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IMPLANT FOR EYE

The present invention relates to an implant for implantation in an eye and a production
5 process thereof.

Glaucoma is a neurodegenerative disease of the optic nerve and the leading cause of
irreversible vision loss worldwide. Elevated intraocular pressure (IOP) is considered to be
the major risk factor for glaucoma and is associated with a disbalance between the
10 production and drainage of aqueous humor (AqH, internal eye fluid), due to an increased
resistance to AqH outflow. Lowering the IOP remains the only proven treatment to halt
progression of the disease and visual field loss. Ophthalmologists use a variety of
approaches to lower IOP, including medication (eye drops), laser procedures, and
incisional surgeries.

15 In the traditional paradigm, topical ocular hypotensive drugs and/or laser therapy
represent the first-line treatment option for glaucoma. Surgery is often performed when
the maximum tolerated medical/laser treatments fail to sufficiently lower IOP and prevent
disease progression. More traditional drainage surgeries such as trabeculectomy
20 (creating a surgical fistula, hole in the eye that is covered by connective tissue) and
implantation of aqueous shunts, although highly effective at lowering IOP, are associated
with serious postoperative complications, require substantial postoperative management,
and have been reported to have high failure rates. In order to provide a safer and less
invasive way of reducing IOP, a new class of glaucoma implants has recently emerged,
25 termed minimally invasive glaucoma surgery (MIGS) devices. These devices help to
reduce the IOP with minimal tissue manipulation/destruction, and are associated with a
relatively high safety profile, short surgery time and rapid recovery. To date, the available
MIGS devices offer a more modest IOP-lowering effect than traditional incisional
surgeries, but with the benefit of a safer risk profile.

30 Since the trabecular meshwork is considered the major site of AqH outflow resistance in
open-angle glaucoma, bypassing this structure and directing the AqH flow from the
anterior chamber into Schlemm's canal seems to be the most reasonable approach to
reduce IOP. MIGS devices using this approach are typically called Schlemm's canal

MIGS devices. Currently, the two most commonly used Schlemm's canal MIGS devices are the iStent inject® (Glaukos Corporation, California, USA) and the Hydrus® Microstent (Ivantis, Inc., California, USA). The iStent inject® is made of heparin-coated implant-grade titanium and is inserted ab interno through a microincision made in the anterior chamber using an injector device.

The iStent inject® has been shown in numerous publications to be a safe and effective procedure in the treatment of different types of open-angle glaucoma, either as a standalone procedure or combined with cataract surgery. In these clinical studies, most patients experienced a clinically significant reduction in IOP and a reduction in reliance on glaucoma medication, with a low incidence of postoperative complications.

US10271989 discloses an implant for implantation in an eye, preferably made of one or more biocompatible materials. Suitable examples of polymers and metals are mentioned. US10271989 discloses that the implant can further include a biodegradable material in or on the implant such as poly(caprolactone). US10271989 discloses that the implants can be manufactured by sintering, micro machining, laser machining, and/or electrical discharge machining.

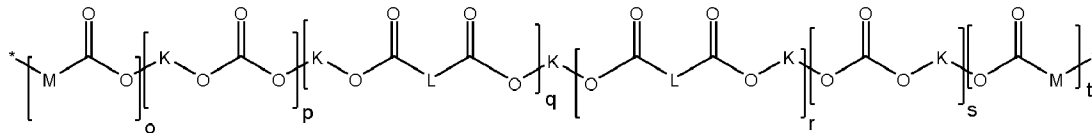
Known issues with existing MIGS devices are that sometimes they are blocked or overgrow in time with a fibrotic capsule, thereby closing the direct opening into systemic circulation leading to an increase in IOP and further progression of the disease. Currently, a new implant is injected in the trabecular meshwork, leaving the old implant. This causes problems for future implants since the location of an overgrown device is not known and no other glaucoma drainage implant can be placed near the same location due to an active fibrotic response.

It is an objective of the present invention to provide an implant in which the above-mentioned and/or other problems are solved.

Accordingly, the present invention provides an implant for implantation in an eye, wherein the implant comprises a thermoplastic elastomer according to the formula $[AB]_n$, wherein:

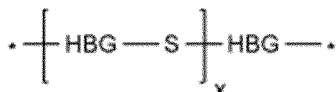
n represents the number of repeats of the AB segment and is an integer of 2 to 100;

A represents a soft block according to formula (I):



(I)

B represents a hard block according to formula (II):



5

(II)

wherein:

K is a C₁ - C₃₆ alkylene group, a C₆ - C₂₄ arylene group, a C₇ - C₂₄ alkarylene group or a C₇ - C₂₄ arylalkylene group;

10 L is a C₁ - C₃₆ alkylene group, a C₆ - C₂₄ arylene group, a C₇ - C₂₄ alkarylene group or a C₇ - C₂₄ arylalkylene group or L is absent;

M is a C₁ - C₃₆ alkylene group, a C₆ - C₂₄ arylene group, a C₇ - C₂₄ alkarylene group or a C₇ - C₂₄ arylalkylene group or M is absent;

o, p, q, r, s and t are independently 0 - 50;

provided that:

15 (a) when o, q, r and t are 0, then p and s are independently 1 - 50;

(b) when p and s are 0, then o, q, r and t are independently 1 - 50;

(c) when o and t are 0, then p, q, r and s are independently 1 - 50;

(d) when q and r are 0, then o, p, s and t are independently 1 - 50;

(e) when o, p, s and t are 0, then q and r are independently 1 - 50;

20 (f) when p, q, r and s are 0, then o and t are independently 1 - 50;

HBG is a simple hydrogen bonding unit independently selected from the group consisting of amide, urea and urethane groups;

S is a C₁ - C₃₆ alkylene group, a C₆ - C₂₄ arylene group, a C₇ - C₂₄ alkarylene group or a C₇ - C₂₄ arylalkylene group or S is absent; and

25 x is 1, 2 or 3.

The present invention further provides a process for making the implant, comprising hot embossing of the thermoplastic elastomer to obtain the implant.

The implant according to the invention is biodegradable and therefore has an advantage that it will be naturally absorbed into the body. The implant degrades slowly, which offers enough time for a proper and sufficient remodeling of the trabecular meshwork to occur around the implant. When degradation is finished, the extra outflow site created by the
5 implant remains patent, thus creating a long-term modification of the trabecular meshwork without the need for a permanent implant that may further scar and lose effectiveness. Being biodegradable is additionally advantageous in case the implant is mispositioned or becomes dislodged. As the implant will degrade over time, there will be no accumulation of “lost” implants inside the eye. For the same reason, if at some point the implant
10 becomes non-functional, it is less of a concern to reoperate the eye and implant a new implant.

The thermoplastic elastomer (TPE) used according to the invention has good processibility (e.g. good solubility, easy to melt), shape persistency (no or very little creep)
15 and elasticity suitable for making an eye implant. The TPE is also a soft material, and it is biodegradable and non-toxic, so it is suitable for application in the biomedical field.

It was found that the thermoplastic elastomer used according to the invention can withstand high temperature and high pressure without its polymer structure and
20 mechanical properties being significantly affected. This allows the thermoplastic elastomer to be subjected to a hot embossing process for producing the implant according to the invention, which process is particularly suitable due to the shape and size of the implant. In contrast, other types of polymers such as polycaprolactone were found to be unsuitable for hot embossing as they cannot be reliably formed into an
25 implant without substantial deformation.

The hot embossing processing allows producing a non-porous, dense implant. The non-porosity of the implant allows the implant to provide an effective fluid flow path. The non-porosity of the implant further results in the implant according to the invention to degrade
30 slower than e.g. a porous scaffold.

Further advantageously, the thermoplastic elastomer used according to the invention is a slow degrading polymer that mainly degrades through hydrolysis of the carbonate and amide groups, either through interaction with water or from enzymatic reactions.

Carbonate and amide groups degrade slower than esters, which are very common in other biodegradable polymers such as polycaprolactone and polylactic acid.

5 Further advantageously, the thermoplastic elastomer used according to the invention is non-cytotoxic.

It is noted that WO2015/194961 discloses the thermoplastic elastomer used according to the invention, but WO2015/194961 does not disclose its application to an implant for implantation in an eye and does not disclose hot embossing.

10

Implant

The implant according to the invention may have forms and dimensions described in US10271989, the contents of which are fully incorporated herein by reference. As described in US10271989, the implant according to the invention can have the following features.

15

As used herein, “implants” refers to ocular implants which can be implanted into any number of locations in the eye. In some embodiments, the ocular implants are drainage implants designed to facilitate or provide for the drainage of aqueous humor from the anterior chamber of an eye into a physiologic outflow pathway in order to reduce intraocular pressure. In some embodiments, the implant can be sized and shaped to provide a fluid flow path for draining aqueous humor from the anterior chamber through the trabecular meshwork and into Schlemm's canal.

20

25 The term “implant” as used herein is a broad term, and is to be given its ordinary and customary meaning to a person of ordinary skill in the art (and it is not to be limited to a special or customized meaning), and refers without limitation to drainage shunts, stents, sensors, drug delivery implants, drugs, therapeutic agents, fluids, or any other device or substance capable of being inserted within an eye. The term “implant” can be

30 interchanged with the words “stent” or “shunt” in various embodiments.

30

In certain embodiments, one or more of the implants are ocular implants for purposes other than drainage (for example, a drug delivery device or an ocular sensor for measuring intraocular pressure or components of ocular fluid, such as glucose). In some

embodiments, an implant comprises two sections or portions tethered together, such as a sensor tethered to a drainage implant, a sensor tethered to an anchor.

In some embodiments, drainage implants define one or more fluid passages. The fluid passage(s) in some embodiments remains patent and, in other embodiments, the passage(s) is fully or partially occluded under at least some circumstances (e.g., at lower intraocular pressure levels). The implants may feature a variety of characteristics which facilitate the regulation of intraocular pressure.

10 Preferably, the implant is configured to provide a fluid flow path for draining aqueous humor from the anterior chamber through the trabecular meshwork and into Schlemm's canal when implanted.

15 Preferably, the implant has a proximal portion, an intermediate portion and a distal portion, wherein the proximal portion is configured to reside in the anterior chamber and the distal portion is configured to reside in the Schlemm's canal, wherein a lumen extends from a proximal end of the proximal portion through the intermediate portion to a distal end of the distal portion to provide fluid communication between the proximal end and the distal end.

20 Preferably, the distance between the proximal end and the distal end is 0.01 to 1.0 mm.

The implant according to the invention can have the structure as described in detail in column 21, lines 20 to column 23, line 21 and Figure 18 of US10271989, incorporated
25 herein by reference.

Method for delivering the implant in an eye

Suitable ways of the method for delivering the implant according to the invention in an eye are described in detail in US10271989, incorporated herein by reference.

