st no.) and hard segment wt. % (2nd no.) in the TPU. Thus A12-30 is a TPU formed from POLYOL 12 with a soft segment PLA content of 12.5% and a hard segment content of 30%.

TABLE 4: Polymer formulations and thermal properties for materials with 30-60 % hard segment content

TPU ID	Polyol PLA %	Hard Seg. %	Tg (C, 1st Heat)	Tg (°C, 2nd Heat)	Tm (°C, 1st Heat)	Hardness A
A0-30	0	30	-47.1	-42.1	67.6	
A0-60	0	60	-10.1	15.9	169.9	
A12-30	12.5	30	-37.2	-30.7	71.8	
A12-45	12.5	45	-30.4	-11.1	65.1	
A12-60	12.5	60	-8	29.4	none	
A25-30	25	30	-26.9	-20.9	67.5	
A25-45	25	45	-23.9	-5.6	59.6/122	
A25-60	25	60	-4.7	20.1	none	
A30-30	30	30	-17.9	-14.4	64.6	70
A30-45	30	45	-11.9	-0.3	54.8	80
A30-60	30	60	-5.2	25.4	none	99
A50-30	50	30	1.1	4.1	58.7/163.5	96
A50-45	50	45	-15.8	-14.1	134.7	
A50-60	50	60	14.5	36.4	none	98

[0136] The degradation of TPUs was measured and the Mw and tensile strength was plotted as a function of the in vitro degradation time for each series of TPUs. Results for a typical series are shown in Table 5. The results indicate that the degradation rate of the polymer is a function of the concentration of biodegradable units in the TPU backbone. The Mw and Mn values in Table 5 are for the TPU.

TABLE 5: Degradation of TPUs

TPU ID	Time Weeks	Tensile Str. (MPa)	Elongation (%)	Mw (kDa)	Mn (kDa)
A0-30	0	30.6	710	172.2	64.8
	1	25.5	909	170.6	80
	2	24.5	699	161.1	74.1
	4	26.3	737	152.2	72.4
	8	24.6	712	144.6	62.6
A0-60	0	55.5	393	145.1	76.5
	1	44.6	392	163	77
	2	44.4	389	152.1	73.7
	4	41.6	370	148.6	69.1
	8	43.5	374	145.2	62.9
A12-30	0	14	701	199.9	92.1
	1	16.5	703	201.6	92
	2	16.3	681	172.7	71.9
	4	16	698	158.1	82.4
	8	15	718	120	55.2
A12-45	0	33.4	550	179.2	94.2
	1	37.4	560	184.2	86.1
	2	35.1	559	186.9	87.2
	4	32.9	530	156.4	59.6
	8	32	549	126.8	57.7
A12-60	0	42.2	376	142	63.6
	1	40.2	353	150	72.4
	2	41.5	352	139.2	64.9
	4	39.7	340	134.4	54.9
	8	41.3	350	120.8	53.7
A25-30	0	9.4	593	107.2	50.3
	1	11.2	675	109.2	54.4
	2	11.9	704	93.9	42.4
	4	11.2	703	87.4	46.9
	8	7.4	739	66.5	32.1
A25-45	0	27.2	544	87.3	44.5
	1	27.9	543	86	43.5
	2	26.6	524	77.1	39.5
	4	25.8	509	71.2	31.4
	8	23.1	521	61.2	21.7
A25-60	0	41.4	349	127.6	63.5

-45-

TPU ID	Time Weeks	Tensile Str. (MPa)	Elongation (%)	Mw (kDa)	Mn (kDa)
	1	40.6	318	130.9	62.7
	2	39.7	314	138.6	68.9
	4	38.6	327	128.9	59.1
	8	39.4	323	107.1	52.2
A30-30	0	17	649	181.5	66.3
	1	15.4	675	185.9	72.6
	2	15.2	671	165.6	70.8
	4	13.9	677	125.3	59.2
	8	9.7	685	74.5	35.3
A30-45	0	39.4	488	141	63.7
	1	34.3	511	146.4	63.4
	2	31.9	486	139.6	68.9
	4	31.9	391	116	56.7
	8	29.9	508	84	40
A30-60	0	53.3	340	98	52
	1	38.5	322	101.5	51.7
	2	39.7	325	99.2	50.7
	4	36.3	309	93	46.9
	8	38.1	314	81.4	40
A50-30	0	27.5	576	124.9	57
	1	14.5	551	115.1	55
	2	14.2	559	103	50.9
	4	13.2	573	75.6	36.8
	8	7.4	522	39.8	18.1
A50-45	0	37.2	371	121.8	60.2
	1	29.6	363	138.5	70.3
	2	29.1	345	125	61.8
	4	30.3	363	95.1	46.5
	8	26.6	368	59.1	29
A50-60	0	43.9	249	92.3	52.1
	1	37.1	251	126.1	60.8
	2	35.2	263	124.4	60.5
	4	37.9	245	110.6	53.5
	8	37	241	88.5	42.7

