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(54) Title: DEGRADABLE PHASE CHANGING POLYMERS FOR DENTAL/MEDICAL APPLICATIONS

(57) Abstract: A method of effectively and efficiently forming an implant. The method employs polymers having suitable mechanical properties and a desirable range of glass transition temperatures. The ability to easily adapt pre-shaped polymer implants based on clinical need and harden the reshaped polymer upon exposure to a liquid medium make it suitable for a variety of clinical applications.



DEGRADABLE PHASE CHANGING POLYMERS FOR DENTAL/MEDICAL APPLICATIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority under 35 U.S.C. § 119(e) to U.S. Provisional Patent Application Serial No. 62/901,548, filed on September 17, 2019, which is hereby incorporated by reference in its entirety.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

[0002] This invention was made with government support under Grant No. DMR-1714882 awarded by the National Science Foundation and Grant No. P41EB001046 awarded by National Institute of Health. The government has certain rights in the invention.

TECHNICAL FIELD

[0003] Disclosed herein is a novel polymer for biomaterial applications that can undergo a two-stage phase change to facilitate clinical handling.

BACKGROUND

[0004] The use of barrier membranes in guided bone and tissue regeneration has been documented extensively in the clinical practice of dentistry and medicine. The mechanism by which new bone regeneration occurs in these types of therapies is by physical separation of soft tissue from active bone formation in order to prevent soft-tissue infiltration into bone defects. These commonly conducted procedures are also known as Guided Tissue Regeneration (GTR) and are utilized in a variety of surgical specialties. For example, in dental surgeries, GTR is accomplished by using a barrier membrane to prevent overlying epithelial and connective tissue cell migration into periodontal defects around teeth in which cells from the periodontal ligament and alveolar bone should predominate. Over time, the use of cell occlusive barrier membranes has also become commonplace in bone augmentation procedures at the time of or after tooth extraction in preparation for dental implants (also known as Guided Bone Regeneration or GBR).

[0005] A variety of dental membranes currently exist and are typically categorized into resorbable versus non-resorbable membranes. While both types of membranes have indicated applications, there are significant shortcomings associated with each, such as the lack of mechanical strength and poor space-maintaining ability of resorbable membranes and the need for a second re-entry surgery to remove the non-resorbable membranes. Clinicians must currently choose between flimsy resorbable membranes, which have poor space-maintaining capability and limited mechanical

strength, and stiff non-resorbable membranes, which are challenging to adapt to irregular defects and must be surgically removed at a later date.

[0006] Thus, improved and alternative materials for dental and medical applications are urgently needed.

SUMMARY

[0007] This document discloses a polymer for biomaterial applications that can undergo a two-stage phase change to facilitate clinical handling. As prepared, it is a firm material that becomes malleable when handled and then rapidly hardens when immersed in a wet environment at a certain temperature range. This polymer thus provides clinicians with versatile products with a combination of properties that simply was not available until now.

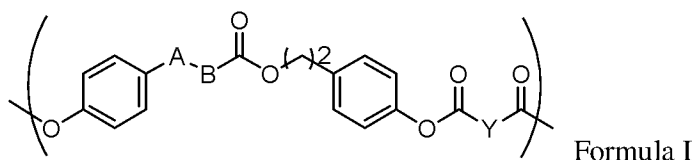
[0008] An aspect of the patent document provides a method of forming and utilizing a medical implant having a pre-determined shape, comprising

heating a pre-shaped polymer above its glass transition temperature (T_g) but below its melting point;

partially reshaping the now malleable polymer to adapt it to the surgical site or clinical application; and

exposing the polymer to a liquid medium to harden the polymer,

wherein the polymer comprises repeating units of Formula I



wherein:

A is C_{1-3} alkyl,

B is either a bond or $-O-CO-C_{2-5}$ alkyl, wherein B is bonded to A via the oxygen of the $-O-CO-C_{2-5}$ alkyl, and optionally two adjacent carbons of said C_{2-5} alkyl have an oxygen inserted therebetween, and

Y is C_{2-10} alkyl or C_{2-10} alkenyl, wherein optionally two adjacent carbons of said C_{2-10} alkyl or C_{2-10} alkenyl have an oxygen inserted therebetween.

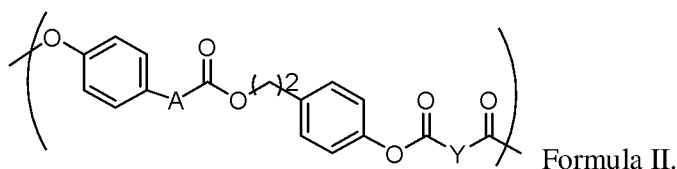
[0009] In some embodiments, the method further includes melt processing and quenching the polymer to generate the pre-determined shape, geometry, or architecture. In some embodiments, the polymer is in an amorphous state after melt processing and quenching. In some embodiments, the glass transition temperature is above room temperature.

[0010] In some embodiments, the step of exposing the polymer to a liquid medium takes place at a temperature ranging from about 35°C to about 40°C. In some embodiments, the step takes place at about 37°C. In some embodiments, the step enables the polymer to reach a tensile modulus of more than 20 MPa at about 37°C within about 20 minutes. In some embodiments, the step enables the polymer to reach a strain-at-break value of less than about 120% at about 37°C within about 20 minutes. In some embodiments, the step enables the polymer to reach a compressive modulus of more than 20 MPa at 37°C within about 20 minutes. In some embodiments, the step enables the polymer to reach a flexural modulus of more than 20 MPa at 37°C within about 20 minutes. In some embodiments, the step enables the polymer to reach a tensile modulus of more than 200 MPa at 37°C within 24 hours. In some embodiments, the step enables the polymer to reach a compressive modulus of more than 200 MPa at 37°C within 24 hours. In some embodiments, the step enables the polymer to reach a flexural modulus of more than 200 MPa at 37°C within 24 hours. In some embodiments, the step takes place in or around a tooth cavity or extraction socket, an alveolar or other bone defect, a nerve defect, a soft tissue defect or injury including skin, gingiva, connective tissue, or vascular tissue, or other suitable location in a subject. In some embodiments, the liquid medium is selected from the group consisting of distilled water, deionized water, normal saline, phosphate-buffered saline (PBS) solution, simulated body fluid (SBF) solution, blood, plasma, serum, saliva, mucous, cerebrospinal fluid, interstitial fluid, synovial fluid, urine, gastric fluid, bile and any combination thereof.

[0011] In some embodiments, the polymer is admixed with an agent selected from the group consisting of antibacterial agents, anti-viral agents, anti-inflammatory agents, anti-oxidants, immunogens, cytotoxins, hemostatic agents, neurotrophic factors, osteoinductive factors, pro-angiogenic factors, growth factors and any combination thereof.