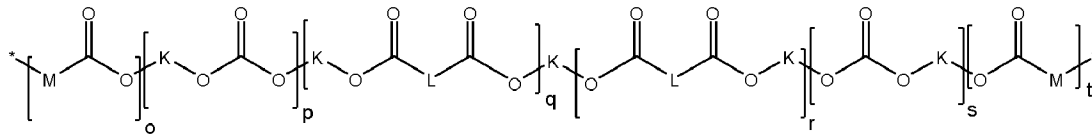
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Thermoplastic elastomer

The thermoplastic elastomer used according to the invention has the formula $[AB]_n$, wherein:

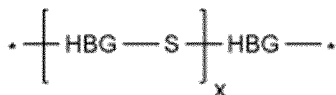
n represents the number of repeats of the AB segment and is an integer of 2 to 100;

A represents a soft block according to formula (I):



(I)

B represents a hard block according to formula (II):



(II)

wherein:

K is a C₁ - C₃₆ alkylene group, a C₆ - C₂₄ arylene group, a C₇ - C₂₄ alkarylene group or a C₇ - C₂₄ arylalkylene group;

L is a C₁ - C₃₆ alkylene group, a C₆ - C₂₄ arylene group, a C₇ - C₂₄ alkarylene group or a C₇ - C₂₄ arylalkylene group or L is absent;

M is a C₁ - C₃₆ alkylene group, a C₆ - C₂₄ arylene group, a C₇ - C₂₄ alkarylene group or a C₇ - C₂₄ arylalkylene group or M is absent;

o, p, q, r, s and t are independently 0 - 50;

provided that:

(a) when o, q, r and t are 0, then p and s are independently 1 - 50;

(b) when p and s are 0, then o, q, r and t are independently 1 - 50;

(c) when o and t are 0, then p, q, r and s are independently 1 - 50;

(d) when q and r are 0, then o, p, s and t are independently 1 - 50;

(e) when o, p, s and t are 0, then q and r are independently 1 - 50;

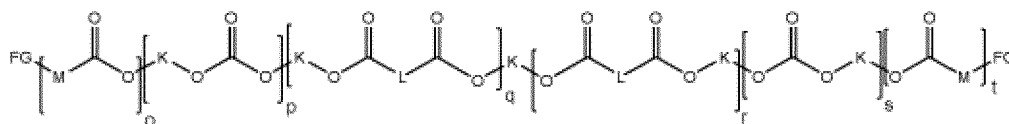
(f) when p, q, r and s are 0, then o and t are independently 1 - 50;

HBG is a simple hydrogen bonding unit independently selected from the group consisting of amide, urea and urethane groups;

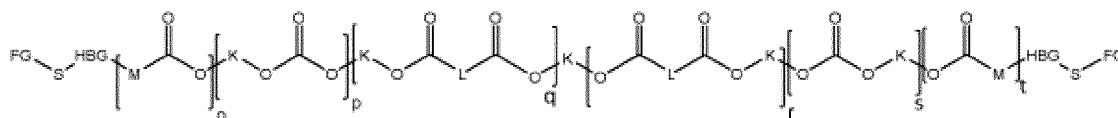
S is a C₁ - C₃₆ alkylene group, a C₆ - C₂₄ arylene group, a C₇ - C₂₄ alkarylene group or a C₇ - C₂₄ arylalkylene group or S is absent; and

x is 1, 2 or 3.

The thermoplastic elastomer may be prepared by a process wherein a prepolymer according to formula (III-A) or (III-B):

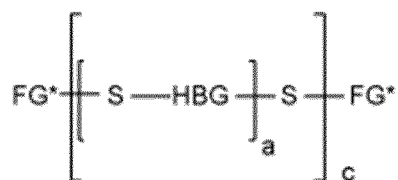


(III-A)



(III-B)

5 is reacted with a reactive compound according to formula (IV):



(IV)

wherein n, K, L, M, o, p, q, r, s, t, S and HBG have the meaning according to above;

10 FG is a functional group selected from the group consisting of hydroxy, azide, activated hydroxy, carboxylic acid, activated carboxylic acid, isocyanate, activated amine, ester, alkenyl, alkynyl and amine; and

FG* is a complementary functional group selected from the group consisting of isocyanate, amine, activated amine, carboxylic acid, activated carboxylic acid, ester,

15 hydroxy, activated hydroxy, azide, alkenyl and alkynyl; a is 0, 1, 2, 3 or 4; and c is 0 or 1.

Preferably, the soft block A does not display a melting transition or has a melting transition $T_{m\text{-SB}}$ of lower than 15 °C, and the hard block B displays a melting transition $T_{m\text{-HB}}$.

20

Suitable examples of the thermoplastic elastomer and the process for preparing the thermoplastic elastomer used according to the invention are described in detail in WO2015/194961, the contents of which are fully incorporated herein by reference.

25 Soft block A

Preferably, A is a (co)poly-carbonate, a (co)poly-ester or a co-poly(ester-carbonate). More preferably, A is a (co)poly-carbonate or a co-poly(ester-carbonate). Most preferably A is a (co)poly-carbonate. In this case, the thermoplastic elastomer has particularly beneficial mechanical properties that are required for making the eye implant according to the invention. Furthermore, (co)poly-carbonates have a preferred biodegradability, as degradation is usually slow.

In case soft block A contains multiple monomeric components (as reflected in o, p, q, r, s and t), then soft block A may be a random polymer, a block-copolymer or a sequence controlled polymer. Preferably, soft block A is then a random polymer.

In case soft block A contains monomeric components of one type only (either o and t, p and s, or q and r), then soft block A may be a homo-polymer or a co-polymer of monomeric components, where the monomeric units can either be randomly distributed over the chain, present in blocks or in a sequenced controlled fashion. Preferably, soft block A is then a homo-polymer.

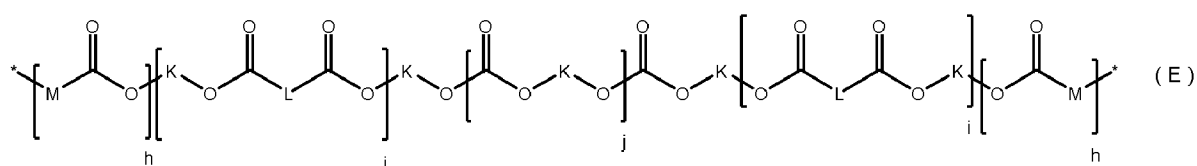
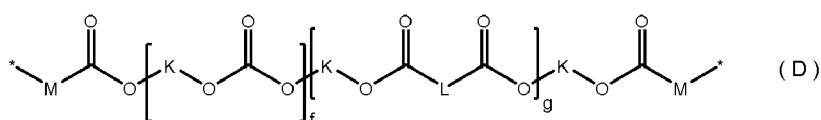
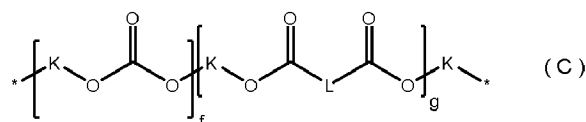
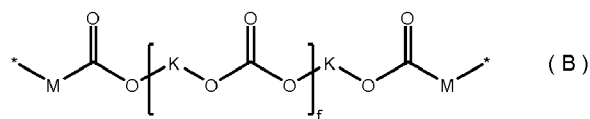
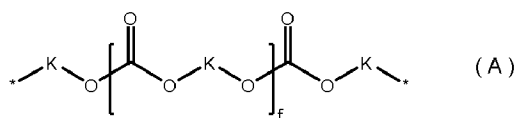
Preferably, the soft block A has a number average molecular weight M_n of 100 to 10,000 Dalton, preferably 500 to 5000 Dalton, wherein the number average molecular weight M_n of soft block A is for example determined by $^1\text{H-NMR}$ analysis. These ranges result in good mechanical properties of the implant according to the invention.

Preferably, K is selected from the group consisting of cyclic, linear or branched C_2 - C_{18} alkylene groups, more preferably from cyclic, linear or branched C_4 - C_{12} alkylene groups.

Preferably, L is absent or an alkylene selected from the group of cyclic, linear or branched C_2 - C_{18} alkylene groups. More preferably, L is selected from cyclic, linear or branched C_4 - C_{10} alkylene groups.

Preferably, M is selected from the group of cyclic, linear or branched C_1 - C_{17} alkylene groups. More preferably, M is selected from cyclic, linear or branched C_5 - C_{10} alkylene groups.

Preferably, soft blocks A are selected from the group consisting of:



(V)

- 5 wherein f, g and j are independently in the range of 1 - 500; and h is 0 (then i is 1) or 2 (then i is 0).

Preferably, f, g and j are independently in the range of 1 - 100, more preferably in the range of 1 - 50, most preferably in the range of 1 - 25.

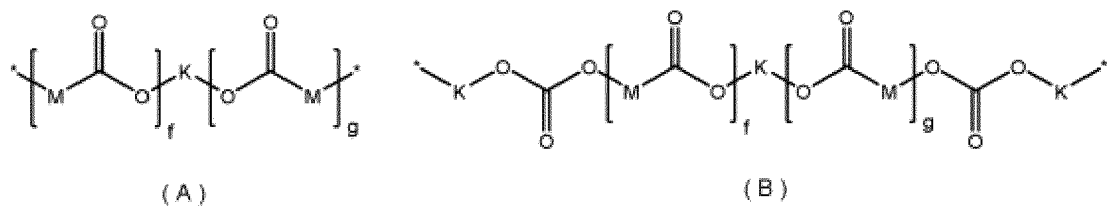
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Formula (V-A) represents a (co)poly-carbonate and formula (V-B) represents a polycarbonate with ester terminal groups. For these two formulas (V-A) and (V-B), the K and M spacers may be independently selected for every K and M in the soft block A and are alkylene, arylene, alkylarylene or arylalkylene groups, preferably alkylene groups. The M-spacer may also be a radical. Preferably, K is a linear, branched or cyclic C₄ - C₁₂ alkylene. Preferably, the two M-spacers in formula (V-B) are identical and are selected from C₁ - C₁₂ linear, branched or cyclic alkenes.

15

Preferably, and in a first particular case for formula (V-A), all K groups are the same, and in this case (V-A) represents a homo-polycarbonate. Then K is preferably selected from the group of linear, branched or cyclic C₄ - C₁₂ alkylenes, more preferably from C₄ - C₇ and C₉ linear alkylenes or C₅ - C₁₀ branched alkylenes that are derived from primary diols. Most preferably K is then selected from C₄ - C₇ linear alkylenes.

Soft block A may have the formula (VI):



the formula weight of the hard block B is not too high, and preferably it is lower than about 530 Dalton, more preferably it is lower than about 300 Dalton.

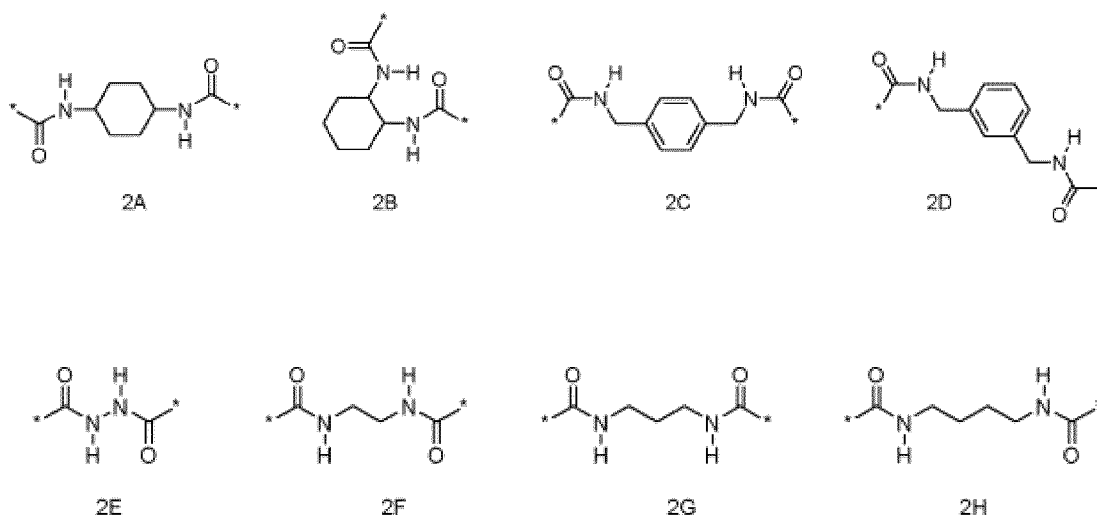
Preferably, S is absent or S is an alkylene selected from the group of cyclic, linear or branched C₁ - C₁₂ alkylene groups. More preferably, S is selected from linear or cyclic C₂ - C₆ alkenes that do not contain heteroatoms, where then n-ethylene, n-propylene, n-butylene, n-pentylene, n-hexylene, and 1,4-trans-cyclohexylene spacers are more preferred. This has an advantage that the thermoplastic elastomer has good processing and thermal properties suitable hot embossing which is particularly suitable for making an eye implant.

