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(54) Title: POLYURETHANE SHEET

(57) Abstract: The present invention relates to a flexible polyurethane foam sheet comprising a pharmacologically active agent, a process of preparing such a sheet, and to the use of such a sheet for treatment and/or prophylaxis of the human or animal body.

POLYURETHANE SHEET

Field of the invention

The present invention relates to a flexible polyurethane foam sheet comprising a pharmacologically active agent, a process of preparing such a sheet, and to the use of such a sheet for the treatment / prophylaxis of the human or animal body.

Background art

Traditionally, a prosthesis, connected with a socket to the body, is the treatment-of-choice for the replacement of a missing body part. However, a prosthesis connected via a socket is associated with many and serious disadvantages, including impaired mobility, pain, sensitivity problems and serious skin ulceration. Recently, bone-anchored percutaneous implants or osseointegration prostheses have been developed, which provide a direct functional and strong connection between the external device and the patient's own bone.

Despite alleviating some of the disadvantages of socket connections, the penetration of the osseointegration prosthesis through the skin introduces a significant risk of infection. The stoma is the skin opening through which the osseointegration prosthesis extends. The stoma can become contaminated with bacteria and thus may cause infections. The clinical picture of a local stoma infection is redness of the skin around the stoma, stump swelling, pus secretion and sometimes severe stoma pain.

A problem with known polyurethane foam wound guards is that they are provided to the user in a certain diameters / shapes that corresponds to envisaged applications, for example rings and cylinders for covering cylindrical elements. EP 2272545 discloses that disadvantages of such wound guards is that it requires adhesive tape to fix it to the skin and the foam disc absorbs serous fluid making the wound guard floppy. Because of these problems, it is necessary to change the wound guard frequently. The wound guard may swell as it absorbs serous fluid and can become difficult to handle.

H Forster *et el* / Journal of Orthopaedic Research 22 (2004) 671-677, discloses a polyurethane sleeve, having a gentamicin impregnated coating on the inner and outer surfaces, has been developed to inhibit bacterial colonization on external fixation pins and wires. The antimicrobial sleeves are placed over the pins and wires, at the time of surgery, and manually pushed through the subcutaneous tissue up to the point of contact with the bone. Polyurethane sleeves as disclosed by H Forster *et al* are not suitable for osseointegration prosthesis because the prosthesis cannot be adjusted to the diameter, length and shape of the sleeve.

WO 2012/007929 A1 discloses a wound dressing device for use with a cannula or a catheter comprising polyurethane MS50P(w) Lendell medical foam available from Filtrona Porous Technologies x, an antimicrobial agent contained within the matrix and a haemostatic agent contained within the matrix. However, similar to the product in EP 2272545, this type of polyurethane foam is mechanically weak and difficult to handle.

There is a need for a polymer material that has the mechanical/ therapeutic agent releasing properties for application to osseointegration prostheses.

Summary of the invention

The inventors have developed a flexible, polyurethane foam sheet which can be shaped to fit the percutaneous element extending from, for example, an osseointegration site. The invention provides an elastic sheet that the user of can easily place around a protruding element and secure it around said element by virtue of the self-adhesive property of the polyurethane foam sheet, dispensing with the need for any secondary attachment means.

Accordingly, the present invention provides a flexible, polyurethane foam sheet comprising a pharmacologically active agent dispersed within said foam,
wherein the polyurethane is a copolymer having the structure according to formula (I):

[HS-SS]n,

wherein HS denotes a hard block segment being prepared from an aliphatic diisocyanate and/or cycloaliphatic diisocyanate and a diol chain extender,
wherein SS denotes a soft block segment being a polyol having a number average molecular weight in the range of 1,000 to 20,000 g/mol,
wherein the polyurethane has a number average molecular weight (Mn) ranging from 4000 to 50,000 g/mol, preferably between 1,000 and 15,000.

Without wishing to be bound by theory, it is proposed that the high average molecular weight of the polyol, in combination with the aliphatic nature of the diisocyanate provides a flexible network that enables the polyurethane foam sheet to be easily deformed and held in place due to self-adhesive property of the polyurethane. The polyurethane foam is able to absorb wound exudate and withstand the pressures exerted between the prosthesis and osseointergration site. The present polyurethane foam is therefore suitable for use as a sheath, wrap or covering for percutaneous elements extending from an osseointegration site.

In a further aspect, the present invention also relates to a polyurethane foam sheet as defined herein for use in a method of treatment or prophylaxis of the human or animal body.