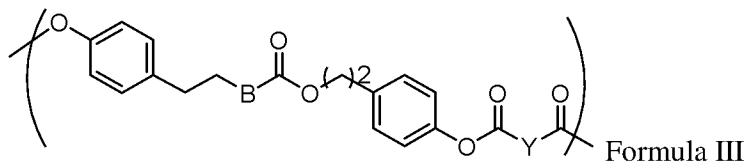
[0012] In some embodiments, Y is selected from the group consisting of $(CH_2)_2$, $(CH_2)_3$, CH_2OCH_2 , $(CH_2)_4$, $CH_2CH=CHCH_2$, $(CH_2)_5$, $(CH_2)_6$, and $(CH_2)_{10}$.

[0013] In some embodiments, the polymer comprises repeating units of Formula II. In some embodiments, A is CH_2 or CH_2CH_2 .



[0014] In some embodiments, the polymer comprises Formula III. In some embodiments, B is selected from the group consisting of

$-\text{O}-\text{CO}-\text{CH}_2\text{CH}_2$, $-\text{O}-\text{CO}-\text{CH}_2\text{CH}_2\text{CH}_2$, and $-\text{O}-\text{CO}-\text{CH}_2\text{OCH}_2$.



[0015] The method is suitable for various clinical applications including dental and medical procedures. In some embodiments, the method is applied to forming and installing a dental implant.

[0016] Another aspect provides a method of placing an implant in a subject in need thereof, comprising

- (a) heating a pre-shaped polymer above its glass transition temperature (T_g) but below its melting point;
- (b) partially reshaping the now malleable polymer to adapt it to the surgical site or clinical application; and
- (c) exposing the polymer to a liquid medium to harden the polymer,

wherein the polymer comprises repeating units of Formula I.

[0017] In some embodiments, the polymer hardens at about or below 37°C . In some embodiments, the implant is placed in or around a tooth cavity or extraction socket, an alveolar or other bone defect, a nerve defect, a soft tissue defect or injury including skin, gingiva, connective tissue, or vascular tissue, or other suitable location in a subject.

[0018] Another aspect of this document provides an implant prepared according to the method disclosed herein. A related aspect provides a kit including the implant and other components for the formation and installation of the implant.

DESCRIPTION OF THE DRAWINGS

[0019] Figure 1 shows the impact of water-induced crystallization on mechanical properties of amorphous 3D-printed poly(HTy glutarate) 3-layer films.

[0020] Figure 2 shows X-ray diffraction data comparing the crystallinity of as prepared poly(HTy glutarate) films ($<1\%$, left) and crystallized poly(HTy glutarate) films (28% , right).

DETAILED DESCRIPTION

[0021] This patent document discloses a medical implant made of the material disclosed here that combines the best aspects of resorbable and non-resorbable materials into a single component. Implants such as dental membranes made from the material disclosed herein are resorbable, readily moldable, easy to place in a clinical setting, and harden in a short span of time, thereby increasing the mechanical strength and space-making capacity to match those of commercially available non-resorbable materials. Specifically, the polymers disclosed herein have the capacity to phase change under clinical conditions and result in unique materials, implants, and medical devices, such as the aforementioned dental membrane, that could revolutionize the biomaterials market.

[0022] While the following text may reference or exemplify specific embodiments of a polymer or a method of forming an implant, it is not intended to limit the scope of the polymer or method to such particular reference or examples. Various modifications may be made by those skilled in the art, in view of practical and economic considerations, such as substituting the polymer, varying the melt processing and quenching parameters, and varying the reshaping temperature for adapting the pre-formed polymer to the surgical site or clinical application.

[0023] The articles "a" and "an" as used herein refer to "one or more" or "at least one," unless otherwise indicated. That is, reference to any element or component of an embodiment by the indefinite article "a" or "an" does not exclude the possibility that more than one element or component is present.

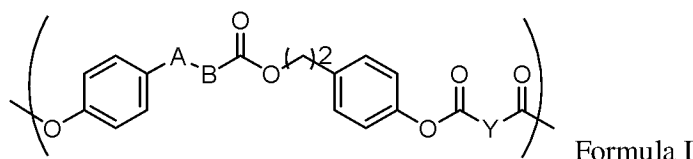
[0024] The term "subject" refers to a human or an animal.

[0025] The term "alkyl" refers to a hydrocarbon chain which may be either straight-chained or branched. The alkyl is bonded to two other moieties or groups at its two terminus positions. The term "C₁₋₃ alkyl" refers to alkyl groups having 1, 2, or 3 carbon atoms. Non-limiting examples include groups such as CH₃, (CH₂)₂, CH₂CH(CH₃), and the like. Similarly, the term "C₂₋₅ alkyl" refers to alkyl groups having 2, 3, 4 or 5 carbon atoms. The term "C₂₋₁₀ alkyl" refers to alkyl groups having a straight or branched chain of carbon atoms ranging from 2 to 10. When two adjacent carbons of a hydrocarbon chain have an oxygen inserted therebetween, the two carbons are each connected to the same oxygen. Nonlimiting examples include CH₂OCH₂ and CH₂CH₂OCH₂, and CH₂CH₂OCH₂CH₂.

[0026] The term "C₂₋₁₀ alkenyl" refers to a hydrocarbon chain, straight-chained or branched, having from 2 to 10 carbon atoms and one or two double bonds in the chain. The alkenyl is bonded to two other moieties or groups at its two terminus positions. As is generally known in

the art, a double bond requires two adjacent sp² hybridized carbons. Nonlimiting examples include CH₂CH=CHCH₂ and CH₂CH=CHCH₂CH₂. When two adjacent carbons of a hydrocarbon chain have an oxygen inserted therebetween, the two carbons are sp³ carbons and are each connected to the same oxygen.

[0027] An aspect of the disclosure provides a polymer containing a repeating unit of Formula I



wherein:

A is C₁₋₃alkyl,

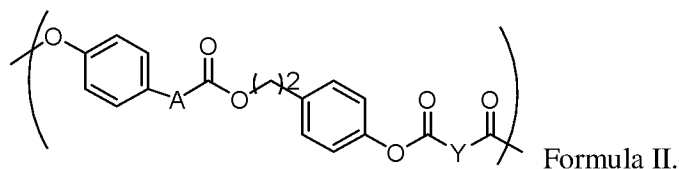
B is either a bond or –O–CO–C₂₋₅ alkyl, where B is bonded to A via the oxygen of the –O–CO–C₂₋₅ alkyl, and optionally two adjacent carbons of said C₂₋₅ alkyl have an oxygen inserted therebetween, and

Y is C₂₋₁₀ alkyl or C₂₋₁₀ alkenyl, wherein optionally two adjacent carbons of said C₂₋₁₀ alkyl or C₂₋₁₀ alkenyl have an oxygen inserted therebetween. The lines crossing the parentheses each represents a bond.