In an embodiment of the invention, the hard block is a bis-amide and S is 1,4-trans-cyclohexylene.

In an embodiment of the invention, the hard block is a bis-urea and S is n-ethylene, n-propylene, n-butylene, n-pentylene or n-hexylene, more preferably n-butylene or n-hexylene.

Preferably, x is 1 or 2.

Examples of preferred bis-amide hard blocks B are shown below. The asterisks represent the radical connections between these hard blocks B and the soft block A.



These are bis-amide (or di-amide) hard blocks B. Hard block 2A is derived from trans 1,4-cyclohexylene diamine, and is therefore not a mixture of isomers, but is a single isomeric form. Hard block 2B may either be derived from trans 1,2-cyclohexylene diamine or from cis 1,2-cyclohexylene diamine, not from both, and is therefore a single isomeric form.

5 Hard block 2E has a radical (i.e. no) spacer between the two amides, hard blocks 2F, 2G and 2H have n-ethylene, n-propylene and n-butylene S spacers, respectively. From this diamide hard block series, preferred hard blocks are 2A, 2C, 2D and 2H and the most preferred hard block is 2A. This has an advantage that the thermoplastic elastomer has good processing properties suitable for hot embossing, particularly suitable for making an
10 eye implant.

The TPE material $[AB]_n$

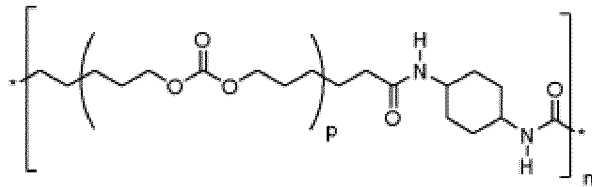
Preferably, the thermoplastic elastomer according to the formula $[AB]_n$ has a number average molecular weight M_n of 500 to 500,000 Dalton, preferably 1,000 to 100,000

15 Dalton, more preferably 10,000 to 50,000 Dalton, wherein the number average molecular weight M_n is determined by gel permeation chromatography. These ranges result in good mechanical properties of the implant according to the invention.

Soft block A is polymeric with a distribution in molecular weight. Preferably, hard block B
20 is the same molecular structure throughout the $[AB]_n$ material and has a single specific molecular weight. Preferably, blocks A and B are strictly alternating in the $[AB]_n$ polymer.

The weight percentage of the hard block B in the $[AB]_n$ polymer according to the invention is preferably between about 1 w/w% and about 60 w/w%, based on the total weight of the
25 $[AB]_n$ polymer. More preferably, it is between about 2 w/w% and about 25 w/w%, even more preferably between about 3 w/w% and about 16 w/w%, yet even more preferably between about 4 w/w% and about 12 w/w% and most preferably between about 5 w/w% and about 10 w/w%.

30 In particularly preferred embodiments, the thermoplastic elastomer is a poly(hexyl carbonate bis-amide represented by the below formula, where the cyclohexyl-diamine is iso-merically pure trans:



The thermoplastic elastomer $[AB]_n$ used according to the invention has good processability (e.g. good solubility, easy to melt), shape persistency (no or very little creep) and elasticity suitable for making an eye implant. The TPE is also a soft material, and it is

5 biodegradable and non-toxic, so it is suitable for application in the biomedical field.

Preferably, the $[AB]_n$ materials of the invention may be solubilized at room temperature in chloroform/methanol (10 v/v% methanol) at a concentration of at least 1 (w/v)%, preferably at a concentration of at least 5 (w/v)%, most preferably at a concentration of at least 10 (w/v)%, thereby producing homogeneous, clear and free flowing solutions (viscous or low viscous solutions). Accordingly, the formation of gels or jellies or inhomogeneities is avoided. More preferably, homogeneous, clear and free flowing solutions are acquired at room temperature in chloroform/methanol (1 v/v% methanol) using a concentration of the $[AB]_n$ material of at least 1 (w/v)%, preferably using a concentration of at least 5 (w/v)%, and most preferably using a concentration of at least 10 (w/v)%.

The mechanical properties of the $[AB]_n$ polymer can be checked by performing uniaxial tensile testing experiments and/or by performing Dynamic Mechanical Thermal Analysis (DMTA) experiments.

Tensile testing experiments provide a stress-strain curve from which for example the Young's modulus (E) can be derived. Preferably, the Young's modulus (E) of the $[AB]_n$ material at room temperature is between about 0.2 MPa and about 200 MPa, more preferably between about 1 MPa and about 100 MPa. The Young's modulus is preferably higher than about 5 MPa, more preferably it is higher than about 10 MPa, and most preferably it is higher than about 15 MPa.

DMTA measurements provide storage moduli (E') and loss moduli (E'') as a function of temperature. Preferably, in DMTA, the storage modulus (E') of the $[AB]_n$ material at 37 °C

is between about 0.2 MPa and about 200 MPa, and more preferably between about 1 MPa and about 100 MPa. This modulus is preferably higher than about 5 MPa, more preferably it is higher than about 10 MPa, and most preferably it is higher than about 15 MPa. Moreover, this storage modulus shows little dependence on temperature between about 20 °C and about 80 °C. Specifically, the storage modulus E' at 80 °C has a value that is at least about 75%, more preferably at least about 90% and most preferably at least about 95% of the E' storage modulus as recorded at 20 °C. Similarly, the storage modulus E' at 50 °C preferably has decreased with less than about 15%, more preferably with less than about 10%, and most preferably with less than about 5%, as compared to the storage E' -modulus as measured at 30 °C.

The Young's modulus (E), the storage modulus (E') and the loss modulus (E'') show the mechanical properties of the material. The indicated preferred ranges for the E and E' moduli indicate that the $[AB]_n$ material is a soft material.

In another preferred embodiment, the $\tan(\delta)$ as determined with DMTA at 37 °C, is lower than about 1. Preferably, this $\tan(\delta)$ is lower than about 0.2, more preferably, the $\tan(\delta)$ is lower than about 0.1, even more preferably it is about 0.06 or lower, and most preferably it is about 0.04 or lower. The $\tan(\delta)$ is a measure for the elasticity of a material at a certain temperature.

The $\tan(\delta)$ value is indicative of the elasticity of the material at a certain temperature. The lower the value for $\tan(\delta)$, the more elastic the material generally is. The indicated preferred ranges for $\tan(\delta)$ indicate that the $[AB]_n$ material is an elastic and shape-persistent material.

DMTA can also be used to determine the flow temperature (T -flow) of a material, where this is the temperature at which the storage E' -modulus suddenly decreases, and here it is defined as the temperature at which the E' -modulus has fallen below about 0.1 MPa. The T -flow of the materials according to the invention is preferably higher than about 100 °C, more preferably higher than about 115 °C and most preferably higher than about 125 °C. Furthermore, the T -flow is preferably lower than about 250 °C, more preferably lower than

about 200 °C, and most preferably it is lower than about 180 °C. The flow temperature is indicative of the temperature at which a material can be processed from the melt.

The thermal properties of the $[AB]_n$ material can be assessed by performing differential scanning calorimetry (DSC) measurements. These measurements provide information on melt and crystallization temperatures (or temperature ranges) as well as on glass transition temperatures.

Process for producing implant

- 10 The invention further provides a process for producing the implant according to the invention by hot embossing. Hot embossing is a micro-fabrication technique in which micron-scale structures on mold is replicated on to a polymer substrate by application of pressure and temperature.
- 15 Thus, the invention provides a process for producing the implant according to the invention comprising hot embossing of the thermoplastic elastomer in a mold to obtain the implant.

- Preferably, the hot embossing involves placing a melt of the thermoplastic elastomer having a temperature of 100 to 150 °C in the mold by applying a pressure of 1 to 10 tons, and solidifying the thermoplastic elastomer in the mold.

- The process may comprise melting the thermoplastic elastomer in a mold made by femtosecond laser-assisted chemical wet etching of a fused silica glass and solidifying the thermoplastic elastomer.

- Femtosecond laser-assisted chemical wet etching is based on a two-step process of ultrashort-pulsed laser radiation in transparent materials, followed by chemical wet etching to selectively remove the exposed material. This is further described in
- 30 Suthisomboon, T., Bargiel, S., Rabenorosoa, K. & Pengwang, E. Design and Simulation of XZ MEMS Micropositioning with 3D-Complex Structure. in *2020 Symposium on Design, Test, Integration and Packaging of MEMS and MOEMS (DTIP)* 1–5 (2020).

Femtosecond laser-assisted chemical wet etching is advantageous for the production of the mold due to its shape and size which would be extremely difficult to achieve using classical micro-manufacturing techniques, such as photolithography or micro-milling.

- 5 Preferably, the mold has been subjected to a process for facilitating the release (demolding) of the implants after the hot embossing step. Before the hot embossing step, the mold may be coated with a superhydrophobic layer e.g. of fluorosilane (e.g. Trichloro(1H,1H,2H,2H-perfluorooctyl)silane, Sigma-Aldrich). Accordingly, in some preferred embodiments, the hot embossing is performed on a mold which has been
- 10 provided with a fluorosilane coating. To improve the adhesion of this coating, the mold may undergo an oxygen plasma treatment performed immediately before coating with the fluorosilane.

- In some embodiments, the mold has at least two cavities corresponding to the shapes of
- 15 the implants and at least two implants are produced by one hot embossing step.

- It is noted that the invention relates to the subject-matter defined in the independent claims alone or in combination with any possible combinations of features described herein, preferred in particular are those combinations of features that are present in the
- 20 claims. It will therefore be appreciated that all combinations of features relating to the composition according to the invention; all combinations of features relating to the process according to the invention and all combinations of features relating to the composition according to the invention and features relating to the process according to the invention are described herein.

25

- It is further noted that the term 'comprising' does not exclude the presence of other elements. However, it is also to be understood that a description on a product/composition comprising certain components also discloses a product/composition consisting of these components. The product/composition consisting of these components
- 30 may be advantageous in that it offers a simpler, more economical process for the preparation of the product/composition. Similarly, it is also to be understood that a description on a process comprising certain steps also discloses a process consisting of these steps. The process consisting of these steps may be advantageous in that it offers a simpler, more economical process.

When values are mentioned for a lower limit and an upper limit for a parameter, ranges made by the combinations of the values of the lower limit and the values of the upper limit are also understood to be disclosed.

- 5 The invention is now elucidated by way of the following figures and examples without however being limited thereto.