Description of embodiments

In a first aspect, there is provided a flexible, polyurethane foam sheet comprising a pharmacologically active agent dispersed within said foam,
wherein the polyurethane is a copolymer having the structure according to formula (I):

[HS-SS]n,

wherein HS denotes a hard block segment being prepared from an aliphatic diisocyanate and/or cycloaliphatic diisocyanate and a diol chain extender,
wherein SS denotes a soft block segment being a polyol having a number average molecular weight in the range of 1,000 to 20,000 g/mol,
wherein the polyurethane has a number average molecular weight (Mn) ranging from 4000 to 50,000 g/mol, preferably between 1,000 and 15,000.

Definitions

The word 'comprising' as used herein is intended to mean 'including' but not necessarily 'consisting of' or 'composed of'. In other words, the listed steps or options need not be exhaustive.

Unless specified otherwise, numerical ranges expressed in the format 'from x to y' or 'x-y' are understood to include x and y. When for a specific feature multiple preferred ranges are described in the format 'from x to y' or 'x-y', it is understood that all ranges combining the different endpoints are also contemplated. For the purpose of the invention ambient temperature is defined as a temperature of about 20°C.

Unless indicated otherwise, weight percentages (wt.%) are based on the total weight of the concentrate.

In the context of the present invention, the terms "segment" and "block" mean a polymeric structure of any length. In the art of polymer technology, a long polymeric structure is often referred to as a block, whereas a short polymeric structure is often referred to as a segment. Both these conventional meanings are understood to be comprised in the term "segment" as well as in the term "block" as used herein.

In the context of the present invention, the term "hard segment" (HS) means a segment of the polyurethane copolymer that is made from the reaction of a diisocyanate and chain extender. A diisocyanate is a molecule with two isocyanate functional groups.

In the context of the present invention, the term "soft segments" means a segment of the polyurethane copolymer that comprises a diol.

In the context of the present invention, the term “biocompatible” means that the sheet of the present invention as well as wear debris and the materials generated during placement do not cause a substantial immune response, sensitization, irritation, cytotoxicity or genotoxicity.

In the context of the present invention, the terms “prosthesis” and “prosthetic are used interchangeably to denote an artificial body part.

Sheet

The polyurethane foam sheet is highly flexible, absorbent, and conformable to different percutaneous elements. Preferably, the sheet has a density of at least 0.25g/cm^3, and more preferably at least 0.30 g/cm^3. Particularly preferred sheets have a density in the range 0.25 to 0.75 g/cm^3. Preferably, the sheet has a Young’s modulus in the range of from 0.3 to 0.7 MPa. The polyurethane foam sheet of the present invention is able to withstand the pressures exerted in, for example, femoral osseointegrated prosthetics.

The sheet has a porosity of at least 50%, preferably a porosity in the range of 60 to 80%. The porosity of the sheet not only enables the sheet to be a reservoir for a pharmacologically active agent but the sheet is also capable of absorbing wound exudates.

The sheet of the present invention and the medical devices made therefrom are biocompatible and have properties that make the devices especially useful including tensile modulus of between about 0.1 MPa to about 30 MPa, preferably about 0.3 MPa to about 15 MPa, a tear strength of greater than or equal to about 3 N/mm, and flexibility (strain at break) of about 100 % or higher. These advantageous properties are in part due to the high molecular weight of the polymers in the foam and in part due to the interconnectivity of the polymers in the foam. This high molecular weight and interconnectivity are achieved by the process of making the polyurethane polymer and by the process of making the foam from the polyurethane polymer.

The sheet preferably has a hardness of a of 60 to 85, more preferably 70 to 85 and most preferably 75 to 85 as measured using a ‘Shore durometer’ using ASTM D2240-03 Standard Test Method for Rubber Property—Durometer Hardness, ASTM International, West Conshohocken, PA, 2003

The polyurethane has a number average molecular weight (Mn) ranging from 1,000 to 50,000 g/mol, preferably between 4,000 and 15,000.

The final average molecular weight of the polymer in the foam is preferably in the range of 2 kDa to 100 kDa. Preferably the average molecular weight of the polymer is in the range of 5 kDa to to 80 kDa. More preferably, the average molecular weight of the polymer in the foam is 10 kDa to 60 kDa.

The sheet preferably has at least one substantially flat surface and at least one straight edge. The at least one flat surface can allow the sheet to be brought into close proximity with a surface about which it is wrapped. The at least one straight edge can allow the edge of the sheet to be brought into close abutment with the body surface from which the osseointegration prosthesis extends. However, the skilled person will appreciate that the shape of the sheet can be adapted to suit the osseointegration site of the prosthesis.