[0028] In some embodiments, the polymer is a copolymer containing one or more types of repeating units. For instance, some repeating units of the copolymer have A as (CH₂)₂ and some other repeating units have A as CH₂. Likewise, a copolymer may contain units differing in B or Y. The terminal groups of the polymer can be an OH, COOH, or a capping alkyl group.

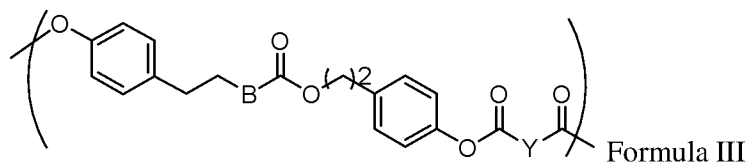
[0029] In some embodiments, Y is selected from (CH₂)₂, (CH₂)₃, CH₂OCH₂, (CH₂)₄, CH₂CH=CHCH₂, (CH₂)₅, (CH₂)₆, and (CH₂)₁₀. In some embodiments, A is CH₂ or (CH₂)₂, and B is –O–CO–CH₂CH₂, –O–CO–CH₂CH₂CH₂, or –O–CO–CH₂OCH₂.

[0030] In some embodiments, the polymer contains repeating units of Formula II, wherein A is CH₂, (CH₂)₂, or (CH₂)₃.



[0031] In some embodiments of Formula II, A is CH₂, or (CH₂)₂, Y is (CH₂)₂, (CH₂)₃, CH₂OCH₂, or (CH₂)₄.

[0032] In some embodiments the polymer contains repeating units of Formula III,



[0033] In some embodiments of Formula III, B is selected from $-\text{O}-\text{CO}-\text{CH}_2\text{CH}_2-$, $-\text{O}-\text{CO}-\text{CH}_2\text{CH}_2\text{CH}_2-$, and $-\text{O}-\text{CO}-\text{CH}_2\text{OCH}_2-$.

[0034] Another aspect of the patent document provides a method of forming and utilizing a medical implant having a pre-determined shape. The method generally includes sequentially:

- i. heating a polymer above its glass transition temperature (T_g) but below its melting point, wherein the polymer can be pre-shaped;
- ii. at least partially reshaping the now malleable polymer to adapt it to the surgical site or clinical application; and
- iii. cooling the polymer at a suitable temperature or exposing the polymer to a liquid medium to harden the polymer.

[0035] In some embodiments, the method also includes, before step (i), melt processing and quenching the polymer to generate a pre-determined shape, geometry, or architecture. In some embodiments of step (ii), the malleable polymer is partially reshaped. In some embodiments, the malleable polymer is fully reshaped.

[0036] The phase change behavior of the polymer disclosed herein is desirable for many clinical applications. For instance, a dental membrane made of the material disclosed here combines the best aspects of resorbable and non-resorbable membranes into a single novel membrane that is completely different from anything else on the market. The resulting membrane is resorbable, readily moldable, easy to place in a clinical setting, and hardens quickly, thereby increasing its mechanical strength and space-making capacity to match those of commercially available non-resorbable membranes. In an exemplary embodiment, when the polymer material is heated (e.g. by handling) above 32°C , it becomes flexible without losing its melt processed architecture, which allows it to be easily adapted into clinically desired conformations. Once molded, the material can be immersed in a 37°C or warmer environment to harden it and freeze the material in its altered shape. This hardening occurs as a result of the polymer chains crystallizing above the glass transition temperature and the initial hardening occurs over a short period of time (e.g. 10-30 minutes), which is an appropriate duration for clinical usage.

[0037] The polymer disclosed herein can also be used for the construction of a 3D porous scaffold for bone regeneration. The polymer is also useful in other medical applications where a membrane can be used to prevent soft tissue infiltration into healing sites. Basically, any application that requires a strong or crystalline implant where there is a clinical need or convenience to being able to shape it during implantation.

[0038] In the step before (i), the polymer can be melt processed to form a desired shape, geometry, or architecture, such as a film, membrane, porous scaffold, extruded fiber, or 3D printed shape. In order for the polymer to solidify into an amorphous state, during or immediately following the melt processing, the polymer must be quenched by cooling rapidly using air, cold surfaces, liquid nitrogen, or other means.

[0039] Depending on its glass transition temperature, the polymer prepared in the step before (i) can be stored in a freezer, in a refrigerator, or at room temperature until needed for a medical/dental procedure. In some embodiments, the polymer has a glass transition temperature ranging from about -10 °C to about 0 °C, from about 0 °C to about 5 °C, from about 5 °C to about 10 °C, from about 10 °C to about 20 °C, from about 20 °C to about 30 °C, from about 30 °C to about 35 °C, from about 35 °C to about 40 °C, from about 30 °C to about 40 °C, or from about 40 °C to about 50 °C. In some embodiments, the polymer has a melting temperature of higher than about 90 °C, higher than 100 °C, higher than 110 °C, or higher than 120 °C. In some embodiments, the polymer has a glass transition temperature above room temperature.

[0040] To adapt the polymer to a surgical site or clinical application, it can be made malleable by heating to about or above its glass transition temperature. In some embodiments, the polymer is heated to a temperature of about 1-5 °C above its glass transition temperature, about 5-10 °C above its glass transition temperature, or about 10-20 °C above its glass transition temperature. In some embodiments, the polymer is heated to a temperature ranging from about 5 °C to 10 °C, from about 10 °C to about 20 °C, from about 20 °C to about 30 °C, from about 30 °C to about 35 °C, from about 35 °C to about 40 °C, from about 30 °C to about 40 °C, from about 40 °C to about 50 °C, or from about 50 °C to about 100 °C.

[0041] The heating step can be accomplished by any suitable means, including for example, exposure of the polymer to hot air, hot surfaces, infrared radiation, and microwave radiation. The polymer may also be heated by manual handling.

[0042] In some embodiments, for the polymer to solidify into an amorphous state in a particular shape, during or immediately following the melt processing or during the heating between its glass transition temperature (T_g) and melting point, the polymer is quenched by cooling

rapidly using air, cold surfaces, liquid nitrogen, or other means. In some embodiments, the polymer is quickly cooled to below its glass transition temperature to harden the polymer.

[0043] In some embodiments, the polymer can be preshaped by melt processing and cooling as described above and then at least partially reshaped to adapt it to the surgical site or clinical application after heating above its glass transition temperature (T_g) but below its melting point. Subsequently, the hardening of the polymer during step (iii) of the method can take place in the presence of a liquid medium and generally at a temperature above the polymer's glass transition temperature. Nonlimiting examples of the liquid medium include distilled water, deionized water, normal saline, phosphate-buffered saline (PBS) solution, simulated body fluid (SBF) solution, blood, plasma, serum, saliva, mucous, cerebrospinal fluid, interstitial fluid, synovial fluid, urine, gastric fluid, bile, and any combination thereof. In the context of adapting the polymer to clinical application, examples include shaping it into a suitable form for implant or for combining with another structural component for medical use.