[0137] TABLE 6 show physical and biodegradation data for the A30-60 and A50-45 samples to demonstrate that similar biodegradation profiles can be achieved with very different initial tensile strength values.

TABLE 6

	A30-60	A50-45
Polyol PLA %	30	50
Hard Seg %	60	45
Hardness	99A	not tested
Tensile Str. (Mpa)	53.3	37.2
Elongation %	340	371
% Degrad. -8 wks	28.5	28.5

[0138] TABLE 7 shows physical and biodegradation data for the samples A50-30 and A25-45 to demonstrate that different biodegradation profiles with the same initial tensile strength values:

TABLE 7

	A50-30	A25-45
Polyol PLA %	50	25
Hard Seg %	30	45
Hardness	96A	not tested
Tensile Str. (Mpa)	27.5	27.2
Elongation %	576	544
% Degrad. -8 wks	73.1	15.1

[0139] The data demonstrate that it is feasible to independently vary the degradation rates and tensile properties even with a relatively small data set. 8 weeks degradation rates for the A30-60 and A50-45 samples (28.5% degradation at 8 weeks) are pretty similar, however the initial mechanical properties for these samples are rather different (53.3 vs. 37.2 MPa). Similarly, samples A50-30 and A25-45 have almost the same initial tensile strengths (27.5 and 27.2 MPa) but the 8 weeks degradation profiles are quite different (73.1% vs. 15.1% degradation).

[0140] It was also observed that for the 45% and 60% hard segment samples, the 1 week and 2 weeks GPC M_w values are greater than the original M_w values. The GPC experiments are all made in the same way

using the same solvent (NMP) and no high molecular weight shoulders are observed in the elution graphs (not reported here). In addition, the same drying procedure is used for every sample suggesting this observation is not due to the analysis procedure. This observation may be due to two mechanisms. (1) The left over or generated NCO groups in water may have reacted with the existing urethane, or more likely with the amine groups that are formed by the hydrolysis of the isocyanate. In fact, the observation that this effect becomes more pronounced with increasing hard segment or diisocyanate concentration supports this inference. It may be that with longer reaction time for the polymerization reaction to reach completion or more carefully matching the molar ratio of diisocyanate to the reactive groups, this observation can be reduced or eliminated. (2) The leaching of low molecular weight polymers or oligomers in the buffer solution. The concurrent drop in the polydispersity index and/or absence of a significant broadening of the polydispersity for these samples are in support of this mechanism.

[0141] During hydrolytic degradation, the polymer is first hydrated and then breaking of the hydrolytically labile linkages takes place. The hydrophilic/hydrophobic balance of the composition determines the wetting rate and accordingly the degradation rate. The hydrolysis can be catalyzed with acidic and basic moieties or specific enzymes in the body. However, the degradation rates in these Examples are measured in buffered solution where the pH of the medium is maintained close to neutral and no enzymes are present. It is to be expected that the measured degradations rates *in vitro* may correspond to higher rates *in vivo*. Accordingly, if the specification provides a desired degradation rate based on *in vivo* comparisons, this can be reduced to compensate for the difference between *in vivo* and *in vitro* results.

[0142] While not wishing to be bound by theory, it is noted that both hard and soft segments (ester and urethane linkages) in these samples are prone to hydrolysis. Crystalline segments are less easy to wet and so they are less susceptible to hydrolysis compared to non-crystalline or less ordered

amorphous regions. Thus, for compositions using the same polyol, as the hard segment (more ordered or hydrophobic segment) content is increased the degradation rate decreases.