In at least some embodiments, the sheet comprises two substantially straight, parallel opposing edges. For example, the sheet can have a square or rectangular shape, more preferably a rectangular shape, wherein the rectangular shape preferably has a width of 5-20mm, length of 10-100mm and a thickness of 0.5-3mm. A rectangular shape enables the sheet to be rolled-up by the patient into a shape that is suitable to fit over elements extending from an osseointegration site. An advantage of the present invention is that the sheet can be tailored to the needs of the patient, and also fitted by the patient. By virtue of the self-adhesive property, overlapping ends of the sheet can be pressed together to secure the sheet around an element.

It is preferred that the polyurethane foam sheet according to the present invention does not require secondary attachment means to secure the sheet in use, i.e. to secure the sheet around a protruding element.

Polyurethane

According to this invention, a diisocyanate is to be understood as a compound having the formula OCN-R-OCN, wherein R is a C2-C14 aliphatic or cycloaliphatic radical, preferably a C2-C14 alkylene or cycloalkylene radical. If R is an aliphatic radical, it is preferred that the OCN-groups are terminal groups. The aliphatic radicals may be linear or branched and are preferably linear. More preferably, R is a C3-C12 aliphatic or cycloaliphatic radical, and even more preferably, R is a C3 examples and preferred embodiments of the diisocyanates are given below.

Aliphatic diisocyanates and cycloaliphatic diisocyanates can be used in the method of the invention include, for example, the known aliphatic cycloaliphatic diisocyanates selected from the group consisting of 4,4'-Methylene dicyclohexyl diisocyanate, 4,4'- dicyclohexanemethane (H12MDI, 4,4'-HMDI or reduced MDI), 1,4-trans cyclohexane-diisocyanate (CHDI), isophorone diisocyanate (IPDI), 1,6-diisocyanatohexane or hexamethylene diisocyanate trimer (HDI trimer), 1,4-butane diisocyanate (BDI), hydrogenated MDI (HMDI), lysine diisocyanate and combinations thereof. Preferably, the aliphatic diisocyanate is a cyloaliphatic diisocyanate, more preferably the cycloaliphatic diisocyanate is isophorone diisocyanate or the mixture of isophorone diisocyanate and lysine diisocyanate.

The polyurethane has a hard segment prepared from the reaction of an aliphatic isocyanate and a diol chain extender. Preferably, the chain extender is selected from the group consisting of ethylene glycol, 1,2-propylene glycol, 1,3-propanediol, 1,4-butanediol, 1,6-hexanediol, diethylene glycol, 2-methyl-1,3-propanediol, 3-methyl-1,5-pentanediol, 2,2-dimethyl-1,3-propanediol, 2,2,4-trimethyl-1,5-pentanediol, 2-methyl-2-ethyl-1,3-propanediol and combinations thereof.

The hard segment is preferably present in an amount ranging from 51 to 70 wt.% and the soft segment is present in an amount ranging from 30 to 49 wt.% of the total weight of the polyurethane. This reaction is based on a preferable ratio of NCO:OH=1.1:1-1.3:1. It has been found that the ratio may determine the foam quality. In cases where the NCO:OH ratio is too high, larger and more closed pores will increase the hardness, while a lower ratio will lead to the foam collapsing, cracking and a low strength.

The polyol is selected from the group of polyether polyols, polyglycolide, and mixtures thereof. The polyol may be a polyester or copolyesters made by ring-opening polymerization of cyclic reactants, based on, for example, e-caprolactone, lactide, glycolide, delta-valerolactone, l,4-dioxane-2-one, l,5-dioxepan-2-one, oxepan-2,7-dione; polycarbonates and copolycarbonates based on, for example 1 ,6-hexanediol polycarbonate; polycarbonates and copolycarbonates made by ring-opening polymerization based on, for example, trimethylenecarbonate (1,3-dioxane- 2-one), tetramethylenecarbonate, 1,3-dioxepan-2-one or 1,3,8,10- tetraoxacyclotetradecane; polymers and copolymers based on combinations of above described components; polymers made ring-opening polymerization are preferred.

Preferred polyols are the ones that are made by ring opening polymerization of oxygen containing compounds. A particularly preferred polyol is poly(glycolide)diol, which is prepared by the ring-opening polymerization of glycolide. Preferably, a poly(glycolide) with a molecular weight between 600 and 3000 g/mol, more preferably between 1000-2200 g/mol, is used.