Figure 1: A schematic view of an example of the implant according to the invention;

Figure 2: A scheme of polycarbonate bisamide (PC-BA) synthesis starting with converting
10 poly(hexamethylene carbonate) diol to a poly(hexamethylene carbonate) di-carboxylic acid (95% yield), and then reacting to a poly(hexamethylene carbonate) di-(tetra-fluorophenol active ester) (80% yield), which was reacted with trans-1,4-diaminocyclohexane to obtain the final polymer with a yield of 91%;

Figure 3: Characterization of the hot embossed polycarbonate bisamide (PC-BA). a,
15 Chromatogram measured with gel permeation chromatography (GPC), from which an apparent number averaged molecular weight $M_n=14.0$ kg/mol and a weight averaged molecular weight $M_w=27.4$ kg/mol are determined. b, Second heating run of the hot embossed polymer measured with differential scanning calorimetry (DSC). c, Stress-strain curve obtained from the average of three measurements in tensile testing ($n = 3$
20 samples tested), from which a Young's modulus of 45.8 ± 3.6 MPa can be calculated. d, Calculated percentage of cytotoxicity of the PC-BA on primary human tenon fibroblasts; each bar represents the mean $\pm$ SD ($n = 3$). ** represents $p \leq 0.01$ and "ns" represents a non-statistically significant difference as analyzed by two-way ANOVA with Tukey's multiple comparisons test.

25 Figure 4: Fabrication process of Schlemm's canal MIGS implant and its final shape and dimensions. a, Representation of the PC-BA molecular structure as well as schematic illustration of the stacking of the PC-BA polymer due to hydrogen bonds. b, Schematic representation of the implant fabrication by replica molding using hot embossing, with femtosecond laser-machined fused silica glass molds. c, Schematic illustration of the
30 femtosecond laser machining process used to fabricate the glass molds. d, Picture of the glass mold, made using femtosecond laser machining, used in the hot embossing of the implants. e, Demolded array of implants.

Figure 5: a, Injector design and its components; the zoomed figure shows the injector tip reloaded with one of the implant according to the invention. b, Front and back view of the

injector device – the back view reveals the “window” created in the housing of the injector to facilitate manipulating the rotating cam.

Figure 6: *Post-mortem* study. Picture showing the proper placement of the implant according to the invention into the trabecular meshwork, after being delivered by the modified injector device.

Figure 7: Polycarbonate bisamide (PC-BA) characterization after degradation. a, Mass loss measured after 2, 30 and 60 days for the samples exposed to a hydrolytic environment through incubation with a PBS solution (pH 7.4) at 70 °C, and after 2, 7 and 14 days for the samples in enzymatic and in oxidative environments both at 37 °C.

Figure 8: A photograph of implants made from PCL.

Figure 9: The table compiles DMTA-data on the PC-BA [AB]_n material. The data indicate that PC-BA is a soft elastic material, given its E' value, its low tan(δ) value and its nearly temperature independent storage modulus E' between 20 °C and 80 °C. Furthermore, PC-BA can be processed from the melt at lower temperatures, given its low flow temperature.

Figure 1 shows a schematic view of an example of the implant according to the invention. In this example, the implant has radial symmetry, and is 420 μm-long and 360 μm-wide. It is composed of three parts: a conical-shaped head designed to seat within Schlemm's canal; a wider flange, which faces the anterior chamber; and the thorax, which is retained by the trabecular meshwork. The central lumen of the device through which the aqueous humor will flow has a diameter of 100 μm. With this device, a direct connection between the anterior chamber and the Schlemm's canal/collector channel is made, thus bypassing the trabecular meshwork. In this example, the implant contains one central outlet.

Examples

Synthesis and characterization of polycarbonate bisamide.

A poly(hexyl carbonate bisamide (hereinafter sometimes referred as PC-BA) was synthesized by reacting trans-1,4-diaminocyclohexane with the prepolymer poly(hexamethylene carbonate) di-(tetra-fluorophenol active ester), as schematically depicted in Figure 2. The activated prepolymer was synthesized by first converting a poly(hexamethylene carbonate) diol to a poly(hexamethylene carbonate) di-carboxylic acid with a yield of 95% and subsequently activating this telechelic di-acid with 2,3,5,6-tetrafluorophenol (80% yield). During the polymerization, the diamine ratio was slowly

increased to one equivalent of the prepolymer, and the reaction was monitored with gel permeation chromatography (GPC). The polymer was obtained with a 91% yield. After purification the polymer structure was confirmed with $^1\text{H-NMR}$.

5 The apparent number averaged molecular weight (M_n) of the hot embossed PC-BA polymer is 14.0 kg/mol and the weight averaged molecular weight (M_w) is 27.4 kg/mol, as determined from the GPC measurement (Figure 3a, Table S1). A differential scanning calorimetry (DSC) measurement revealed that the polymer has a glass transition temperature for the PC soft block around $-39.6\text{ }^\circ\text{C}$ and three different melting transitions
10 around 8.2, 97 and $152.7\text{ }^\circ\text{C}$ in the second heating run (Figure 3b, Table S1). The melting transitions have enthalpies of 5.7, 0.09 and 2.9 J/g , respectively. The first melting peak originates from the soft polycarbonate block and the other two melting peaks originate from the melting of the amide hard block. The hard block has strong hydrogen bonding interactions resulting in a higher melting transition compared to the much weaker dipole
15 interactions of the soft block. The molecular weights, glass transition temperature and melting transitions of the polymer before hot embossing are similar to the values after the polymer has been hot embossed (Table S1). Looking into the thermal stability of the polymer with thermogravimetric analysis reveals that the PC-BA starts to quickly degrade at a temperature around $270\text{ }^\circ\text{C}$. The mechanical behavior of the hot embossed material
20 was determined with tensile testing and showed a typical curve of a thermoplastic elastomer (Figure 3c). The PC-BA has a Young's modulus of $45.8 \pm 3.6\text{ MPa}$. The cytotoxicity of the embossed PC-BA on primary human tenon fibroblasts was investigated by means of a lactate dehydrogenase (LDH) release assay. LDH is released into the cell culture medium upon damage to the cell's plasma membrane. The percentage of
25 cytotoxicity obtained for all test conditions is shown in Figure 3d. This experiment reveals that the PC-BA polymer is non-cytotoxic.

Table S1. Thermal properties and molecular weight distributions of polycarbonate bisamide (PC-BA) unprocessed/raw polymer as well as after hot embossing.

	First heating run						Second heating run						M_n^{GPC} (kg/mol)	M_w^{GPC} (kg/mol)	$\bar{D}_m$		
	T_{cc} (°C)	ΔH_{cc} (J/g)	T_{m1} (°C)	ΔH_{m1} (J/g)	T_{m2} (°C)	ΔH_{m2} (J/g)	T_g (°C)	T_{m1} (°C)	ΔH_{m1} (J/g)	T_{m2} (°C)	ΔH_{m2} (J/g)	T_{m3} (°C)				ΔH_{m3} (J/g)	
Polymer	72.6	1.3	97.1	0.21	148.9	3.2	-39.7	7.5	5.7	97.2	0.04	151.3	4		16.6	25.6	1.5
Hot embossed polymer			96.7	0.11	149.3	3.2	-39.6	8.2	5.7	97	0.09	152.7	2.9		14.0	27.4	2.0

All reagents, chemicals, materials and solvents were obtained from commercial sources and used without further purification, except the poly(hexamethylene carbonate) diol, which was a generously provided by Bayer. Drying of solvents, when necessary, was done using molsieves. Reactions were run under an inert atmosphere (Ar) whenever appropriate. ¹H-NMR spectroscopy was performed using either a Varian Mercury or a Bruker AVANCE III HD spectrometer at 400 MHz and 298 K. All shifts are reported with respect to TMS at 0 ppm. Infrared spectroscopy was performed using a Perkin Elmer Spectrum One ATR FT-IR spectrometer. Gel permeation chromatography (GPC, SEC) was performed on Varian/Polymer Laboratories PL-GPC 50 equipment using a Shodex GPC KD-804 column that was operated at 50°C using dimethylformamide, or DMF (with 10 mM LiBr and 0.3% water), as the eluent or on a Shimadzu LC-10ADVP system with a Shimadzu RID-10A refractive index detector, a Shimadzu SPD-M10AVP UV-Vis detector, and a combination of a PLgel 5-μm mixed-C column and a PLgel 5-μm mixed-D column, using tetrahydrofuran, or THF, as eluent.

Poly(hexamethylene carbonate) di-carboxylic acid (1)

Telechelic poly(hexamethylene carbonate) diol ($M_n = 2.0$ kg/mol; 32 g, 16 mmol) was dissolved in 150 mL dichloromethane. MeO-TEMPO (0.1 g, 0.5 mmol) was added to this DCM solution, as well as a solution of NaBr (0.7 g, 7 mmol) in 200 mL 1M NaHCO₃. The resulting two-phase system was stirred vigorously and cooled in an ice bath. Aqueous NaOCl (13%, approx. 3.7 M, 60 mL) was added slowly to the reaction mixture, which was allowed to warm to room temperature after addition of the hypochlorite. Stirring was continued for 1 hour, after which ¹H NMR confirmed full conversion of the alcohol end groups. The reaction mixture was subsequently cooled in an ice-bath and adjusted to pH = 1–2 with a concentrated aqueous HCl solution. The organic phase was separated from the aqueous phase, which was subsequently extracted with CHCl₃ (2x100 mL). The combined organic phases were washed with water (150 mL), dried with MgSO₄, and evaporated to yield the crude product (colorless oil). This oil was stirred vigorously with diisopropyl ether (iPr₂O; 100 mL), after which the product was allowed to settle at -20 °C overnight. The supernatant was removed, and the resulting white solid was dried *in vacuo* to yield 30.8 g (95%) of the desired material 1.

¹H-NMR (400 MHz, CDCl₃): δ = 4.1 (t, n*4H), 2.4 (t, 4H, CH₂COOH), 1.8–1.2 (br. m, CH₂) ppm. No CH₂OH protons were detectable by NMR, confirming full conversion. FT-IR

(ATR): ν = 2940, 2885, 1740, 1588, 1465, 1404, 1251, 1067, 957, 792, 735 cm^{-1} . ^1H NMR showed $n \approx 15.5$ (M_n = ca. 2.4 kg/mol). GPC (THF): M_n = 4.7 kg/mol; PDI = 1.75.

Poly(hexamethylene carbonate) di-(tetra-fluorophenol active ester) (2)

- 5 Telechelic poly(hexamethylene carbonate) di-carboxylic acid **1** (20 g, 8.7 mmol) was dissolved in DCM (75 mL) with 2,3,5,6-tetrafluorophenol (3.6 g, 22 mmol) and DMAP (89 mg). N,N' -diisopropylcarbodiimide (DiC, 3.6 mL, 23 mmol) was added to the reaction mixture, causing almost immediate formation of a crystalline precipitate. After 3 hours, NMR confirmed full conversion of the two carboxylic acid end groups to active ester end
- 10 groups. The reaction mixture was filtered, evaporated to dryness, stirred with *n*-pentane and decanted (2x) to afford crude product as a white solid. This solid was redissolved in toluene, stirred with flash silica remove impurities, filtered, and evaporated to dryness. The resulting solid was again dissolved in toluene, stirred with a mixture of flash silica and MgSO_4 , filtered, and evaporated to dryness. This procedure was repeated twice more with
- 15 just flash silica and using chloroform as the solvent. The resulting solid was stirred with *n*-pentane, allowed to settle at -20°C , decanted, and dried in vacuo to yield 18.2 g (80%) of the prepolymer product **2**.
- ^1H -NMR (400 MHz, CDCl_3): δ = 7.0 (q, 2H), 4.1 (t, $n^*4\text{H}$), 2.7 (t, 4H, CH_2COO), 1.8–1.2 (br. m, CH_2) ppm. FT-IR (ATR): ν = 2940, 2870, 1789, 1733, 1645, 1525, 1485, 1466,
- 20 1406, 1346, 1329, 1240, 1180, 1083, 1070, 935, 791, 735, 716 cm^{-1} . ^1H -NMR showed $n \approx 16.1$ (M_n = ca. 2.8 kg/mol).