[0044] The polymer becomes hardened after being exposed to the liquid medium. In some embodiments, the hardened polymer reaches a tensile modulus ranging from about 15 to about 20 MPa, from about 20 to about 30 MPa, from about 30 to about 40 MPa, from about 40 to about 50 MPa, or more than 50 MPa within a short period of time, which is less than about 10 minutes, less than about 15 minutes, less than about 20 minutes, less than about 30 minutes, less than about 45 minutes, or less than 60 minutes. In some embodiments, the hardened polymer reaches a tensile modulus of more than 50 MPa, more than 80 MPa, more than 100 MPa, more than 120 MPa, more than 140 MPa, more than 160 MPa, more than 180 MPa, more than 200 MPa, more than 220 MPa, more than 250 MPa, or more than 300 MPa within about 1 hour, within about 1.5 hours, within about 2 hours, within about 2.5 hours, within about 3 hours, within about 5 hours, within about 10 hours, within about 20 hours, or within about 24 hours. In some embodiments, the process takes place at a temperature of about 30°C, about 33°C, about 37°C, about 40°C, or about 45°C.

[0045] The change in mechanical properties for the hardened polymer can also be characterized in terms of the strain at break, which is also known as fracture strain or tensile elongation at break. This property is defined as the ratio between the final length (failure length) and the initial length of a polymer sample subjected to tensile testing. It provides a measure of a polymer's ability to resist changing shape without cracking. In some embodiments, the hardened polymer reaches a strain-at-break value of less than about 200%, less than about 180%, less than about 160%, less than about 140%, less than about 120%, less than about 100%, less than about 80%, or less than about 50% within about 8 minutes, within about 10 minutes, within about 15

minutes, within about 20 minutes, within about 25 minutes, within about 30 minutes, within about 45 minutes, or within about 60 minutes. In some embodiments, the process takes place at a temperature of about 30°C, about 33°C, about 37°C, about 40°C, or about 45°C.

[0046] The method described herein can enable the polymer to reach a desirable range of compressive modulus. In some embodiments, the compressive modulus reaches more than about 10 MPa, more than about 15 MPa, more than 20 MPa, more than 30 MPa, or more than 40 MPa within about 15 minutes, within about 20 minutes, within about 30 minutes, or within about 40 minutes. In some embodiments, the hardened polymer reaches a compressive modulus of more than 50 MPa, more than 80 MPa, more than 100 MPa, more than 120 MPa, more than 140 MPa, more than 160 MPa, more than 180 MPa, more than 200 MPa, more than 220 MPa, more than 250 MPa, or more than 300 MPa within about 5 hours, within about 10 hours, within about 20 hours, or within about 24 hours. In some embodiments, the process takes place at a temperature of about 30°C, about 33°C, about 37°C, about 40°C, or about 45°C.

[0047] The method described herein can further enable the polymer to reach a desirable range of flexural modulus. In some embodiments, the flexural modulus reaches more than about 10 MPa, more than about 15 MPa, more than 20 MPa, more than 30 MPa, or more than 40 MPa within about 15 minutes, within about 20 minutes, within about 30 minutes, or within about 40 minutes. In some embodiments, the hardened polymer reaches a flexural modulus of more than 50 MPa, more than 80 MPa, more than 100 MPa, more than 120 MPa, more than 140 MPa, more than 160 MPa, more than 180 MPa, more than 200 MPa, more than 220 MPa, more than 250 MPa, or more than 300 MPa within about 5 hours, within about 10 hours, within about 20 hours, or within about 24 hours. In some embodiments, the process takes place at a temperature of about 30°C, about 33°C, about 37°C, about 40°C, or about 45°C.

[0048] The polymer can also be admixed or functionalized with a biologically active agent to supplement its inherent characteristics, e.g. by tailoring the bioactivity of a polymer-derived membrane through the incorporation of drugs or growth factors to achieve a specific outcome. Incorporation of specific peptides, growth factors, or drugs into or onto the surface of an implant or device could be used to direct tissue specific regeneration at several interfaces within the body. Non-limiting examples of the biologically active agents include antibacterial agents, anti-viral agents, anti-inflammatory agents, anti-oxidants, immunogens, cytotoxins, hemostatic agents, neurotrophic factors, osteoinductive factors, pro-angiogenic factors, growth factors, and any combination thereof.

[0049] The hardening of the polymer can be conducted at any suitable location depending on the intended use of the polymer. In some embodiments, it can take place inside or outside the body of a subject in need thereof. In some embodiments, the hardening takes place in or around a dental cavity, a bone cavity, a bone defect, a nerve defect, a soft tissue defect or injury including skin, gingiva, connective tissue, or vascular tissue, or other suitable location in a subject.

[0050] Accordingly, the method disclosed herein can be used for placing an implant in a subject in need thereof. The hardening of the implant in a short period of time and at a suitable temperature range in the subject offers tremendous flexibility and desirable mechanical properties for various medical procedures. Implants made from the polymer described herein can be of any suitable shape or size and nonlimiting examples include a film, membrane, porous scaffold, and fiber. For instance, the method can be employed to fill a dental cavity with a polymer material described herein. Other dental and medical implants such as endosseous implants, temporary dental fillings, dental and orthodontic splints, archwires, intermaxillary fixation screws, Erich arch bars, tacking screws, tenting screws, fixation plates and screws, bone void fillers, barrier membranes, hard and soft tissue scaffolds, sutures, stents, and protective dressings can also be in-situ formed and installed after they are modified from a pre-existing shape or conformation at or above the polymer's glass transition temperature and exposed to a liquid medium. The method can also be used to implant a barrier or separation membrane in any type of surgery or procedure. The use of barrier membranes in guided bone and tissue regeneration has been documented extensively in the clinical practice of dentistry and medicine. Membranes prepared from the polymer disclosed herein incorporate the best aspects of resorbable and non-resorbable membranes. They have excellent flexibility and are easy to handle. Meanwhile, they demonstrate desirable mechanical strength and space-maintaining capability. For instance, a membrane formed according to the method described herein can serve as a separation between allograft bone mix and soft tissue in dental procedures or in bone grafting medical procedures. The ability to release biologically active agents such as antibiotics and growth factors provides the additional benefits of promoting healing and growth.

[0051] In some embodiments, the method further includes identifying a location in the subject to place the implant into or over the location. In some embodiments, the glass transition temperature of the polymer is at about or below 37°C. In some embodiments, the glass transition temperature is higher than room temperature. In some embodiments, the glass transition temperature is higher than room temperature but lower than the body temperature of a subject in need of the implant.