The reaction to form the polyol can be carried out in accordance with procedures which are known in polyurethane chemistry. Polyols made by ring opening polymerization are normally synthesized in the presence of a catalyst (e.g. stannous octoate, dibutyl stannous laurate).

In a preferred embodiment, the polyol polyether has the formula $H(OCH_2(CH_2)_xCH_2)_yOH$, wherein x an integer from 2 to 8, preferably 4 to 6, and y is in the range of 30-500, preferably 50-400, more preferably 100-300. Preferred polyol polyethers include poly(tetramethylene ether) glycols.

In another preferred embodiment, the polyglycolide is a polyglycolide of formula $[CH_2-(CH_2)_4-COO]_n$, $HO[OCCH(CH_3)]_nOH$, $HO[COCH(CH_3)O]_m[COCH_2O]_nH$, or $H[OCH_2CH_2]_nOH$.

The polyether polyol and/or polyglycolide has a number average molecular weight (M_n) ranging from 1,000 to 20,000 g/mol, preferably between 2,000 and 18,000.

It may be appreciated that, as is common in the field of polymer chemistry, the polyurethane of the present invention may in fact have a certain polymeric weight distribution. When referring herein to the polyurethane, also a mixture of polyurethanes based on different compounds is meant. This mixture may be the result of different types of polyol (soft) segment and/or of different types of the urethane segment. For instance, the urethane segment may be based on a mixture of different diols and/or diisocyanates. Similarly, a single polyurethane polymer molecule may comprise a mixture of hard segments.

In a preferred embodiment, the polyurethane is the reaction product of an aliphatic diisocyanate, a polyol and a chain extender, said chain extender being a diol.

In another preferred embodiment, the foamed polyurethane sheet is obtainable by a process comprising reacting:

i) an aliphatic and/or cycloaliphatic diisocyanate,

ii) a polyol having a number average molecular weight in the range of 1,000 to 20,000 g/mol,

iii) a diol chain extender,

to provide a pre-polymer, and subsequently reacting the pre-polymer in the presence of a foaming agent to provide the foamed polyurethane sheet,

wherein the polyurethane has a number average molecular weight (Mn) ranging from 1,000 to 50,000 g/mol and wherein a pharmacologically active agent is provided prior to or post foaming of the pre-polymer.

In a second aspect, the present invention relates a process for the preparation of a polyurethane foam sheet as defined herein, wherein the process comprises the steps of:

i) reacting an aliphatic diisocyanate and/or cycloaliphatic with a polyol, to form a prepolymer,

ii) reacting the prepolymer with a diol, and optionally with a cross-linking catalyst, to form a cross-linked prepolymer,

iii) foaming the crosslinked polymer with an aqueous foaming agent to form a polyurethane foam,

wherein a pharmacologically active agent is added to the cross-linked prepolymer before or after step iii).

The process allows for incorporation of a pharmacologically active agent either pre- or post-foaming. The resulting elastic sheet provides a sustained release of the active overtime. Without wishing to be bound by theory, it is proposed that the high average molecular weight of the polyol, in combination with the aliphatic nature of the diisocyanate provides a flexible network that enables the polyurethane foam sheet to be easily deformed. The polyurethane foam is able to absorb wound exudate and withstand the pressures exerted between the prosthesis and osseointergration site. The present polyurethane foam is therefore suitable for use as a covering for percutaneous elements extending from an osseointegration site.

The embodiments described for the polyurethane described above apply mutatis mutandis to the polyurethane obtainable by the abovementioned process.

The diisocyanate used in step i) is to be understood as a compound having the formula OCN-R-OCN, wherein R is a C2-C14 aliphatic or cycloaliphatic radical, preferably a C2-C14 alkylene or cycloalkylene radical. If R is an aliphatic radical, it is preferred that the OCN-groups are terminal groups. The aliphatic radicals may be linear or branched and are preferably linear. More preferably, R is a C3-C12 aliphatic or cycloaliphatic radical, and preferred embodiments of the diisocyanates are given above.

The polyol used in step i) is selected from the group of polyether polyols, polyglycolide, and mixtures thereof. The polyol may be a polyester or copolyesters made by ring-opening polymerization of cyclic reactants, based on, for example, e-caprolactone, lactide, glycolide, delta-valerolactone, l,4-dioxane-2-one, l,5-dioxepan-2-one, oxepan-2,7-dione; polycarbonates and copolycarbonates based on, for example 1 ,6-hexanediol polycarbonate; polycarbonates and copolycarbonates made by ring-opening polymerization based on, for example, trimethylenecarbonate (1,3-dioxane- 2-one), tetramethylenecarbonate, 1,3-dioxepan-2-one or 1,3,8,10- tetraoxacyclotetradecane; polymers and copolymers based on combinations of above described components; polymers made ring-opening polymerization are preferred, with preferred polyols further described above.

