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(54) Title: SHAPE MEMORY POLYMERS CONTAINING DEGRADATION ACCELERANT

(57) Abstract: The present disclosure relates to a polymer composition including a lactic acid based polymer material and a fatty acid, wherein the polymer material includes shape memory qualities.

SHAPE MEMORY POLYMERS CONTAINING DEGRADATION ACCELERANT

Cross-Reference to Related Applications

[0001] This application is a PCT International Application of United States Patent Application No. 60/912,821 filed on April 19, 2007, the disclosure of which is incorporated by reference in its entirety.

Background of the Invention

1. Field of the Invention

[0002] This present disclosure relates generally to shape memory polymers and, more particularly, shape memory polymers having degradation accelerants.

2. Related Art

[0003] Resorbable shape memory polymers have had various applications in medical devices including stents, fracture fixation devices, and tissue fasteners. Control of degradation rates of shape memory polymers is normally achieved by changing the type and/or ratio of monomer species used to produce the polymers. However, it is difficult to tailor shape memory polymers with properties for specific applications as the mechanical properties and degradation rate are interdependent, so changes to the formulation to achieve specification for one may be detrimental to the other.

[0004] There remains a need in the art for a shape memory polymer composite that maintains good mechanical properties and shape memory characteristics, while offering a tailored degradation rate once the primary role of the shape memory polymer is no longer needed.

Summary of the Invention

[0005] In one aspect, the present disclosure relates to a polymer composition including a lactic acid based polymer material and a fatty acid, wherein the polymer material includes shape memory qualities. In one embodiment, the fatty acid comprises between about 0.5% to about 10% by weight of the polymer composition. In another embodiment, the fatty acid comprises between about 2% to about 5% by weight of the polymer composition. In another embodiment, the polymer material includes Poly L,D lactic acid. In yet another embodiment, the fatty acid includes lauric acid.

[0006] Further features, aspects, and advantages of the present disclosure, as well as the structure and operation of various embodiments of the present disclosure, are described in detail below with reference to the accompanying drawings.

Brief Description of the Drawings

[0007] The accompanying drawing, which is incorporated in and forms a part of the specification, illustrates the embodiments of the present disclosure and together with the description, serves to explain the principles of the disclosure. In the drawing:

[0008] Fig. 1 shows the changes in molecular weight of shape memory polymers during in-vitro degradation.

Detailed Description of the Embodiments

[0009] The following description of the preferred embodiment(s) is merely exemplary in nature and is in no way intended to limit the disclosure, its application, or uses.

[0010] The present disclosure relates to a shape memory polymer material including a fatty acid or derivative that enables a pre-determined strength retention profile to be produced in

the shape memory polymer without having to compromise its shape memory qualities, specifically its relaxation flow characteristics, or its mechanical strength.

[0011] For the purposes of this disclosure, the polymer includes a polylactide based polymer. However, any biocompatible, resorbable, polymeric material may be used, including, without limitation, poly-alpha-hydroxy acids, polycaprolactones, polydioxanones, polyesters, polyglycolic acid, polyglycols, polylactides, polyorthoesters, polyphosphates, polyoxaesters, polyphosphoesters, polyphosphonates, polysaccharides, polytyrosine carbonates, polyurethanes, and copolymers or polymer blends thereof.

[0012] The acid or derivative may be selected from a group including hexanoic acid, octanoic acid, decanoic acid, lauric acid, myristic acid, crotonic acid, 4-pentanoic acid, 2-hexanoic acid, undecylenic acid, petroselenic acid, oleic acid, erucic acid, 2, 4-hexadienoic acid, linoleic acid, linolenic acid, benzoic acid, hydrocinnamic acid, 4-isopropylbenzoic acid, ibuprofen, ricinoleic acid, adipic acid, suberic acid, phthalic acid, 2-bromolauric acid, 2,4-hydroxydodecanoic acid, monobutryrin, 2-hexyldecanoic acid, 2-butyloctanic acid, 2-ethylhexanoic acid, 2-methylvaleric acid, trans beta-hydromuconic acid, isovaleric anhydride, hexanoic anhydride, decanoic anhydride, lauric anhydride, myristic anhydride, 4-pentanoic anhydride, oleic anhydride, linoleic anhydride, benzoic anhydride, poly (azelaic anhydride), 2-octen-1-yl succinic anhydride, and phthalic anhydride.