Poly(hexamethylene carbonate) 1,4-cyclohexyl bisamide, PC-BA (3)

- Prepolymer **2** (18 g, 6.3 mmol), DIPEA (5.6 mL, 32 mmol) and trans-1,4-
- 25 diaminocyclohexane (0.686 g, 6.0 mmol, 0.95 eq.) were dissolved in mixture of 50 mL DCM and 20 mL DMF. The reaction mixture was initially turbid but became clear and more viscous over time. After stirring for 16 hours an aliquot was analyzed with NMR and GPC. To improve the chain extension another 0.2 g of the prepolymer **2** and, in steps over the next 40 hours while checking with GPC, 25.4, 11.8 and 8.3 mg of the diamine
- 30 were added, gradually increasing the diamine ratio to 1.0 equivalents with respect to **2**. The resulting material was precipitated in a mixture of 1.2 L MeOH and 0.2 L water, decanted, stirred with 0.5 L MeOH, decanted, and dried in vacuo at 50°C . The resulting material was redissolved in 100 mL CHCl_3 with 30 mL MeOH and reprecipitated in 1 L

MeOH, decanted, and dried in vacuo at 60°C, yielding 15.3 g of a tan, rubbery solid (91%).

¹H-NMR (400 MHz, CDCl₃): δ = 5.3 (br. s, 2H), 4.1 (t, n*4H), 3.8 (br. s, 2H), 2.1 (t, 4H), 2.0 (m, 4H), 1.8–1.3 (br. m, CH₂), 1.2 (m, 4H) ppm. FT-IR (ATR): ν = 3294, 2938, 2861, 1737, 1637, 1544, 1464, 1403, 1240, 1062, 960, 904, 792, 731 cm⁻¹.

Differential Scanning Calorimetry.

The material was weighed and sealed in Tzero aluminum pans before differential scanning calorimetry (DSC) measurements were done on a DSC Q2000 (TA instruments, United States). The samples were first brought to an isotropic state at 40 °C and then heated to 180 °C at 10 °C/min, which marked the first heating run, and cooled to -70 °C at the same rate. Then the material was further subjected to two heating/cooling cycles from -70 to 180 °C with a heating/cooling rate of 10 °C/min. The data was quantified and analysed using Universal Analysis software (V4.5A, TA Instruments).

Mechanical testing: tensile test and DMTA.

A mechanical tensile test was performed on PC-BA thin films using a tensile test machine (ZwickRoell Z010) with a crosshead speed of 20 mm/min and a 100 N static load cell. For the preparation of the test specimens, first a 200 µm-thick film was fabricated in a hot embossing machine (Specac limited). We used 130 °C to melt the polymer and 5 tons of pressure press the polymer into the shape of a film. The demolding took place after the hot embossing had cooled down to room temperature. Thereafter, the film obtained was cut into three small rectangular specimens of approximately 30x10x0.2 mm (length x width x thickness). The Young's modulus was determined as the slope of the linear portion of the obtained stress-strain curve.

In addition to the above tensile test on PC-BA, PC-BA was also analyzed by DMTA.

Thermogravimetric Analysis.

Measurements were done on a Perkin-Elmer TGA 7 using the high-resolution dynamic mode. Samples were put in platinum pans. The measurements were started at room temperature and heated to 400 °C at a heating rate of 10 °C/min, performed under an atmosphere of air or nitrogen (flow rate 20 mL/min).

***In vitro* cytotoxicity.**

To determine the cytotoxicity of the PC-BA polymer on primary human tenon fibroblasts we used the CyQUANT™ Lactate dehydrogenase (LDH) cytotoxicity assay (Invitrogen™, ThermoFisher Scientific). LDH release into culture medium due to membrane damage of cultured cells was used as an indicator of cytotoxicity. For making the test samples used in this experiment, a 200 µm-thick film was first fabricated using hot embossing, and thereafter cut to small circular pieces of 7 mm in diameter. The samples were then sterilized by immersing in 70% ethanol for 20 minutes and treated with UV for 15 minutes, after which they were rinsed in phosphate-buffered saline (PBS, pH 7.4) before transferring to a sterile 96-well plate. The cells were then seeded at 3.2×10^3 cells/well into the well plate containing the test samples (three replicates) using complete Advanced Dulbecco's modified Eagle Medium (DMEM) supplemented with 10% of Fetal Bovine Serum (FBS), 100 U/mL penicillin and streptomycin, and 0.2 mM L-glutamine (now referred to as culture medium). Cells were seeded in triplicate, after which they were incubated at 37 °C in 5% CO₂ for 48 hours along with the positive and negative controls. Untreated cells in culture medium alone served as negative control and used to give the Spontaneous LDH activity. An amount of 10 µL of 10X Lysis Buffer was added to untreated cells (no contact with the test material), and used as the Maximum LDH Activity (positive control). After 45 minutes incubation, 50 µL of the medium from all three conditions was collected and gently mixed with 50 µL of the Reaction Mixture in a new 96-well plate, and thereafter placed on ice for another 45 minutes. The absorbance of each well was then measured at 490 and 680 nm. To determine LDH activity, first the absorbance at 680 nm (background signal from instrument) was subtracted from the absorbance at 490 nm. The percentage of cytotoxicity was then calculated as follows

$$\% \text{ Cytotoxicity} = 100 \times \frac{\text{Treatment group activity} - \text{Negative control activity}}{\text{Positive control activity} - \text{Negative control activity}} . \quad (1)$$

Implant fabrication and characterization.

We employed our own innovative microfabrication technique to fabricate the Schlemm's canal MIGS implant. The method involved replica molding using hot embossing and fused silica glass molds created by femtosecond laser micromachining, as demonstrated in Figure 4b.

The molecular structure of the PC-BA polymer from which the implants are made is represented in Figure 4a, which also includes schematic illustration of the stacking of the PC-BA polymer due to hydrogen bonds. As mentioned earlier, the mold used to give the PC-BA the shape indicated in Figure 1b was fabricated by femtosecond laser

5 micromachining of fused silica glass. Femtosecond laser-assisted chemical wet etching is based on a two-step process of ultrashort-pulsed laser radiation in transparent materials, followed by chemical wet etching to selectively remove the exposed material (Figure 4c). The laser beam, focused inside the glass, locally modifies its refractive index and chemical properties, and patterns written by the laser are then chemically etched to form
10 three-dimensional structures with high precision, aspect ratio and complexity. The complexity of the shape of our implant would be extremely difficult to achieve using classical micro-manufacturing techniques, such as photolithography or micro-milling.

When the machining program was finished, the glass slide was immersed in a
15 concentrated solution of 45% potassium hydroxide (KOH, Sigma-Aldrich) diluted in water to remove the exposed material. Finally, the mold was rinsed thoroughly with acetone and DI water to remove all debris. To facilitate the release (demolding) of the implants after the hot embossing step, the femtosecond laser-machined glass mold was first coated with a superhydrophobic layer of fluorosilane (Trichloro(1H,1H,2H,2H-perfluorooctyl)silane,
20 Sigma-Aldrich). To improve the adhesion of this coating, the mold underwent an oxygen plasma treatment performed immediately before the fluorosilane vapor deposition. After the silanization treatment, the mold was ready to be used in the hot embossing machine together with the PC-BA pellets to fabricate the implants.

25 A picture of the fabricated glass mold is shown in Figure 4d, which also includes a zoomed microscopic view of the features in the mold showing the 100 μm -diameter glass pillar used to form the central lumen of the implant. Using this mold, many implants can be fabricated in one single hot embossing step.

30 The polymer was heated to a temperature of 130 °C to provide a melt of the polymer and 5 tons of pressure was applied to help the melted polymer to flow into the cavities of the mold (Figure 4b).

The demolding took place after the hot embossing had cooled down to room temperature. Figure 4e shows a microscopic image of the fabricated implants.

Adaptation and *in vitro* testing of the iStent *inject*® W injector.

- 5 The design and components that comprise the injector device are represented in Figure 5a. The working principle of the injector is explained in the patent no. US10271989B2. The injector is designed to deliver the stents automatically through the trabecular meshwork and into Schlemm's canal when activated by the surgeon. The portion of the injector that enters the anterior chamber is a 23-gauge stainless steel insertion sleeve.
- 10 When inside the anterior chamber, the sleeve of the injector is retracted using the insertion sleeve retraction button, revealing the micro-insertion tube and the trocar. The surgeon then advances the micro-insertion tube across the anterior chamber to the desired site of implantation, while visualizing the tube through direct gonioscopy (using a gonioscope). After locating the trabecular meshwork and selecting the implant location,
- 15 the trabecular meshwork is penetrated with the trocar. By pressing the surgeon-activated delivery button on the housing, the stent moves over the small guiding trocar to exit the injector. A single audible click will indicate that the first stent has been delivered.

- Two stents can be implanted with a single entry into the eye, and they should be
- 20 separated by 2–3 clock hours apart (separated by an angle of 60 to 90 degrees). A total of four positions are available on the injector to position the two stents. A rotating cam hidden within the housing of the injector rotates in a clockwise manner to deploy the stents when the release button is pressed. After the stent delivery button has been pressed for the fourth time, the rotating cam will no longer rotate, and the injector will no
- 25 longer function. Therefore, in order to have a functioning injector again, the cam has to be manually rotated counter-clockwise (up to four times). This rotation was possible by releasing the engagement between the trigger stop and the first cam flat, which thereby allows the cam to freely rotate. In order to get a clear view over the cam and to allow manipulating it easily, a small "opening/window" was created in the housing at the
- 30 opposite side of the sleeve retractor and stent-release button, as can be seen in Figure 5b. This was done before reloading the injector with our biodegradable implant. The reloading was performed under microscopic view and with the help of sharp and thin-pointed tweezers. It was shown that the recharged injector successfully shoots our biodegradable implant into a spongy-like substrate, a very simplified *in vitro* model of the

trabecular meshwork porous structure. It was shown that the implant stays fixed and correctly positioned into the sponge, i.e., with the flange at the surface of the sponge and facing the camera used for recording.

5 Post-mortem study.

We performed a post-mortem experiment on an eye of a euthanized rabbit to investigate if the modified injector delivery system is capable of injecting our devices into a real trabecular meshwork as it does for the iStent *inject* W. For this experiment, the injector device was first reloaded with our biodegradable implant as previously demonstrated.

10 Subsequently, a corneal incision was made in the eye, and the injector was inserted through it into the anterior chamber to deliver our implant into the trabecular meshwork. It was confirmed that our implant was successfully delivered into the trabecular meshwork. The zoomed picture of Figure 6 shows that the flange of our device is visible in the anterior chamber, proving the proper placement of the implant in the trabecular
15 meshwork.