In step iii) of the process according to the present invention, foaming of the polymer is carried out. Preferably, the foaming agent is water or sodium hydrogen carbonate, more preferably water. It has been found that the using water or sodium hydrogen carbonate as foaming agent enables the production of a sleeve without the need for organic solvents in the foaming step, increasing the biocompatibility of the foam.

In an embodiment there is provided a process wherein the pharmacologically active agent is added after step iii), preferably wherein the pharmacologically active agent is chlorhexidine.

Preferably, the pharmacologically active agent is added during step ii), and wherein a second pharmacologically active agent is added after step iii).

Even more preferably, the pharmacologically active agent added during step ii) does not react with the pre-polymer or cross-link catalyst.

Pharmacologically active agent

The pharmacologically active agent is selected from the group consisting of analgesics, anti-inflammatory agents, antimicrobial agents and combinations thereof. It has been found that a flexible polyurethane sheet according to the present invention provides a simple, user friendly way to apply analgesics, anti-inflammatory agents, antimicrobial agents and combinations thereof directly to the site of osseointegration implantation.

Preferably, the pharmacologically active agent is an analgesic selected from the group consisting amido-esters or amido-amiides. The amido-amides preferably being selected from the group consisting of N-(2,6-Dimethylphenyl)-N2,N2-diethylglycinamide (lidocaine), 1-Butyl-N-(2,6-dimethylphenyl)-2-piperidinecarboxamide (bupivacaine), N-(2-Methylphenyl)-2-(1-pyrrolidinyl)propanamide (aptocaine) and salts thereof. The amido-esters are preferably selected from the group consisting of procaine, and tetracaine In a particularly preferred embodiment, the analgesic is an amido-amide selected from the group consisting of N-(2,6-Dimethylphenyl)-N2,N2-diethylglycinamide or N-(2,6-Dimethylphenyl)-N2,N2-diethylglycinamide hydrochloride monohydrate.

In another preferred embodiment, the pharmacologically active agent is an antimicrobial agent and preferably the antimicrobial agent is N,N""-1,6-Hexanediylbis[N'-(4-chlorophenyl)(imidodicarbonimidic diamide)] (chlorhexidine) or N,N""-1,6-Hexanediylbis[N'-(4-chlorophenyl)(imidodicarbonimidic diamide)] digluconate (chlorhexidine digluconate) and preferably the antimicrobial agent is selected from the group consisting of triclosan, povidone iodine, polyhexamethyelene biguanide, N,N""-1,6-Hexanediylbis[N'-(4-chlorophenyl) (imidodicarbonimidic diamide)] (chlorhexidine).

Preferably, the anti-inflammatory agent is a non-steroidal anti-inflammatory. Preferably, the non-steroidal anti-inflammatory is a propionic acid selected from the group consisting of 2-(3-Phenoxyphenyl)propanoic acid (Fenoprofen), (2R)-2-(2-Fluoro-1,1'-biphenyl-4-yl)propanoic acid (tarenflurbil), 2-(3-Benzoylphenyl)propanoic acid (ketoprufen), (2S)-2-(4-Isobutylphenyl)propanoic acid (ibuprofen), (2S)-2-(6-Methoxy-2-naphthyl)propanoic acid (naproxen), 3-(4,5-Diphenyl-1,3-oxazol-2-yl)propanoic acid (oxaprozin).

In a preferred embodiment, the pharmacologically active agent is incorporated into the polyurethane post-synthesis. The pharmacologically active agent is dissolved or suspended in a suitable solvent such as water at a concentration typically of from about 0.01% to about 20% w/v, for example from about 0.1% to about 10 wt.%, will be contacted with the polyurethane foam by immersion. Suitable temperatures for the immersion are in the range of 0 °C to 80 °C, preferably in the range of 5 °C to 50° C.

The foam is then removed from the solvent. It may be dried in air or other atmosphere, for example at a temperature in the range of 20 °C to 80 °C, or it may be freeze-dried.

Preferably, the resulting material is sterilized, for example by gamma-irradiation. The loading of the foam with the therapeutic agent may readily be determined based upon the weight of the solution taken up by the foam. Suitable loadings for antimicrobials such as chlorhexidine salts, are from about 0.1 wt.% to about 10 wt.%, for example from about 0.5 wt.% to about 5 wt.%, based on the dry weight of the foam.