[0013] The fatty acids or their derivatives reduce the transition temperature of the polymer material, as will be further described below. High concentrations of the fatty acid will reduce the transition temperature of the material and weaken it to a degree where the shape memory properties are compromised. For the purposes of this disclosure, a high concentration of fatty acid would be one that represents more than 10% by weight of the polymer

composition. Therefore, the fatty acid concentration should between about 0.5% to about 10% by weight of the polymer composition and, in some circumstances, is between about 2% to about 5% by weight of the composition. The fatty acid concentration is dependent on the polymer and fatty acid composition used.

[0014] Generally, polymers that display shape memory qualities show a large change in modulus of elasticity at the glass transition temperature (T_g). The shape-memory function can be achieved by taking advantage of this characteristic. Namely, the mixture of polymer and fatty acid is processed, via processes known to one of skill in the art, to make a macroscopic body of polymer material. The body is then processed to include shape memory qualities via a process including, without limitation, zone drawing, hydrostatic extrusion, die drawing, compression flow molding, thermoforming, rolling, and roll drawing. During this process, a definite shape (the original shape) is imparted to the macroscopic body. The body may then be softened by providing it with energy to increase its temperature to a temperature (T_f) higher than the T_g of the polymer, but lower than the melting temperature (T_m). At this temperature, the material may be deformed so as to form a different macroscopic shape (the deformed shape). The polymeric material is then cooled to a temperature lower than the T_g, while maintaining its deformed state. When the polymeric material is heated again to a temperature higher than the secondary molding temperature T_f, but lower than the T_m, the deformed state disappears and the polymeric material relaxes to recover its original shape. The glass transition temperature of the polymer material will vary based on a variety of factors, such as molecular weight, composition, structure of the polymer, and other factors known to one of ordinary skill in the art.

[0015] The macroscopic body of polymer material may include fixation devices such as, without limitation, rods, pins, nails, screws, plates, anchors, and wedges for use in repair of bone and soft tissue. In addition, the body of polymer material may include a sleeve of polymer material, including a central channel, which allows the sleeve to be placed on a fixation device, such as the fixation devices listed above, for subsequent use in fixating the fixation device to bone, as is described in PCT International Application No. PCT/US08/56828 (the '828 application), the disclosure of which is incorporated herein by reference in its entirety.

[0016] Examples of adding energy to the polymer material include electrical and thermal energy sources, the use of force, or mechanical energy, and/or a solvent. The thermal energy source may include a heated liquid, such as water or saline. It is also within the scope of this disclosure that once the macroscopic body is placed in the bone, body heat would be transferred from blood and tissue, via thermal conduction, to provide the energy necessary to deform the shape memory polymer material. In this instance, body temperature would be used as the thermal energy source. Examples of electrical energy sources include heat generating devices such as a cauterizing device or insulated conductor, as more fully described in the '828 applicatio, or a heating probe, as more fully described in PCT Application No. PCT/US2008/056836, the disclosure of which is incorporated herein by reference in its entirety.

[0017] Any suitable force that can be applied either preoperatively or intra-operatively can be used. One example includes the use of ultra sonic devices, which can relax the polymer material with minimal heat generation. Solvents that could be used include organic-based solvents and aqueous-based solvents, including body fluids. Care should be taken that the selected solvent is not contra indicated for the patient, particularly when the solvent is used intra-operatively. The choice of solvents will also be selected based upon the material to be

relaxed. Examples of solvents that can be used to relax the polymer material include alcohols, glycols, glycol ethers, oils, fatty acids, acetates, acetylenes, ketones, aromatic hydrocarbon solvents, and chlorinated solvents.

[0018] The polymeric material may include a composite or matrix having reinforcing material or phases such as glass fibers, carbon fibers, polymeric fibers, ceramic fibers, ceramic particulates, rods, platelets, and fillers. Other reinforcing material or phases known to one of ordinary skill in the art may also be used. In addition, the polymeric material may be porous. Porosity may allow infiltration by cells from surrounding tissues, thereby enhancing the integration of the material to the tissue. Also, one or more active agents may be incorporated into the material. Suitable active agents include bone morphogenic proteins, antibiotics, anti-inflammatories, angiogenic factors, osteogenic factors, monobutyrin, thrombin, modified proteins, platelet rich plasma/solution, platelet poor plasma/solution, bone marrow aspirate, and any cells sourced from flora or fauna, such as living cells, preserved cells, dormant cells, and dead cells. It will be appreciated that other bioactive agents known to one of ordinary skill in the art may also be used. Preferably, the active agent is incorporated into the polymeric shape memory material, to be released during the relaxation or degradation of the polymer material. Advantageously, the incorporation of an active agent can act to combat infection at the site of implantation and/or to promote new tissue growth.