[0143] While not wishing to be bound by theory, it is noted that in comparing results for different hardness content TPUs with the same lactic acid content polyol, as the hard segment content of the TPU was increased the degradation rate is generally decreased. This is expected because the number of ester groups in the TPU's backbone are decreased as the hard segment content is increased. They are replaced by urethane linkages which, while still hydrolysable, are considered more resistant to hydrolysis compared to the ester units that are present in a higher concentration in the softer TPUs. In addition, the hard segments of these formulations may be more hydrophobic than the soft segments and as the ratio of the hard segments to soft segments increases, the overall hydrophobicity of the TPU would be expected to increase. The hydrophobicity/hydrophilicity ratio of bioabsorbable polymers is a significant factor in the rate of the bioabsorption. Therefore, on this basis, as well as on the basis of the concentration more easily hydrolyzed ester groups, it can be expected that the TPUs which contain higher percent hard segment would degrade more slowly in the *in vitro* bioabsorption tests. The degradation data support this expected trend.

[0144] Each of the documents referred to above is incorporated herein by reference. Except in the Examples, or where otherwise explicitly indicated, all numerical quantities in this description specifying amounts of materials, reaction conditions, molecular weights, number of carbon atoms, and the like, are to be understood as modified by the word "about." Unless otherwise indicated, each chemical or composition referred to herein should be interpreted as being a commercial grade material which may contain the isomers, by-products, derivatives, and other such materials which are normally understood to be present in the commercial grade. However, the amount of each chemical component is presented exclusive of any solvent or diluent oil, which may be customarily present in the commercial material,

unless otherwise indicated. It is to be understood that the upper and lower amount, range, and ratio limits set forth herein may be independently combined. Similarly, the ranges and amounts for each element of the invention may be used together with ranges or amounts for any of the other elements. As used herein, the expression "consisting essentially of" permits the inclusion of substances that do not materially affect the basic and novel characteristics of the composition under consideration. As used herein any member of a genus (or list) may be excluded from the claims.

[0145] It will be appreciated that variants of the above-disclosed and other features and functions, or alternatives thereof, may be combined into many other different systems or applications. Various presently unforeseen or unanticipated alternatives, modifications, variations or improvements therein may be subsequently made by those skilled in the art which are also intended to be encompassed by the following claims.

WHAT IS CLAIMED IS:

1. A process of making a bioabsorbable thermoplastic polyurethane compound tailored for a medical application, said process comprising:

(I) reacting a polyisocyanate component, a diol chain extender component, and optionally a polyol component, wherein at least one of the components contains hydrolyzable units such that the resulting compound contains hydrolyzable units in its backbone;

wherein a degradation rate of the compound is set by adjusting one or more degradation rate parameters and wherein at least one physical property of the compound is set by adjusting one or more physical property parameters, resulting in a bioabsorbable thermoplastic polyurethane compound having at least one desired physical property of the compound, and a desired degradation rate of the compound, independently set.

2. The process of claim 1 wherein the degradation rate parameter includes at least one of the following:

(i) the quantity of bioabsorbable units in the backbone of the overall compound;

(ii) the molecular weight of the polyol component;

(iii) the hydrophilicity of the overall compound;

(iv) the molecular weight of the overall compound;

(v) the hard segment content of the overall compound;

(vi) the crystallinity of the overall compound.

3. The process of claim 1 wherein the physical property includes at least one of the following:

(a) the tensile strength of the overall compound;

(b) the hardness of the overall compound;

(c) the stiffness (flexibility) of the overall compound;

(d) the resilience of the overall compound;

(e) the abrasion resistance of the overall compound;

(f) the water swell of the overall compound;

-51-

- (g) the moisture permeability of the compound;
- (h) the impact strength/resistance of the compound;
- (i) the coefficient of friction (on the surface) of the compound;
- (j) the creep of the compound;
- (k) the modulus of elasticity of the compound;
- (l) the thermal transition points (T_g , T_m) of the compound;

and wherein the physical property parameter includes at least one of the following:

- (i) the hard segment content of the overall compound;
- (ii) the molecular weight the overall compound;
- (iii) the stoichiometry of the overall compound;
- (iv) the molecular weight of a polyol component;
- (v) the hydrophilicity of the overall compound;
- (vi) the difference in polarity between the soft segments and the hard segments of the overall compound;
- (vii) the difference in the degree of hydrogen bonding between the soft segments and hard segments;
- (viii) the molecular weight of the soft segment;
- (ix) the crystallinity of the overall compound;

4. The process of claim 1 wherein the physical property parameter includes the stoichiometry of the overall compound, which is adjusted by varying a molar ratio of the polyol derived component to the chain extender derived component; and/or a molar ratio of isocyanate to hydroxyl groups in the formulation.