In a third aspect, the present invention relates to a polyurethane foam sheet as defined herein for use in a method of treatment or prophylaxis of the human or animal body.

The embodiments described for the first aspect of the present invention apply mutatis mutandis to the third aspect of the present invention.

The inventors provide for the first time a polyurethane foam that is suitable for the treatment or prophylaxis of the human or animal body. The polyurethane as defined herein is suitable for the treatment or prophylaxis of patients with osseointegrative implants. The patients may be human or animal, for example companion animals such as cats and dogs.

Preferably, the treatment involves at least partially covering a percutaneous element of an implant with the polyurethane foam sheet. Preferably, the implant is an osseointegrated prosthesis. Currently, following surgical implantation of an osseointegrated prosthetic, a patient is provided with information concerning daily stoma care. As part of the care plan, painkillers and antibiotics may be provided. Advantageously, the present invention overcomes the need for painkillers and/or antibiotics to be prescribed as the polyurethane foam sheet of the present invention provides local administration of pharmacologically active agents such as painkillers and antibiotics.

The polyurethane foam sheet when located on a percutaneous element, is not in contact with bone. Osseointegrated implants extend through a stoma that is located in muscle, subcutaneous fat or skin tissue. The polyurethane foam sheet can be fitted around the

percutaneous element by the user, for example a patient, therefore the method of treatment does not involve an invasive surgical procedure in order to place the polyurethane foam sheet in position.

Preferably, the treatment is selected from the treatment of infection(s), pain or inflammation associated with an osseointegration prosthetic.

Brief description of figures

Fig. 1 shows the release profiles for polyurethane foam sheets made according to the present invention:

- Panel A shows the percentage release of chlorhexidine (1 wt.%, circles; 5 wt.%, squares) over time.
- Panel B shows the percentage release of lidocaine (1 wt.%, circles; 2 wt.%, squares; 4 wt.%, up triangle; 8 wt.% down triangle) over time.
- Panel C shows the mass (mg) release of chlorhexidine (1 wt.%, circles; 5 wt.%, squares) over time.
- Panel D shows the mass (mg) release of lidocaine (1 wt.%, circles; 2 wt.%, squares; 4 wt.%, up triangle; 8 wt.% down triangle) over time

The invention will now be illustrated by the following non-limiting examples.

Examples

General methods

Porosity

The porosity of the open pores in the materials was measured by liquid displacement method as reported by L. Li, Y. Zuo, Q. Zou, B. Yang, L. Lin, J. Li, Y. Li, Hierarchical Structure and Mechanical Improvement of an n-HA/GCO–PU Composite Scaffold for Bone Regeneration, ACS Applied Materials & Interfaces, 7 (2015) 22618-22629. In this method, water (density, ρ) was employed as the displacement liquid. A dry sample with weight W1 and volume V was immersed in ultrapure water and vacuum-repressurized until no air bubbles released from the sample. The total weight of the water impregnated material was recorded as W2. 5 samples from each group was measured.

The porosity (P) of the material was calculated by:

$$P(\%)=(W2-W1)/\rho V \times 100.$$

Mechanical properties

The tensile strength and modulus of the samples were determined using a mechanical testing machine (AUTOGRAPH AG-IC 20/50KN, Japan). Specimens were cut to 2mm-thick sheets and then trimmed according to the American Standard Test and Measurement (ASTM D 638-02a) norm (specimen type V). The cross-head speed was set to 1 mm/min. Prior to the measurement, all specimens were conditioned for at least 48 h at 20℃ under relative humidity of 45-55% and the values were averaged from five measurements.

Durometer testing was done using Tacklock FO GS-744G, a durometer designed for measurement of sponge and foam materials. The measurements of hardness were made according to the standard measuring procedures for durometers, ASTM D2240-03 Standard Test Method for Rubber Property—Durometer Hardness, ASTM International, West Conshohocken, PA, 2003, www.astm.org.