EXAMPLE

[0019] Two mixtures of 70g of Poly (L-co-D, L-Lactide) (PLDLA) 70:30 and 1.43g of lauric acid were placed in two 500 ml jars, one mixture in each jar. 400 ml of dichloromethane solvent was then added to each jar and the jars were placed on rollers to mix the contents until they had completely dissolved. The resulting solutions were cast into a single sheet by pouring

them into a tray and allowing the solvent to evaporate overnight. The polymer sheet was vacuum dried at up to about 40°C for two days, then ground into granules via a granulator fitted with a 3 mm aperture grating. The resulting granules were then vacuum dried at 30°C for a further 10 days to remove any residual solvent.

[0020] Approximately 140 g of the above granules and 140g of PLDLA granules without lauric acid, were each molded to produce two 30 mm diameter rods suitable for die drawing. The PLDLA rods not containing lauric acid were used as the control. These rods were drawn through a 15 mm die at 75°C at a rate of 30 mm/minute to produce rods with a diameter of approximately 15 mm. The shape recovery properties of these rods were then demonstrated by placing samples of the rods in hot water (about 90°C) for 5 minutes. The changes in diameter due to recovery are shown in Table 1. It is observed that the addition of lauric acid did not affect the shape memory properties of the rod, as both samples returned to their original diameter of 30 mm.

TABLE 1

Sample	Diameter (mm)	
	Pre-recovery	Post-recovery
Control PLDLA SMP rod	15	30
PLDLA + 2% Lauric acid SMP rod	14	30

[0021] Samples of both the control rods and the lauric acid rods were degraded in-vitro in phosphate buffered saline (PBS) at 37°C for up to 42 weeks. Specifically, 0.35g to 0.50g of each sample were placed in 20 ml of PBS then put in a 37°C incubator. At two week intervals one sample of each type was removed from the incubator and placed in the freezer to halt the degradation.

[0022] After the 42 week time point, the samples were removed from the freezer and their molecular weight distributions determined via the following process: Samples were prepared in chloroform + 0.1% toluene at concentrations of approximately 1mg/mL. The samples were allowed to dissolve over night with occasional, gentle agitation. The resultant solutions were filtered through 0.45μm PTFE syringe filters before analysis. Molecular weight was determined by gel permeation chromatography (GPC) in chloroform using a Polymer labs Mixed-B column. Calibration was achieved using narrowly disperse polystyrene standards.

[0023] The number average molecular weights (Mn) obtained for both polymer rods are shown in Fig. 1. Only a small decline in the Mn of the control rod was observed over the 43 week degradation period. However, the Mn of the lauric acid rod fell substantially, dropping to less than 10% of its starting value after 28 days.

[0024] Hence it can be concluded that the addition of lauric acid may significantly increase the degradation rate of the polymer material, without compromising the shape memory characteristics. It is believed, especially with the low percentage of fatty acid used, that the addition of the fatty acid will also not compromise the initial mechanical stability of the polymer material.

[0025] In view of the foregoing, it will be seen that the several advantages of the disclosure are achieved and attained.

[0026] The embodiments were chosen and described in order to best explain the principles of the disclosure and its practical application to thereby enable others skilled in the art to best utilize the disclosure in various embodiments and with various modifications as are suited to the particular use contemplated.

[0027] As various modifications could be made in the constructions and methods herein described and illustrated without departing from the scope of the disclosure, it is intended that all matter contained in the foregoing description or shown in the accompanying drawings shall be interpreted as illustrative rather than limiting. Thus, the breadth and scope of the present disclosure should not be limited by any of the above-described exemplary embodiments, but should be defined only in accordance with the following claims appended hereto and their equivalents.

What is Claimed Is:

1. A polymer composition comprising a lactic acid based polymer material and a fatty acid, wherein the polymer material includes shape memory qualities.

2. The polymer composition of claim 1 wherein the fatty acid comprises between about 0.5% to about 10% by weight of the polymer composition.

3. The polymer composition of claim 2 wherein the fatty acid comprises between about 2% to about 5% by weight of the polymer composition.