5. The process of claim 1 wherein the physical property includes tensile strength and/or hardness; and

wherein the physical property parameter includes the molecular weight the overall compound and/or the hard segment content.

6 The process of claim 1 wherein the physical property includes stiffness; and

wherein the physical property parameter includes the hard segment content and/or the hydrophilicity of a polyol-derived component of the base thermoplastic polyurethane.

7. The process of claim 1 wherein the degradation rate parameter includes the quantity of bioabsorbable units in a backbone structure of the base thermoplastic polyurethane compound, wherein bioabsorbable units includes hydrolysable units, enzymatically cleavable units, or combinations thereof.

8. The process of claim 7 wherein the hydrolysable units and enzymatically cleavable units are derived from the chain extender and/or the polyol.

9. The process of claim 1 wherein the desired degradation rate is higher than that of a base thermoplastic polyurethane compound, and wherein the adjusting of the degradation rate of the thermoplastic polyurethane is accomplished, independent of any adjustment of one or more physical properties of the base thermoplastic polyurethane compound, by at least one of:

- (a) increasing the number of bioabsorbable units in the backbone structure of the base thermoplastic polyurethane compound per unit length of the backbone;

- (b) increasing the hydrophilicity of the base thermoplastic polyurethane compound;

- (c) increasing the molecular weight of the polyol-derived component;

- (d) decreasing the hard segment content of base thermoplastic polyurethane compound; and

- (e) decreasing the crystallinity of the base thermoplastic polyurethane compound;

resulting in a bioabsorbable thermoplastic polyurethane compound with the desired degradation rate.

10. The process of claim 1 wherein the desired degradation rate is lower than that of a base thermoplastic polyurethane compound, and wherein the adjusting

of the degradation rate of the thermoplastic polyurethane is accomplished, independent of any adjustment of one or more physical properties of the base thermoplastic polyurethane compound, by at least one of:

- (a) decreasing the number of bioabsorbable units in the backbone structure of the base thermoplastic polyurethane compound per unit length of the backbone;

- (b) decreasing the hydrophilicity of the base thermoplastic polyurethane compound;

- (c) decreasing the molecular weight of the polyol-derived component;

- (d) increasing the hard segment content of base thermoplastic polyurethane compound; and

- (e) increasing the crystallinity of the base thermoplastic polyurethane compound;

resulting in a bioabsorbable thermoplastic polyurethane compound with the desired degradation rate.

11. The process of claim 1 wherein the desired tensile strength of the thermoplastic polyurethane compound is higher than the tensile strength of a base thermoplastic polyurethane compound, and wherein the adjusting of the tensile strength the thermoplastic polyurethane is accomplished, independent of any adjustment of the degradation rate of the thermoplastic polyurethane, by at least one of:

- (a) increasing the hard segment content of the base thermoplastic polyurethane compound by altering a ratio of a polyol to a chain extender in the formulation;

- (b) increasing the molecular weight of the base thermoplastic polyurethane compound by varying a stoichiometric ratio of isocyanate to an amount of active hydrogen groups in the thermoplastic polyurethane compound;

- (c) increasing the crystallinity of the polyol-derived component; and

- (d) increasing the difference in polarity between hard segment components and soft segment components of the base thermoplastic polyurethane;

-54-

resulting in a bioabsorbable thermoplastic polyurethane compound with the desired tensile strength.

12. The process of claim 1 wherein the desired tensile strength of the thermoplastic polyurethane compound is lower than the tensile strength of a base thermoplastic polyurethane compound, and wherein the adjusting of the tensile strength of the thermoplastic polyurethane is accomplished, independent of any adjustment of the degradation rate of the thermoplastic polyurethane, by at least one of:

- (a) decreasing the hard segment content of the base thermoplastic polyurethane compound by altering the ratio of a polyol to a chain extender in the formulation;

- (b) decreasing the molecular weight of the base thermoplastic polyurethane compound by varying a stoichiometric ratio of isocyanate to an amount of active hydrogen groups in the thermoplastic polyurethane compound;

- (c) decreasing the crystallinity of a polyol-derived component; and

- (d) decreasing the difference in polarity between hard segment components and soft segment components of the base thermoplastic polyurethane;

resulting in a bioabsorbable thermoplastic polyurethane compound with the desired tensile strength.

13 The process of claim 1 wherein the degradation rate is expressed as a function of at least one of:

- a change in molecular weight with time;

- a change in tensile strength with time; and

- a change in weight of the polymer with time.