Drug release

The samples (n = 5) were weighed and placed into 15 ml Falcon™ conical centrifugal tubes containing 10ml phosphate buffer saline (PBS, Gibco™, Invitrogen Corp., Paisley, Scotland). The tubes were incubated at 37 °C with gentle agitation. At each predetermined time point, all supernatants were collected for further analysis and refreshed with 10ml PBS. The concentration of lidocaine and chlorhexidine was detected by reverse-phase (RP)-HPLC according to previously reported methods: [Y. Xue, M. Tang, Y. Hieda, J. Fujihara, K. Takayama, H. Takatsuka, H. Takeshita, High-performance liquid chromatographic determination of chlorhexidine in whole blood by solid-phase extraction and kinetics following an intravenous infusion in rats, J. Anal. Toxicol., 33 (2009) 85-91; and S. Salas, B. Talero, A.M. Rabasco, M.L. Gonzalez-Rodriguez, Development and validation of a reverse-phase liquid chromatographic method for the assay of lidocaine hydrochloride in alginate-Gantrez (R) microspheres, J. Pharm. Biomed. Anal., 47 (2008) 501-507.

The HPLC system consisted of a Hitachi L-2130 pump, a Hitachi L-2400 UV detector, a Hitachi L-2200 autosampler, and a LiChrospher RP-18 endcapped HPLC column (125 mm × 4 mm, particle size 5 µm). For lidocaine detection, the mobile phase consisted of acetonitrile: ammonium acetate (0.0257 M), pH 4.85 (adjusted with acetic acid) in the ratio of 60/40 (v/v). The injection volume was 20 µL with a flow rate of 0.5 mL/min. The concentration of lidocaine was quantified at 254 nm using a standard calibration curve in the concentration range between 5 and 1000 µg/mL. Regarding the CHX detection, the mobile phase consisted of acetonitrile/ultrapure water (40:60, v/v, containing 0.1 v/v% trifluoroacetic acid and 0.1 v/v% triethylamine). 50 µL supernatants were

injected with a flow rate of 1 mL/min at chamber temperature of 40°C. The concentration of CHX was quantified at 260 nm using a standard calibration curve in the concentration range between 0.1 and 200 µg/mL.

Example 1 – synthesis of foamed polyurethane

A polyurethane according to the invention was prepared by copolymerization and simultaneous forming process. 45 g of polytetramethylene ether glycerol (PTMG, Mn~2000) and 11.2 g Isophorone diisocyanate (IPDI) was stirred in a plastic beaker at 200 revolutions per minute at 70℃ and the reaction was kept for 3 hours to form the prepolymer. 2 ml 1,4-Butanediol was used as chain extender to crosslink the prepolymer for 2 hours. After that, 10 µl ditinbutyl dilaurate was used as a catalyst to accelerate the crosslinking process. When the stirring torque reached to 25N, 1ml 2% $NaHCO_3$ was added as a foaming agent and the reaction was kept for another 30 min or until the stir was stopped.

Finally, the mixture was incubated at 90 ℃ overnight to react thoroughly and form porous polyurethane. At this step, the mixture was either kept in a beaker to form a bulk material or smeared on a Petri-dish to form membranes. All the process was conducted at a relative humidity of 45-55%.

Mechanical properties of polyurethane of example 1 is compared to two comparative polyurethanes in Table 1

Table 1

Property	**Example. 1 mean ± SD**	**Comparative Example A Polyurethane of WO 2012/007929 A1***
Density(g/cm^3)	0.3821 ± 0.0105	0.096
Porosity (%)	65.9 ± 4.2	50 %
Young's Modulus (MPa)	0.424 ± 0.140	ND
Durometer (shore)	83.9 ± 1.44	47
Maximal extension rate (%)	999.8 ± 224.7	194
Self-adhesive	yes	no
Flexibility	+++	+

* D1 states the polyurethane foam used is type MS50P(w) Lendell medical foam available from Filtrona Porous Technologies.

Example 2

To embed the drugs in the polyurethane matrix of example 1, different amounts of drugs (corresponding to 1 and 5 wt.%) were dissolved in 2 ml acetone for further usage, e.g. 0.6 g lidocaine was needed to make 1% lidocaine to polyurethane. The drug solutions were added to the crosslinked prepolymer and stirred for 1 hour. After that, 10 µl ditinbutyl dilaurate was used as a catalyst to accelerate the crosslinking process. When the stirring torque reached to 25 N, 1 ml 2% $NaHCO_3$ was added as a foaming agent and the reaction was kept for another 30 minutes or until the stirring was stopped.

Finally, the mixture was incubated at 90 ℃ overnight to react thoroughly and form porous polyurethane. At this step, the mixture was either kept in a beaker to form a bulk material or smeared on a Petri-dish to form membranes. All the processes were conducted at a relative humidity of 45-55%.