In vitro degradation.

Degradation of the hot embossed PC-BA polymer via hydrolytic or oxidative pathways was studied. The hydrolytic pathway was investigated by incubating the polymeric
20 material in phosphate-buffered saline (PBS, pH 7.4) in an accelerated experiment at 70 °C to study hydrolysis by water for 2, 30 and 60 days. After 60 days, 1% mass loss was observed in the hydrolytic experiment in PBS, as shown in Figure 7a. The molecular weight of the polymer did not change after two days of incubation, but M_n decreased from 16.7 ± 0.8 kg/mol to 13.8 ± 0.7 kg/mol after 30 days, and after 60 days the molecular
25 weight decreased further to 12.8 ± 0.6 kg/mol (Table S2). Enzyme-mediated hydrolysis was studied by incubating the material in lipase at 37 °C for 2, 7 and 14 days. After 14 days, a small decrease in mass of 1–2 % was observed (Figure 7). The molecular weight M_n was 13.2 ± 0.8 kg/mol after two days and it did not decrease further with 7 or 14 days of incubation (Table S2). Oxidative degradation was investigated by incubating the
30 polymeric material in a solution of 0.1 M Co(II)Cl₂·6H₂O in 20 % (w/w) H₂O₂ in DI water at 37 °C for 2, 7 and 14 days. No mass loss of the material was observed after 14 days (Figure 7a). The molecular weight of the polymer showed similar behavior to the that under enzymatic degradation. The molecular weight M_n was 13.5 ± 0.1 kg/mol after two days and it did not decrease any further (Table S2).

	M_n^{GPC} (kg/mol)	M_w^{GPC} (kg/mol)	$\bar{D}_m$
Hydrolytic			
Day 0	16.7 ± 0.8	33.8 ± 0.1	2.05 ± 0.07
Day 2	16.6 ± 0.5	32.8 ± 0.3	2.0 ± 0.1
Day 30	13.8 ± 0.7	29.9 ± 0.2	2.2 ± 0.1
Day 60	12.8 ± 0.6	26.2 ± 0.4	2.1 ± 0.1
Enzymatic			
Day 2	13.2 ± 0.8	29.1 ± 0.8	2.2 ± 0.06
Day 7	13.9 ± 0.7	28.9 ± 0.4	2.1 ± 0.1
Day 14	13.9 ± 0.4	29.0 ± 0.4	2.1 ± 0.1
Oxidative			
Day 2	13.5 ± 0.1	28.7 ± 0.2	2.1 ± 0.0
Day 7	14.1 ± 0.5	28.4 ± 0.4	2.0 ± 0.06
Day 14	14.1 ± 0.5	28.1 ± 0.3	2.0 ± 0.1

Table S2. Molecular weight distributions of hot embossed polycarbonate bisamide (PC-BA) polymer before and after incubating in PBS at 70 °C after 2, 30 or 60 days and after incubating in an enzymatic or oxidative solution at 37 °C after 2, 7 or 14 days.

5

These results show that the polymer favors hydrolytic degradation over oxidative degradation. However, for the hydrolytic degradation we found conflicting indications regarding the polymer degrading through surface or bulk erosion. The hydrolytic degradation results over longer time in PBS indicate that bulk erosion happens, because the molecular weight decreased more than did the mass. The enzymatic degradation showed initially a decrease in molecular weight and 1–2 % mass loss after 14 days incubation, which might indicate surface erosion. Enzymes could potentially degrade the

10

surface of the test samples through surface erosion, while the samples would also slowly suffer from bulk erosion when exposed to water.

Polycaprolactone (PCL) implant fabrication. (comparative example)

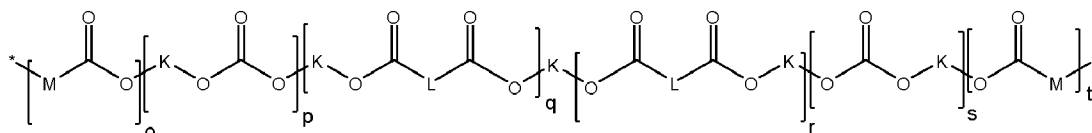
- 5 The fabrication of implants with polycaprolactone (PCL) (number averaged molecular weight $M_n = 80\,000$ kg/mol) was performed using the same technique used for fabricating the Polycarbonate Bisamide (PC-BA) implants described above. The mold used to give the PCL the desired shape of the implant was fabricated by femtosecond laser micromachining of fused silica glass. This glass mold was then brought together with the
- 10 PCL pellets in a hot embossing machine to fabricate the implants by replica molding. We used 70 °C to melt the polymer and 5 tons of pressure to help the melted polymer to flow into the cavities of the mold. The demolding took place after the hot embossing had cooled down to room temperature. Fig. 8 shows an array of demolded implants, where it can be seen that all fabricated implants are either deformed or already broken. Therefore,
- 15 we can conclude that the PCL material is not suitable for this MIGS implant since it easily suffers from permanent deformation.

CLAIMS

1. An implant for implantation in an eye, wherein the implant comprises a thermoplastic elastomer according to the formula $[AB]_n$, wherein:

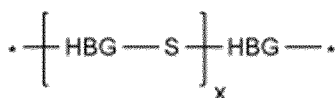
5 n represents the number of repeats of the AB segment and is an integer of 2 to 100;

A represents a soft block according to formula (I):



(I)

B represents a hard block according to formula (II):



(II)

wherein:

K is a $C_1 - C_{36}$ alkylene group, a $C_6 - C_{24}$ arylene group, a $C_7 - C_{24}$ alkarylene group or a $C_7 - C_{24}$ arylalkylene group;

15 L is a $C_1 - C_{36}$ alkylene group, a $C_6 - C_{24}$ arylene group, a $C_7 - C_{24}$ alkarylene group or a $C_7 - C_{24}$ arylalkylene group or L is absent;

M is a $C_1 - C_{36}$ alkylene group, a $C_6 - C_{24}$ arylene group, a $C_7 - C_{24}$ alkarylene group or a $C_7 - C_{24}$ arylalkylene group or M is absent;

o, p, q, r, s and t are independently 0 - 50;

provided that:

20 (a) when o, q, r and t are 0, then p and s are independently 1 - 50;

(b) when p and s are 0, then o, q, r and t are independently 1 - 50;

(c) when o and t are 0, then p, q, r and s are independently 1 - 50;

(d) when q and r are 0, then o, p, s and t are independently 1 - 50;

(e) when o, p, s and t are 0, then q and r are independently 1 - 50;

25 (f) when p, q, r and s are 0, then o and t are independently 1 - 50;

HBG is a simple hydrogen bonding unit independently selected from the group consisting of amide, urea and urethane groups;

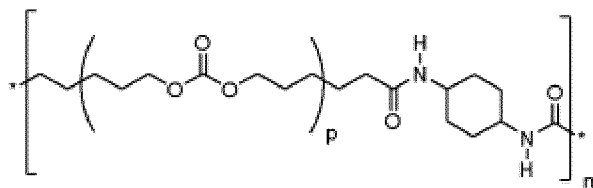
S is a $C_1 - C_{36}$ alkylene group, a $C_6 - C_{24}$ arylene group, a $C_7 - C_{24}$ alkarylene group or a $C_7 - C_{24}$ arylalkylene group or S is absent; and

x is 1, 2 or 3.

2. The implant according to claim 1, wherein the implant is configured to provide a fluid flow path for draining aqueous humor from the anterior chamber through the trabecular meshwork and into Schlemm's canal when implanted.
3. The implant according to claim 2, wherein the implant has a proximal portion, an intermediate portion and a distal portion, wherein the proximal portion is configured to reside in the anterior chamber and the distal portion is configured to reside in the Schlemm's canal, wherein a lumen extends from a proximal end of the proximal portion through the intermediate portion to a distal end of the distal portion to provide fluid communication between the proximal end and the distal end, preferably wherein the distance between the proximal end and the distal end is 0.01 to 1.0 mm.
4. The implant according to any one of the preceding claims, wherein the soft block A is a (co)poly-carbonate, a (co)poly-ester or a co-poly(ester-carbonate), preferably the soft block A is a (co)poly-carbonate.
5. The implant according to any one of the preceding claims, wherein the hard block B is selected from the group consisting of bis-urea hard blocks, bis-amide hard blocks, tri-amide hard blocks, mono-urea-bis-amide hard blocks, bis-urethane-bis-amide hard blocks and tetra-amide hard block, preferably the hard block B is a bis-urea or a bis-urea hard block.
6. The implant according to any one of the preceding claims, wherein S is absent, or S is an alkylene selected from the group of cyclic, linear or branched C₁ - C₁₂ alkylene groups, preferably wherein S is selected from linear or cyclic C₂ - C₆ alkylenes that do not contain heteroatoms, more preferably wherein S is selected from the group consisting of n-ethylene, n-propylene, n-butylene, n-pentylene, n-hexylene, and 1,4-trans-cyclohexylene.
7. The implant according to any one of the preceding claims, wherein the thermoplastic elastomer has a number average molecular weight M_n of 500 to 500,000 Dalton, preferably 1,000 to 100,000 Dalton, more preferably 10,000 to 50,000 Dalton, wherein

the number average molecular weight M_n is determined by gel permeation chromatography.

8. The implant according to any one of the preceding claims, wherein the soft block A has a number average molecular weight M_n of 100 to 10,000 Dalton, preferably 500 to 5000 Dalton, wherein the number average molecular weight M_n of soft block A is determined by $^1\text{H-NMR}$ analysis.
9. The implant according to any one of the preceding claims, wherein the hard block B has a single (monodispersed) molecular weight of 85 to 1000 Dalton.
10. The implant according to any one of the preceding claims, wherein the thermoplastic elastomer is a poly(hexyl carbonate bis-amide) with trans-cyclohexyl-amide groups as represented by:



11. A process for producing the implant any one of the preceding claims comprising hot embossing of the thermoplastic elastomer in a mold to obtain the implant.
12. The process according to claim 11, wherein the hot embossing involves placing a melt of the thermoplastic elastomer having a temperature of 100 to 150 °C in the mold by applying a pressure of 1 to 10 tons, and solidifying the thermoplastic elastomer in the mold.
13. The process according to claim 11 or 12, wherein the mold is obtained by femtosecond laser-assisted chemical wet etching of a fused silica glass.
14. The process according to any one of claims 11 to 13, wherein the mold comprises a fluorosilane coating.

15. The process according to any one of claims 11 to 14, wherein the mold has at least two cavities corresponding to the shapes of the implants and at least two implants are produced by one hot embossing step.