14. The process of claim 1 wherein the polyisocyanate comprises an aliphatic diisocyanate;

wherein the polyol is selected from the group consisting of polyester polyols, polyether polyols, and combinations and derivatives thereof;

wherein the chain extender is selected from the group consisting of diols, diamines, and combinations thereof.

15. The process of claim 1 wherein the isocyanate is selected from the group consisting of 4,4'-methylene diphenyl diisocyanate (HMDI), 1,6-hexane diisocyanate (HDI), 1,4-butane diisocyanate (BDI), L-lysine diisocyanate (LDI), 2,4,4-trimethylhexamethylenediisocyanate, di-cyclohexyl diisocyanate (H12MDI), and combinations thereof;

wherein the polyol is selected from the group consisting of poly lactic acid (PLA), polyglycolic acid (PGA), polybutylene adipate, polybutylene succinate, poly-1,3-propylene succinate, polycaprolactone, poly(lactide-co-caprolactone), copolymers of two or more thereof, and mixtures thereof;

wherein the chain extender is selected from the group consisting of 1,4-butanediol, 2-ethyl-1,3-hexanediol (EHD), 2,2,4-trimethyl pentane-1,3-diol (TMPD), 1,6-hexanediol, 1,4-cyclohexane dimethylol, 1,3-propanediol, dimethanol, and combinations thereof.

16. The process of claim 1 wherein the bioabsorbable unit of the polyol is derived from lactic acid, glycolic acid, caprolactone, or a combination thereof.

17. A bioabsorbable thermoplastic polyurethane compound, tailored for a medical application, said compound comprising the reaction product of a polyisocyanate component, a diol chain extender component, and optionally a polyol component, wherein at least one of the components contains hydrolyzable units such that the resulting compound contains hydrolyzable units in its backbone;

wherein a degradation rate of the compound is set by adjusting one or more degradation rate parameters and wherein at least one physical property of the compound is set by adjusting one or more physical property parameters;

resulting in a bioabsorbable thermoplastic polyurethane compound having at least one physical property of the compound, and the degradation rate of the compound, independently set.

18. The bioabsorbable thermoplastic polyurethane compound of claim 17, wherein the bioabsorbable thermoplastic polyurethane compound has a degradation rate higher than that of a base thermoplastic polyurethane compound, and wherein the degradation rate of the base thermoplastic polyurethane compound is adjusted to the higher rate of the bioabsorbable thermoplastic polyurethane compound, independent of any adjustment of one or more physical properties of the base thermoplastic polyurethane compound, by at least one of:

- (a) increasing the number of bioabsorbable units in the backbone structure of the base thermoplastic polyurethane compound per unit length of the backbone;
- (b) increasing the hydrophilicity of the base thermoplastic polyurethane compound;
- (c) increasing the molecular weight of the polyol-derived component;
- (d) decreasing the hard segment content of base thermoplastic polyurethane compound; and
- (e) decreasing the crystallinity of the base thermoplastic polyurethane compound.

19. The bioabsorbable thermoplastic polyurethane compound of claim 17, wherein the bioabsorbable thermoplastic polyurethane compound has a degradation rate lower than that of a base thermoplastic polyurethane compound, and wherein the degradation rate of the base thermoplastic polyurethane compound is adjusted to the lower rate of the bioabsorbable thermoplastic polyurethane compound, independent of any adjustment of one or more physical properties of the base thermoplastic polyurethane compound, by at least one of:

- (a) decreasing the number of bioabsorbable units in the backbone structure of the base thermoplastic polyurethane compound per unit length of the backbone;

-57-

(b) decreasing the hydrophilicity of the base thermoplastic polyurethane compound;

(c) decreasing the molecular weight of the polyol-derived component;

(d) increasing the hard segment content of base thermoplastic polyurethane compound; and

(e) increasing the crystallinity of the base thermoplastic polyurethane compound.

20. The bioabsorbable thermoplastic polyurethane compound of claim 17, wherein the bioabsorbable thermoplastic polyurethane compound has a tensile strength higher than that of a base thermoplastic polyurethane compound, and wherein the a tensile strength of the base thermoplastic polyurethane compound is adjusted to the higher tensile strength of the bioabsorbable thermoplastic polyurethane compound, independent of any adjustment of the degradation rate of the thermoplastic polyurethane, by at least one of:

(a) increasing the hard segment content of the base thermoplastic polyurethane compound by altering a ratio of a polyol to a chain extender in the formulation;

(b) increasing the molecular weight of the base thermoplastic polyurethane compound by varying a stoichiometric ratio of isocyanate to an amount of active hydrogen groups in the thermoplastic polyurethane compound;

(c) increasing the crystallinity of the polyol-derived component; and

(d) increasing the difference in polarity between hard segment components and soft segment components of the base thermoplastic polyurethane.