[0052] Another aspect of this document provides a kit including the polymer comprising repeating units of Formula I and a manual or instruction for reshaping the polymer and adapting it to a surgical site or clinical application. The kit may further includes one or more components selected from a shaping device or a mold, a heater, a cooler, a liquid medium, an attaching component, and a biological component. For instance, the kit may contain a 3-D printer and the polymer to manufacturing a suitable shaped structure. Alternatively, a kit may include a heater and / cooler for reshaping the polymer. Examples of attachment component include tacks and tenting screws for securing the shaped polymer to desirable surgical site or device component.

[0053] Also disclosed in this document is an implant prepared according the method disclosed herein. A further aspect of the document provides a kit including the implant and one or more components facilitating the formation and installation of the implant. Additional exemplary components of the kit include a mold, a heater, a liquid medium, a cutter, a guide manual, and any combination thereof.

[0054] Examples

[0055] Example 1

[0056] A variety of tyrosol-derived polyarylates were prepared. The synthesis of these polymers was based on the procedure disclosed in U.S. Patent Application No. 2016/0376401, the entire disclosure of which is hereby incorporated by reference.

Synthesis of 4-hydroxyphenethyl 2-(4-hydroxyphenyl)acetate (HTy)

[0057] A 2 L 3-neck round bottom flask was attached to an overhead stirrer and a Dean-Stark apparatus with water-cooled condenser and a heating mantle was placed beneath the flask. 4-hydroxyphenylacetic acid (157.4 g, 1.03 mol), Tyrosol (142.9 g, 1.03 mol), phosphoric acid (5.07 g, 51.7 mmol), and 315 mL of toluene were added to the flask. The reaction mixture was stirred and heated at reflux until no more water was collected by azeotropic distillation. The reaction mixture was allowed to cool and phase separate and the upper layer was decanted leaving a thick syrup. The syrup was dissolved in 600 mL of ethyl acetate and washed twice with 150 mL of 5% sodium bicarbonate solution and twice with 150 mL of brine solution. The ethyl acetate solution was dried over magnesium sulfate and concentrated *in vacuo* to obtain a thick syrup. The syrup was concentrated *in vacuo* several times with cold dichloromethane to obtain a white powdered residue. The powder was recrystallized from a dichloromethane:hexane mixture, collected by vacuum filtration, and dried in a vacuum oven at 40 °C for 72 h. Yield: 223 g, 79%.

Melting Point: 94 °C. ¹H NMR (500 MHz, DMSO-*d*₆, δ in ppm): 9.27 (s, 1H), 9.18 (s, 1H), 7.02 - 6.94 (m, 4H), 6.71 - 6.64 (m, 4H), 4.14 (t, *J* = 6.9 Hz, 2H), 3.48 (s, 2H), 2.74 (t, *J* = 6.9 Hz, 2H).

[0058] Example 2

[0059] Synthesis of poly(HTy glutarate)

[0060] HTy (140 g, 0.514 mol, 1.00 eq), glutaric acid (65.9 g, 0.499 mol, 0.97 eq), and 1,4-dimethylpyridinium p-toluenesulfonate (DPTS) (49.9 g, 0.170 mol, 0.33 eq) were combined in a 5 L 3-neck round bottom flask equipped with overhead stirring and submerged in a water bath. Dichloromethane (2 L) was added to the flask and the mixture was stirred for 45 min. N,N'-diisopropylcarbodiimide (DIC) (170 mL, 1.08 mol, 2.1 eq) was added slowly using an addition funnel. The reaction mixture was allowed to stir for 48 hours. The reaction mixture was transferred to a 10 L plastic beaker equipped with overhead stirring and precipitated by slowly adding isopropanol (5 L) using an addition funnel while stirring. The precipitate was collected by vacuum filtration, redissolved in DCM (1.5 L), and reprecipitated using isopropanol (3 L), twice. The final precipitate was collected by vacuum filtration and dried in a vacuum oven at 40 °C for 72 hours.

Yield: 170 g, 92%. DSC: *T_g* = 32 °C, *T_{m1}* = 124 °C, *T_{m2}* = 140 °C; ¹H NMR (500 MHz, CDCl₃, δ in ppm): 7.25 (d, 2H), 7.15 (d, 2H), 7.06 - 7.00 (m, 4H), 4.29 (t, *J* = 6.9 Hz, 2H), 3.59 (s, 2H), 2.91 (t, *J* = 6.9 Hz, 2H), 2.72 (t, *J* = 7.3 Hz, 4H), 2.18 (p, *J* = 7.3 Hz, 2H).

[0061] Example 3

[0062] 3D Printing of poly(HTy glutarate)

[0063] A variety of polymer scaffold geometries and architectures were printed using a 3D Bioplotter® Manufacturer Series (EnvisionTEC GmbH, Germany), including 1-3 layer fused films of various shapes and 10-20 layer porous scaffolds. Specifically, poly(HTy glutarate) powder was packed into a stainless steel cartridge with a 22G stainless steel needle tip and loaded into a high temperature print head. The cartridge was heated to 160°C to melt the poly(HTy glutarate) and the various scaffolds were printed at a pressure of 8.0 bar, a 10 mm/s print speed, a 0.3 mm offset, and a layer orientation alternating between 0° and 90°. When printed onto a temperature controlled stainless steel platform, the crystallinity of the printed scaffold could be controlled by changing

the platform temperature with 20°C resulting in a transparent, amorphous material and 70°C resulting in an opaque, crystalline material.

[0064] Example 4

[0065] Compression Molding of poly(HTy glutarate)

[0066] Compression molded films were fabricated using a Carver press (Carver 2625) at 150°C and 3000 psi. Briefly, 0.5 g of poly(HTy glutarate) powder was placed between two Kapton films in a steel mold, placed in the Carver press, and compressed for 3 minutes. The thickness of the films was adjusted by using spacer shims. Following compression, the Kapton film covered poly(HTy glutarate) film was immediately removed from the steel mold and placed on an ice-water slurry to quench the polymer by rapid cooling and obtain a transparent, amorphous film.

[0067] Example 5

[0068] Water-Induced Crystallization of poly(HTy glutarate)

[0069] The water-induced crystallization of poly(HTy glutarate) was characterized qualitatively on amorphous 3D printed films and scaffolds and amorphous compression molded films. Specifically, the preformed amorphous poly(HTy glutarate) shapes were heated above their glass transition temperature (32°C) by holding them briefly between two hands and then reshaped to fit into or cover a model surgical defect. The surgical model containing the reshaped poly(HTy glutarate) was then submerged in 37°C phosphate-buffered saline solution for 15 minutes. Finally, the poly(HTy glutarate) was removed and assessed visually and by handling to confirm that crystallization had occurred.