4. The polymer composition of claim 1 wherein the polymer material includes Poly L,D lactic acid.

5. The polymer composition of claim 1 wherein the fatty acid includes lauric acid.

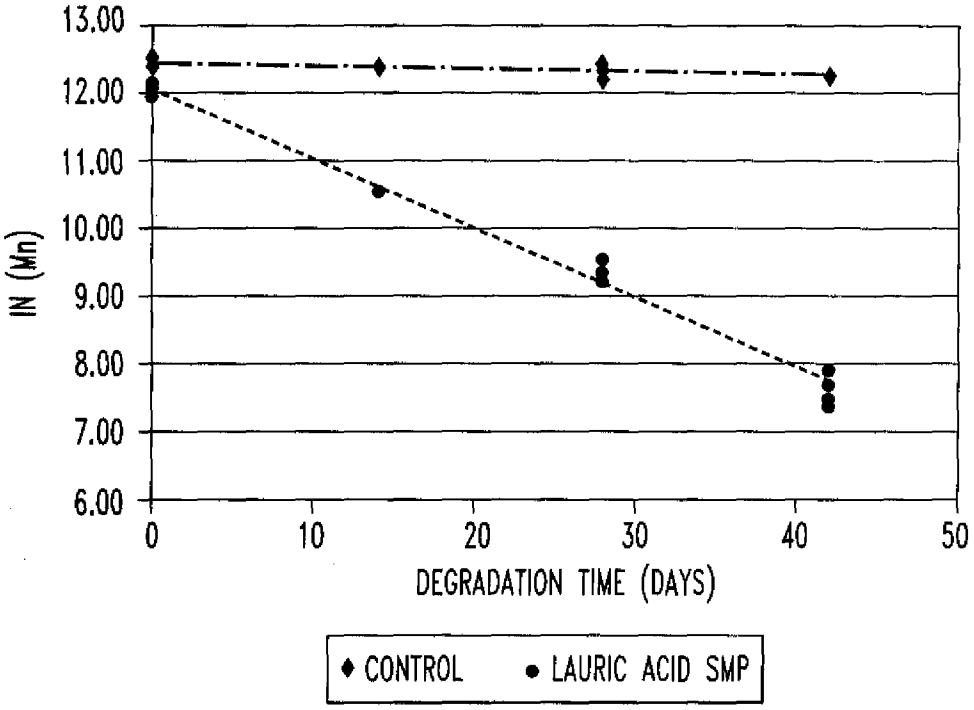
13.00
12.00
11.00
10.00
9.00
8.00
7.00
6.00
IN (Mn)
0
10
20
30
40
50
DEGRADATION TIME (DAYS)
♦ CONTROL
● LAURIC ACID SMP

FIG.1

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2008/060325

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61L27/50 A61L31/14 C08K5/00 C08K5/09

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)
A61L C08K C08L

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 1 000 958 A (TAKIRON CO [JP]) 17 May 2000 (2000-05-17) paragraphs [0001], [0014], [0032], [0036]; claims 1,2,24-26; example all	1-5
A	WO 00/56376 A (METABOLIX INC [US]) 28 September 2000 (2000-09-28) pages 8-9; claims 1-3,24 page 15, line 15 - page 18, line 27 page 56; table 1	1-5
A	US 2002/123546 A1 (BIGG DONALD M [US] ET AL) 5 September 2002 (2002-09-05) paragraphs [0062], [0063]; claims 1,41-44 tables 1-3	1-5

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

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document 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	Date of mailing of the international search report
14 July 2008	22/07/2008

Name and mailing address of the ISA/	Authorized officer
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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: -

The present claims 1-5 are characterised in that the polymeric composition "comprises" a lactic acid based polymer material. Hence, the subject matter claimed also encompasses compositions wherein said lactic acid based polymer is only present as a minor component. The claims, thus, relate to an extremely large number of possible compositions. Support and disclosure in the sense of Article 6 and 5 PCT is to be found however for only a very small proportion of said compositions, namely only those wherein the polymeric component of the composition "consists essentially" in a lactic acid polymer (see examples).

Besides, many of the additives recited in par. 12 as suitable "fatty acids" as claimed are acutally no "fatty acid" according to their usual definition, namely monobasic acids containing only the elements carbon, hydrogen and oxygen and consisting of an opt. unsaturated alkyl radical attached to the carboxyl group (see e.g. Römpps dictionary). Hence, the subject matter for which protection is sought is unclear.

The non-compliance with the substantive provisions is to such an extent, that the search was performed taking into consideration the non-compliance in determining the extent of the search of claim .1-5 (PCT Guidelines 9.19 and 9.23). The search of claims 1-5 was restricted to those claimed compositions which appear to be supported namely the subject matter of claims 1-5 wherein the polymeric component of the composition consists essentially in a lactic acid polymer or a blend thereof and containing as additive a fatty acid i.e. a monobasic acid containing only the elements carbon, hydrogen and oxygen and consisting of an opt. unsaturated alkyl radical attached to the carboxyl group.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.2), should the problems which led to the Article 17(2)PCT declaration be overcome.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2008/060325

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: –
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search reportcovers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2008/060325

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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