21. The bioabsorbable thermoplastic polyurethane compound of claim 17, wherein the bioabsorbable thermoplastic polyurethane compound has a tensile strength lower than that of a base thermoplastic polyurethane compound, and wherein the tensile strength of the base thermoplastic polyurethane compound is adjusted to the lower tensile strength of the bioabsorbable thermoplastic

polyurethane compound, independent of any adjustment of the degradation rate of the thermoplastic polyurethane, by at least one of:

(a) decreasing the hard segment content of the base thermoplastic polyurethane compound by altering the ratio of a polyol to a chain extender in the formulation;

(b) decreasing the molecular weight of the base thermoplastic polyurethane compound by varying a stoichiometric ratio of isocyanate to an amount of active hydrogen groups in the thermoplastic polyurethane compound;

(c) decreasing the crystallinity of a polyol-derived component; and

(d) decreasing the difference in polarity between hard segment components and soft segment components of the base thermoplastic polyurethane.

22. The bioabsorbable thermoplastic polyurethane compound of claim 17 wherein the polyisocyanate comprises an aliphatic diisocyanate;

wherein the polyol is selected from the group consisting of polyester polyols, polyether polyols, and combinations and derivatives thereof;

wherein the chain extender is selected from the group consisting of diols, diamines, and combinations thereof.

23. The bioabsorbable thermoplastic polyurethane compound of claim 17 wherein the isocyanate is selected from the group consisting of 4,4'-methylene diphenyl diisocyanate (HMDI), 1,6-hexane diisocyanate (HDI), 1,4-butane diisocyanate (BDI), L-lysine diisocyanate (LDI), 2,4,4-trimethylhexamethylenediisocyanate, di-cyclohexyl diisocyanate (H12MDI), and combinations thereof;

wherein the polyol is selected from the group consisting of poly lactic acid (PLA), polyglycolic acid (PGA), polybutylene adipate, polybutylene succinate, poly-1,3-propylene succinate, polycaprolactone, poly(lactide-co-caprolactone), copolymers of two or more thereof, and mixtures thereof;

wherein the chain extender is selected from the group consisting of 1,4-butanediol, 2-ethyl-1,3-hexanediol (EHD), 2,2,4-trimethyl pentane-1,3-diol

-59-

(TMPD), 1,6-hexanediol, 1,4-cyclohexane dimethylol, 1,3-propanediol, dimethanol, and combinations thereof.

24. The bioabsorbable thermoplastic polyurethane compound of claim 17 wherein the bioabsorbable unit of the polyol is derived from lactic acid, glycolic acid, caprolactone, or a combination thereof.

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2013/047222

A. CLASSIFICATION OF SUBJECT MATTER

INV. C08G18/75 C08G18/42
ADD.

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)

C08G

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 practicable, 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 2006/010278 A1 (SYNTHES AG [CH]; SYNTHES USA [US]; GOGOLEWSKI SYLWESTER [CH]) 2 February 2006 (2006-02-02) page 1, line 1 - page 10, line 12; claims 1-52; examples I,II,V,VI -----	1-24
X	WO 2009/043099 A1 (POLYNOVO BIOMATERIALS LTD [AU]; MOORE TIMOTHY GRAEME [AU]; GUNATILLAKE) 9 April 2009 (2009-04-09) page 4, line 25 - page 17, line 15; claims 1-15; examples 1,6 -----	1-24
X	WO 2006/115799 A1 (UNIV CONNECTICUT [US]; MATHER PATRICK T [US]; LIU CHANGDENG [US]; GE Q) 2 November 2006 (2006-11-02) paragraph [0008] - paragraph [0052]; claims 1-3; figure 5 ----- -/-	1,2, 7-10,13, 16-19,24

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

☒ See patent family annex.

* Special categories of cited documents :

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

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"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

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INTERNATIONAL SEARCH REPORT

International application No

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2004/092695 A1 (HU PING [CN] ET AL) 13 May 2004 (2004-05-13) paragraph [0001] - paragraph [0028]; claims 1-12; figures 3,5,6; examples -----	1-3, 7-10, 13-19, 22-24
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Information on patent family members

International application No

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