[0070] Mechanical properties of the hardened polymers were characterized with the following ASTM methods:

Tensile Modulus:

- D638 -Standard Test Method for Tensile Properties of Plastics
 - Samples 1-14 mm thick
- D882 -Standard Test Method for Tensile Properties of Thin Plastic Sheetings
 - For thin films

Compressive Modulus:

- D695 -Standard Test Method for Compressive Properties of Rigid Plastics

Flexural Modulus:

- D790 -Standard Test Methods for Flexural Properties of Unreinforced and Reinforced Plastics and Electrical Insulating Materials

[0071] Example 6

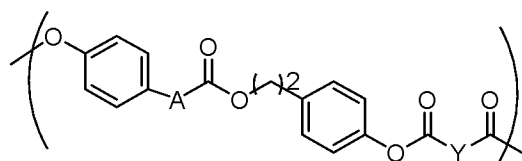
[0072] Clinical Example Workflow for poly(HTy glutarate) Films

[0073] Amorphous 3D printed or compression molded poly(HTy glutarate) films can be stored dry at or below room temperature for subsequent clinical use in the body. In one example of their use as a barrier membrane for bone regeneration, the steps are as follows: A full thickness incision was made through the overlying soft tissue down to the level of the bone. The soft tissue flap was then reflected with blunt instruments to expose a bony defect. Once the defect was visualized, cleaned, and grafted with a bone void filler (which is common practice in dentistry and medicine), the poly(HTy glutarate) film is placed between the soft tissue flap and the newly grafted bone defect. Just prior to implanting the film, it was warmed slightly above its glass transition temperature by being held in the surgeon's sterile gloved hands. This allowed the stiff film to become malleable. Subsequently, the film was inserted as previously described and adapted to the desired conformation with or without the use of tacks or tenting screws around the bony defect that is also common practice in surgery.

[0074] The soft tissue was then allowed to rest over the freshly implanted membrane which began to soak with blood inside the body. After being soaked above its T_g in blood at body temperature (37°C), the material crystallized and hardened to retain its newly adapted shape over 10-30 minutes depending on thickness and porosity. As it crystallized, the film became more opaque and harder. At this point, the overlying soft tissue was sutured above the membrane with ease, while the membrane resisted deformation from external compressive forces during suturing or after repeated function in the postoperative healing period. As the bone defect healed, the barrier membrane degraded and there was no need to retrieve the membrane during a second stage surgery.

[0075] Example 7

[0076] The glass transition temperature and melt temperature of polymers of the present invention are listed in Table 1 and Table 2. The polymers of Table 1 contain repeating units of Formula II-A.



Formula II-A

A is CH₂ (HTy) or CH₂CH₂ (DTy). Y is defined as follows:

Y = (CH ₂) ₂ ,	Succinate
Y = (CH ₂) ₃ ,	Glutarate
Y = CH ₂ OCH ₂ ,	Diglycolate
Y = (CH ₂) ₄ ,	Adipate
Y = CH ₂ CH=CHCH ₂ ,	t-Hexene
Y = (CH ₂) ₅ ,	Pimelate
Y = (CH ₂) ₆ ,	Suberate
Y = (CH ₂) ₁₀ ,	DD

Table 1: Glass transition temperature and melt temperature of polymers of Formula II-A

Polymer	Glass Transition (T _g) (°C)	Melt Temperature (°C)
Poly(HTy Glutarate)	32	138
Poly(DTy Glutarate)	29	154
Poly(HTy Diglycolate)	45	86
Poly(HTy Adipate)	21	99
Poly(DTy Adipate)	24	184
Poly(HTy t-Hexene)	36	116
Poly(DTy t-Hexene)	35	139
Poly(HTy DD)	4	102
Poly(DTy DD)	4	153

Polymers of Formula III-A has B defined as –O–CO–CH₂CH₂CH₂ (DiTyGlutarate) or –O–CO–CH₂OCH₂ (DiTyDiglycolate). Y is defined as follows:

$Y = (CH_2)_2$, Succinate
 $Y = (CH_2)_3$, Glutarate
 $Y = CH_2OCH_2$, Diglycolate
 $Y = (CH_2)_4$, Adipate
 $Y = CH_2CH=CHCH_2$, t-Hexene
 $Y = (CH_2)_5$, Pimelate
 $Y = (CH_2)_6$, Suberate
 $Y = (CH_2)_{10}$, DD

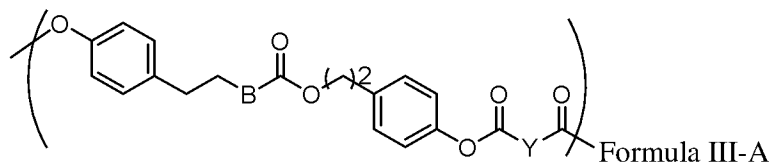


Table 2: Glass transition temperature and melt temperature of polymers of Formula III-A

Polymer	Glass Transition (T_g) (°C)	Melt Temperature (°C)
Poly(DiTyGlutarate Glutarate)	6	106
Poly(DiTyGlutarate Diglycolate)	19	73
Poly(DiTyGlutarate DD)	-6	99
Poly(DiTyGlycolate DD)	7	88

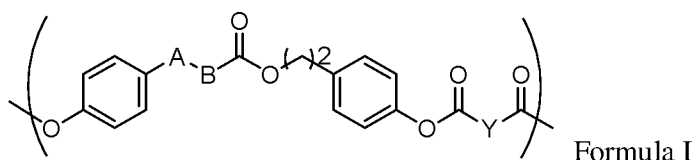
[0077] Poly(HTy glutarate) (Table 1) has proven to be an excellent material to use for medical/dental applications with a glass transition temperature of 32°C and the capability to undergo water-induced crystallization at 37°C in 10-30 minutes depending on device thickness, molecular weight, etc. The water-induced crystallization has been characterized by using mechanical testing (Figure 1) and X-ray diffraction (XRD) (Figure 2).

[0078] It will be appreciated by persons skilled in the art that the invention described herein is not limited to what has been particularly shown and described. Rather, the scope of the invention is defined by the claims which follow. It should further be understood that the above description is only representative of illustrative examples of embodiments. The description has not attempted to exhaustively enumerate all possible variations. The alternate embodiments may not have been presented for a specific substituent of the polymer or implant, or a step of the method, and may result from a different combination of described substituent or agent, or that other undescribed alternate embodiments may be available for a polymer or implant or method, is not to be considered

a disclaimer of those alternate embodiments. It will be appreciated that many of those un-described embodiments are within the literal scope of the following claims, and others are equivalent.