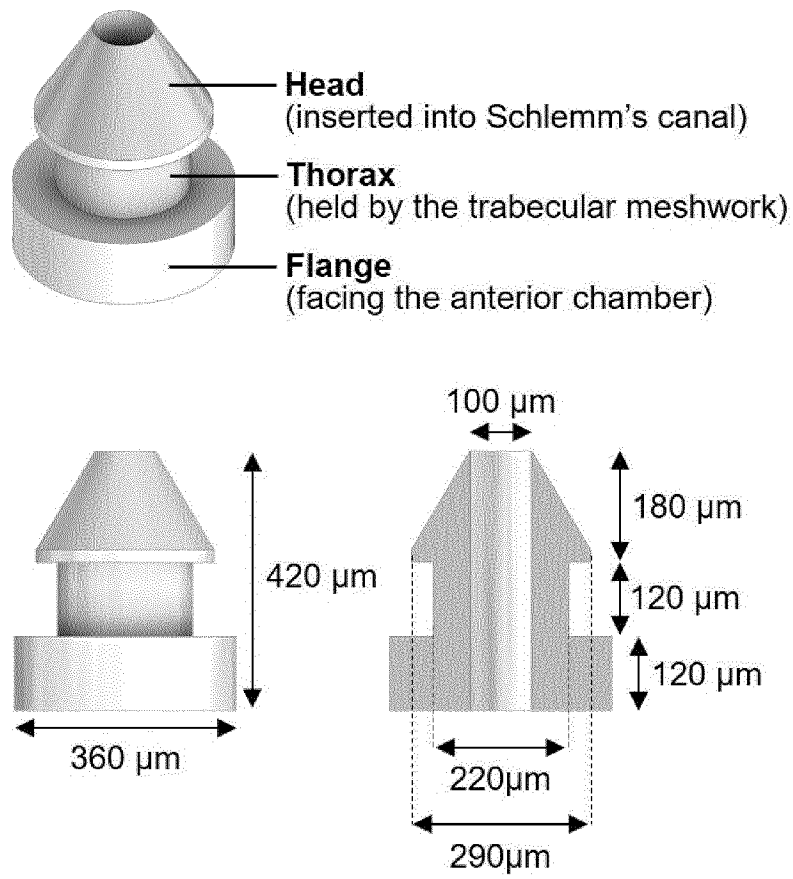


Figure 1

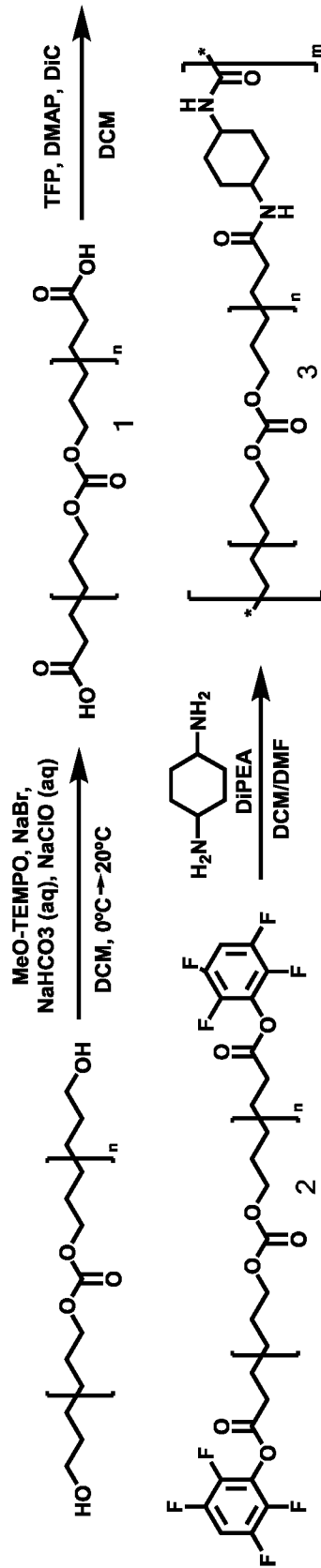


Figure 2

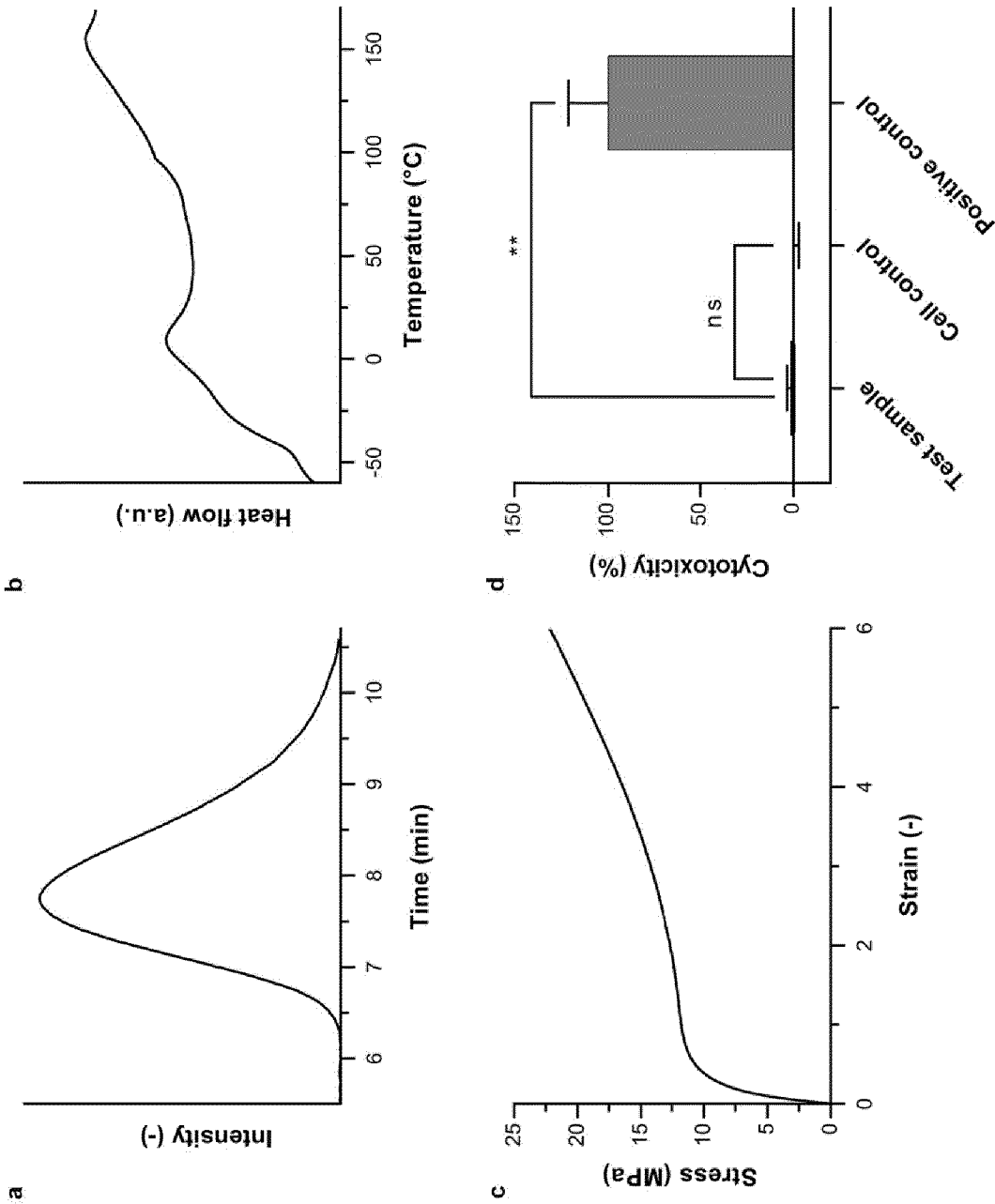


Figure 3

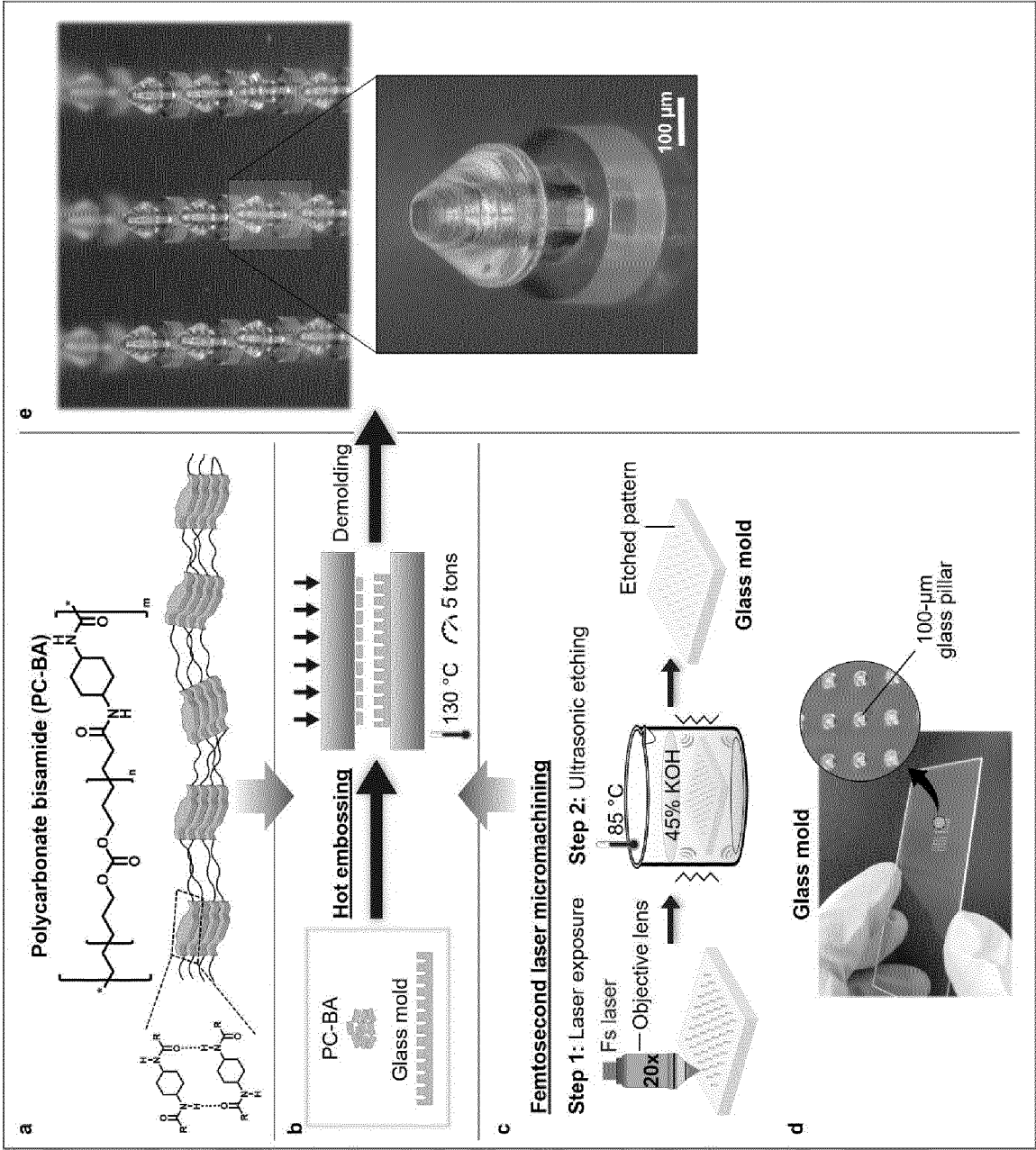


Figure 4

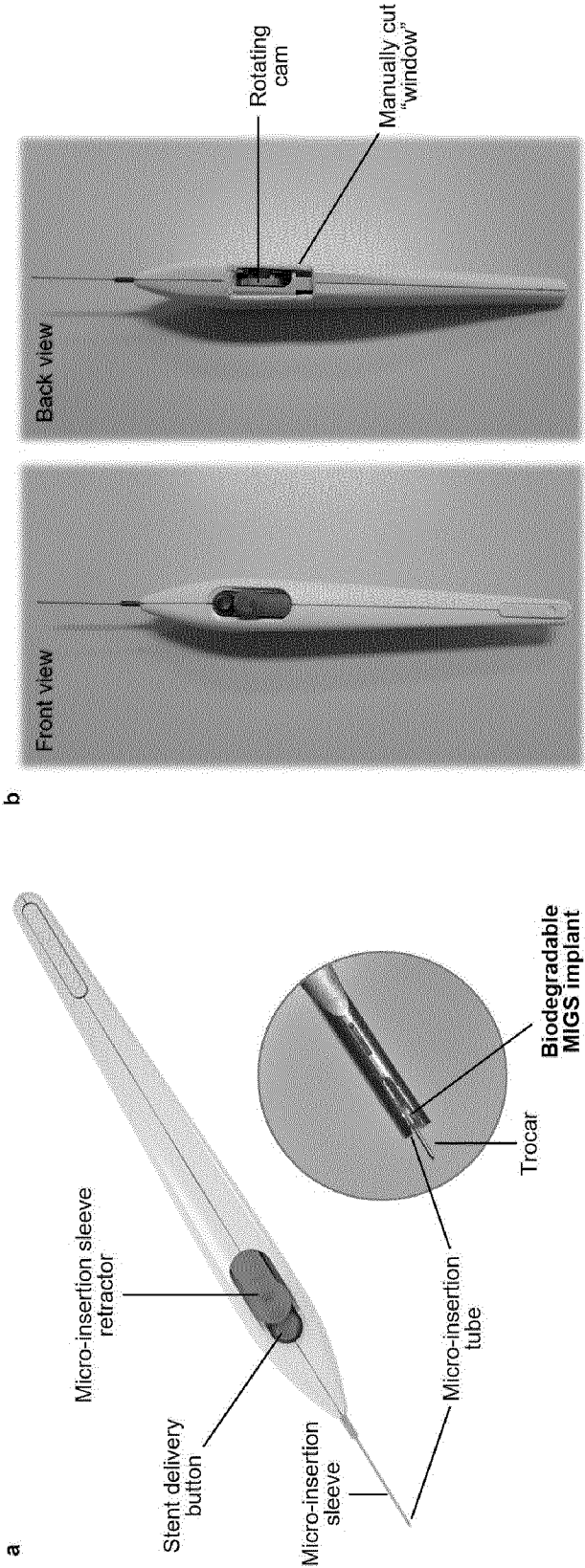


Figure 5

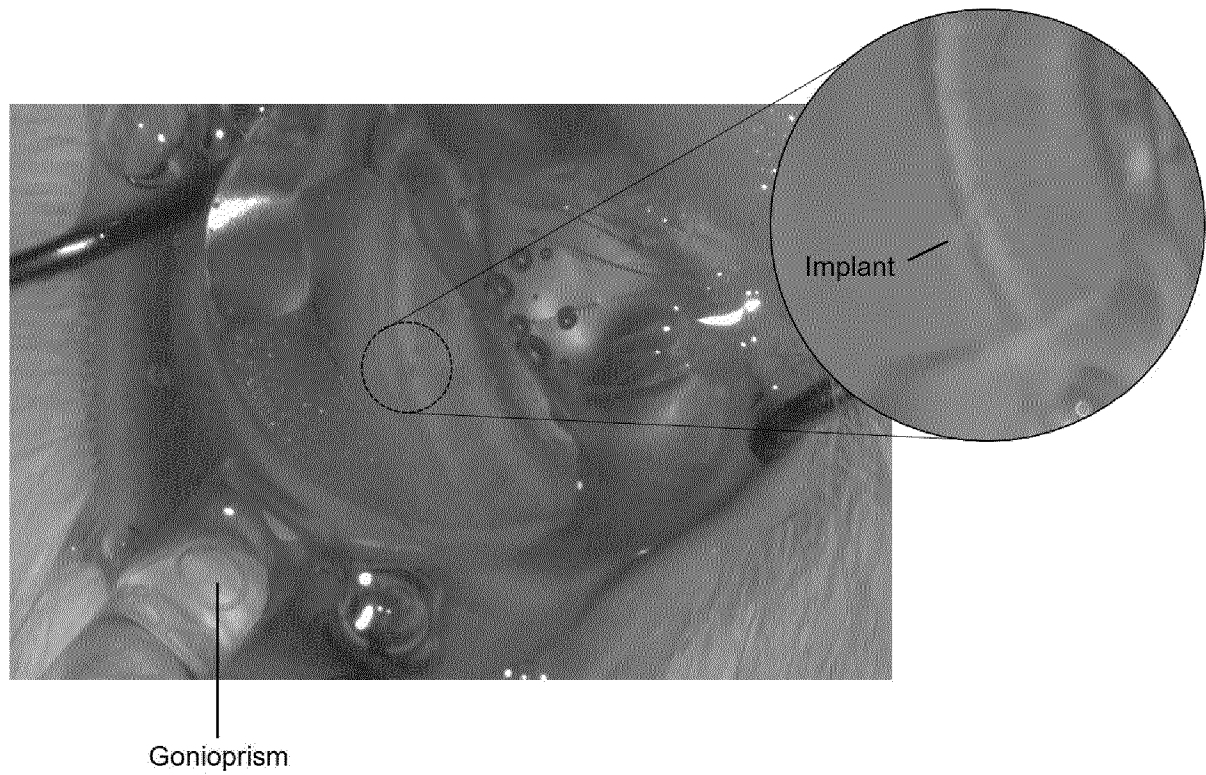


Figure 6

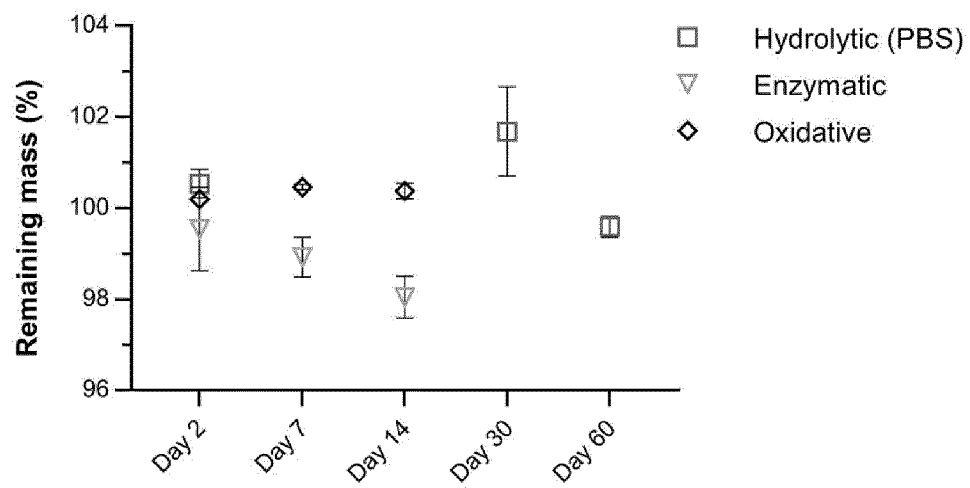


Figure 7

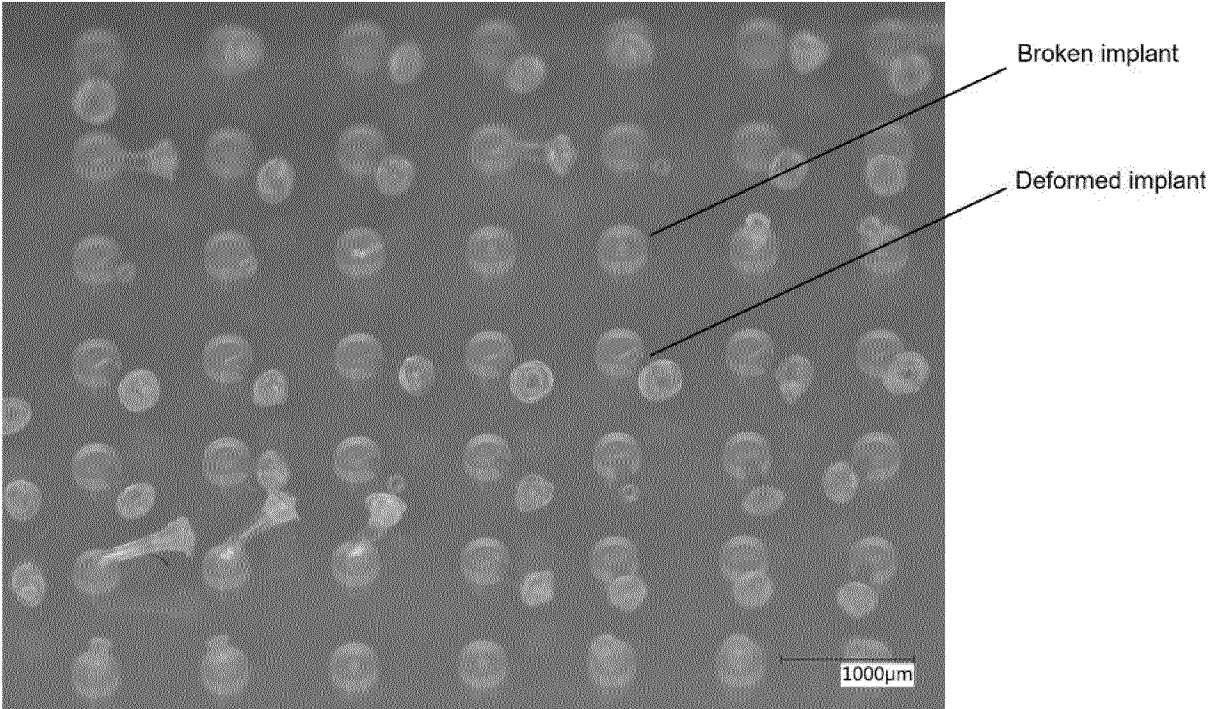


Figure 8

[AB] _n	E'	E'	E'	E'	E'	T _{flow}	Tan δ
	@20°C (MPa)	@30°C (MPa)	@37°C (MPa)	@50°C (MPa)	@80°C (MPa)		@37°C (-)
PC-BA	33	32	32	32	30	154	0.03

Figure 9

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2024/064496

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61L27/18 C08G64/00
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)

A61L C09J 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**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2015/194961 A1 (SYMO CHEM B V [NL] ; SUPRAPOLIX BV [NL]) 23 December 2015 (2015-12-23)	1,4 - 10
Y	claim 1 page 1, paragraph 1 -----	2,3
Y	US 2020/390601 A1 (IANCHULEV TSONTCHO [US]) 17 December 2020 (2020-12-17) paragraph [0075] -----	2,3, 11 - 15
Y	US 2019/046696 A1 (PARIKH KUNAL S [US] ET AL) 14 February 2019 (2019-02-14) paragraph [0099] -----	2,3, 11 - 15
Y	US 2012/251587 A1 (VAN APELDOORN AART ALEXANDER [NL] ET AL) 4 October 2012 (2012-10-04) paragraph [0054] -----	11 - 15



Further documents are listed in the continuation of Box C.



See patent family annex.

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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

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"&" document member of the same patent family

Date of the actual completion of the international search

21 August 2024

Date of mailing of the international search report

10/09/2024

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Authorized officer

Siebum, Bastiaan

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2024/064496

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