CLAIMS

1. A method of forming and utilizing a medical implant having a pre-determined shape, comprising
 - (a) melt processing and quenching a polymer to generate a pre-determined shape, geometry, or architecture;
 - (b) heating the pre-shaped polymer above its glass transition temperature (T_g) but below its melting point;
 - (c) at least partially reshaping the polymer to adapt it to the surgical site or clinical application; and
 - (d) exposing the polymer to a liquid medium to harden the polymer,
 wherein the polymer comprises repeating units of Formula I



wherein:

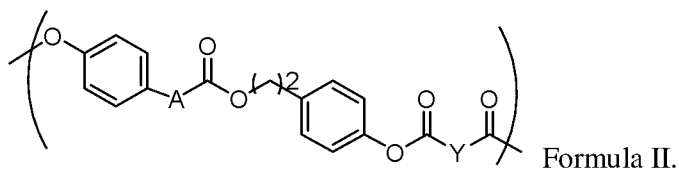
A is C_{1-3} alkyl,

B is either a bond or $-O-CO-C_{2-5}$ alkyl, where B is bonded to A via the oxygen of the $-O-CO-C_{2-5}$ alkyl, and optionally two adjacent carbons of said C_{2-5} alkyl have an oxygen inserted therebetween, and

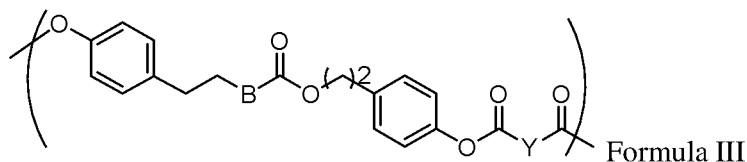
Y is C_{2-10} alkyl or C_{2-10} alkenyl, wherein optionally two adjacent carbons of said C_{2-10} alkyl or C_{2-10} alkenyl have an oxygen inserted therebetween.

2. The method of claim 1, wherein the polymer is in an amorphous state following step (a).
3. The method of claim 1, wherein the glass transition temperature is above room temperature.
4. The method of claim 1, wherein step (d) takes place at a temperature ranging from about 35°C to about 40°C .
5. The method of claim 1, wherein step (d) takes place at about 37°C .
6. The method of claim 1, wherein step (d) enables the polymer to reach a tensile modulus of more than 20 MPa at about 37°C within about 20 minutes.
7. The method of claim 1, wherein step (d) enables the polymer to reach a strain-at-break value of less than about 120% at about 37°C within about 20 minutes.

8. The method of claim 1, wherein step (d) enables the polymer to reach a compressive modulus of more than 20 MPa at 37°C within about 20 minutes.
9. The method of claim 1, wherein step (d) enables the polymer to reach a flexural modulus of more than 20 MPa at 37°C within about 20 minutes.
10. The method of claim 1, wherein step (d) enables the polymer to reach a tensile modulus of more than 200 MPa at 37°C within 24 hours.
11. The method of claim 1, wherein step (d) enables the polymer to reach a compressive modulus of more than 200 MPa at 37°C within 24 hours.
12. The method of claim 1, wherein step (d) enables the polymer to reach a flexural modulus of more than 200 MPa at 37°C within 24 hours.
13. The method of claim 1, wherein step (d) takes place in or around a tooth cavity or extraction socket, an alveolar or bone defect, a nerve defect, a soft tissue defect or injury including skin, gingiva, connective tissue, or vascular tissue in a subject.
14. The method of claim 1, wherein the liquid medium of step (d) is selected from the group consisting of distilled water, deionized water, normal saline, phosphate-buffered saline (PBS) solution, simulated body fluid (SBF) solution, blood, plasma, serum, saliva, mucous, cerebrospinal fluid, interstitial fluid, synovial fluid, urine, gastric fluid, bile and any combination thereof.
15. The method of claim 1, wherein the polymer is admixed with an agent selected from the group consisting of antibacterial agents, anti-viral agents, anti-inflammatory agents, antioxidants, immunogens, cytotoxins, hemostatic agents, neurotrophic factors, osteoinductive factors, pro-angiogenic factors, growth factors and any combination thereof.
16. The method of claim 1, wherein Y is selected from the group consisting of $(CH_2)_2$, $(CH_2)_3$, CH_2OCH_2 , $(CH_2)_4$, $CH_2CH=CHCH_2$, $(CH_2)_5$, $(CH_2)_6$, and $(CH_2)_{10}$.
17. The method of claim 1, wherein the polymer comprises repeating units of Formula II

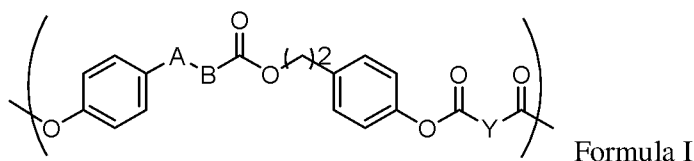


18. The method of claim 17, wherein A is CH_2 or CH_2CH_2 .
19. The method of claim 1, wherein the polymer comprises Formula III



Formula III

20. The method of claim 19, wherein B is selected from the group consisting of $-O-CO-CH_2CH_2$, $-O-CO-CH_2CH_2CH_2$, and $-O-CO-CH_2OCH_2$.
21. An implant prepared according to the method of claim 1.
22. A medical kit comprising the implant of claim 21.
23. A method of placing an implant in a subject in need thereof, comprising
- (d) heating a pre-shaped polymer above its glass transition temperature (T_g) but below its melting point;
 - (e) partially reshaping the now malleable polymer to adapt it to the surgical site or clinical application; and
 - (f) exposing the polymer to a liquid medium to harden the polymer,
- wherein the polymer comprises repeating units of Formula I



Formula I

wherein:

A is C_{1-3} alkyl,

B is either a bond or $-O-CO-C_{2-5}$ alkyl, where B is bonded to A via the oxygen of the $-O-CO-C_{2-5}$ alkyl, and optionally two adjacent carbons of said C_{2-5} alkyl have an oxygen inserted therebetween, and

Y is C_{2-10} alkyl or C_{2-10} alkenyl, wherein optionally two adjacent carbons of said C_{2-10} alkyl or C_{2-10} alkenyl have an oxygen inserted therebetween.

24. The method of claim 23, wherein the polymer hardens at about or below 37°C .
25. The method of claim 23, wherein the implant is placed in or around a tooth cavity or extraction socket, an alveolar or other bone defect, a nerve defect, a soft tissue defect or injury including skin, gingiva, connective tissue, or vascular tissue in a subject.

Figures

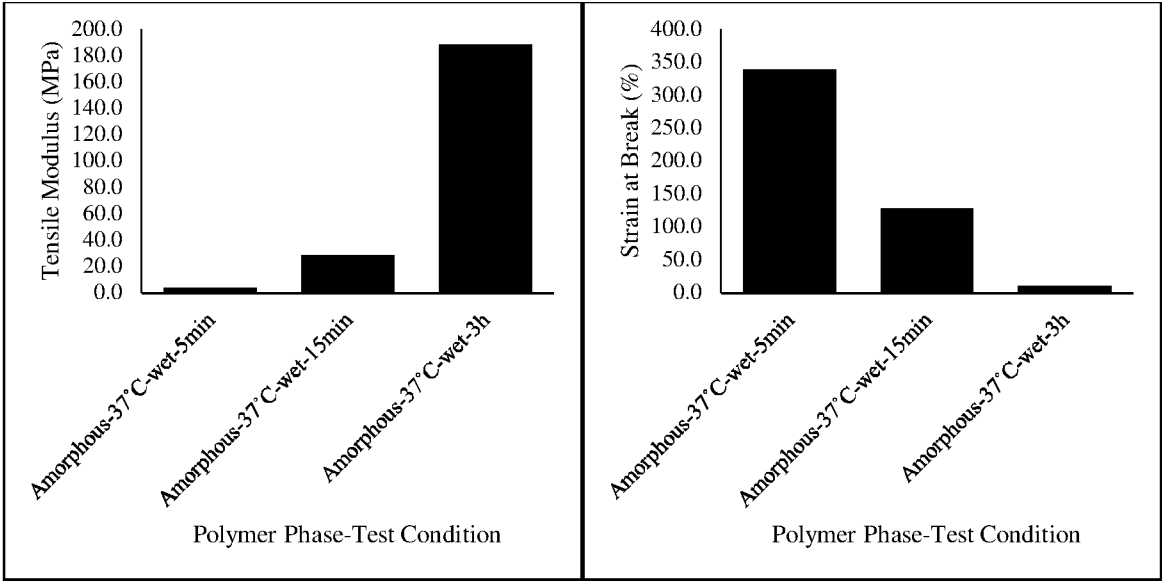


Figure 1

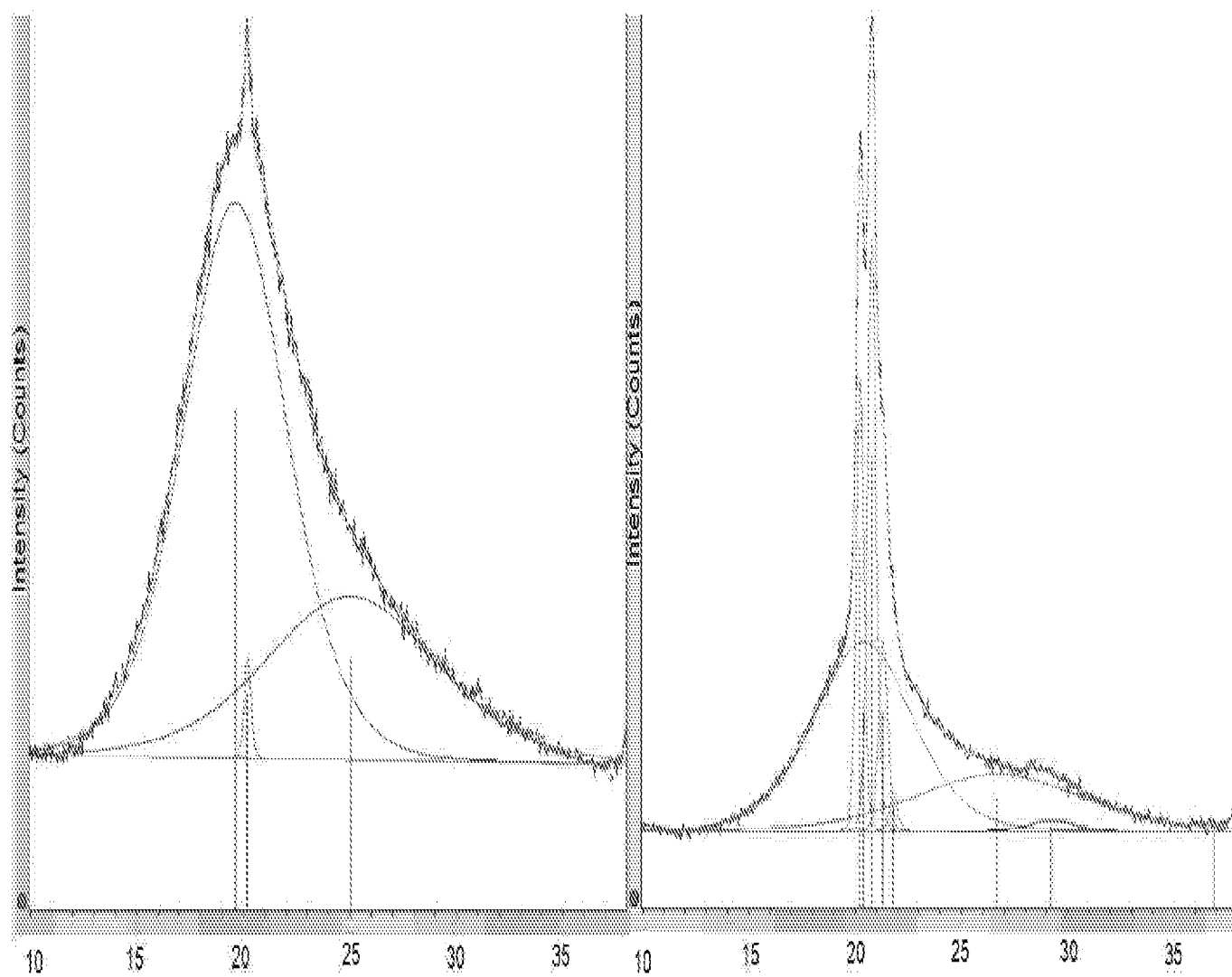


Figure 2

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 20/42518

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 47/34; A61L 31/14; C08G 63/64; C08G 63/66 (2020.01)

CPC - A61K 47/34; A61L 31/148; C08G 63/64; C08G 63/66

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)

See Search History document

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

See Search History document

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

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2016/0376401 A1 (RUTGERS, THE STATE UNIVERSITY OF NEW JERSEY) 29 December 2016 (29.12.2016) para [0011], [0026], [0036]	1-25
A	US 2015/0045451 A1 (RUTGERS, THE STATE UNIVERSITY OF NEW JERSEY) 12 February 2015 (12.02.2015) para [0205]	1-25
A	WO 2016/028292 A1 (TEPHA, INC.) 25 February 2016 (25.02.2016) pg 6, ln 4-8; pg 12, ln 17-25; pg 15, ln 8-30; pg 16, ln 30 to pg 17, ln 6; pg 19, ln 3-13	1-25
A	US 2009/0288753 A1 (CALHOUN et al.) 26 November 2009 (26.11.2009) para [0024]-[0028], Fig 1; claim 1	1-25

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

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"D" document cited by the applicant in the international application

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

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

17 September 2020

Date of mailing of the international search report

15 OCT 2020

Name and mailing address of the ISA/US

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