If the post-loading of drugs were preferred, the bulky porous polyurethane was first cut into desired shapes, e.g. rectangular sheets (width 5-20 mm, length 10-10 0mm) of 0.5-3 mm thickness. The polyurethane sheets were immersed in drug solutions and vacuumed. The sheets were then lyophilized.

Polyurethane foams prepared comprising pharmacologically active agents in Table 3

Table 3

Sample	**Pharmacologically active agent**	**amount / wt.%**	**Loading**
1	Chlorhexidine	1	Post-foaming
2	Chlorhexidine	5	Post-foaming
3	Lidocaine	1	Pre-foaming
4	Lidocaine	2	Pre-foaming
5	Lidocaine	4	Pre-foaming
6	Lidocaine	8	Pre-foaming

Drug release profiles for sample 1-6 are shown in Figure 1.

Claims

1. A flexible, polyurethane foam sheet comprising a pharmacologically active agent dispersed within said foam,
wherein the polyurethane is a copolymer having the structure according to formula (I):
$[HS\text{-}SS]_n$,
wherein HS denotes a hard block segment being prepared from an aliphatic diisocyanate and/or cycloaliphatic diisocyanate and a diol chain extender,
wherein SS denotes a soft block segment being a polyol having a number average molecular weight in the range of 1,000 to 20,000 g/mol,
wherein the polyurethane has a number average molecular weight (Mn) ranging from 4000 to 50,000 g/mol, preferably between 1,000 and 15,000.

2. Polyurethane foam sheet according to claim 1, wherein the aliphatic and cycloaliphatic diisocyanates are selected from the group consisting of 4,4'-Methylene dicyclohexyl diisocyanate, , 1,4-trans cyclohexane-diisocyanate isophorone diisocyanate, 1,6-diisocyanatohexane or hexamethylene diisocyanate trimer, 1,4-butane diisocyanate, lysine diisocyanate and combinations thereof.

3. Polyurethane foam sheet according to claim 1 or 2, wherein the polyol is a polyether polyol or polyglycolide polyol.

4. Polyurethane foam sheet according any of the preceding claims, wherein the polyether polyol and/or polyglycolide has a number average molecular weight (M_n) ranging from 2,000 to 18,000, even more preferably from 4,000 to 16,000.

5. Polyurethane foam sheet according any of the preceding claims, wherein the chain extender is selected from the group consisting of ethylene glycol, 1,2-propylene glycol, 1,3-propanediol, 1,4-butanediol, 1,6-hexanediol, diethylene glycol, 2-methyl-1,3-propanediol, 3-methyl-1,5-pentanediol, 2,2-dimethyl-1,3-propanediol, 2,2,4-trimethyl-1,5-pentanediol, 2-methyl-2-ethyl-1,3-propanediol and combinations thereof.

6. Polyurethane foam sheet according to any of the preceding claims, wherein the polyurethane foam sheet has a porosity in the range of 50-80 %, preferably in the range of 60-70%.

7. Polyurethane foam sheet according to any of the preceding claims, wherein the HS segment is present in an amount ranging from 51 to 70 wt.% and the SS segment is present in an amount ranging from 30 to 49 wt.% of the total weight of the polyurethane.

8. Polyurethane foam sheet according any of the preceding claims, wherein the pharmacologically active agent is selected from the group consisting of an analgesics, anti-inflammatory agents, antimicrobial agents and combinations thereof.

9. Polyurethane foam sheet according any of the preceding claims according to any of the preceding claims, wherein the pharmacologically active agent is an analgesic selected from the group consisting of lidocaine, procaine, bupivacaine, tetracaine, aptocaine and salts thereof, preferably the analgesic is lidocaine or lidocaine hydrochloride monohydrate

10. Polyurethane foam sheet according any of the preceding claims according to any of the preceding claims, wherein the pharmacologically active agent is an antimicrobial agent selected from the group consisting of triclosan, povidone iodine, polyhexamethyelene biguanide and chlorhexidine, preferably the antimicrobial agent is chlorhexidine or chlorhexidine digluconate.

11. Polyurethane foam sheet according to any of the preceding claims, wherein the polyurethane foam is a flexible, self-adhesive sheet, wherein the sheet preferably has a square or rectangular shape, preferably a rectangular shape, wherein the rectangular shape preferably has a width of 5-20mm, length of 10-100mm and a thickness of 0.5-3mm.

12. Process for preparing a flexible, polyurethane foam sheet comprising a pharmacologically active according to claims 1-11, wherein the process comprises the steps of:

i) reacting an aliphatic and/or cylcoaliphatic diisocyanate with a polyol, to form a prepolymer,

ii) reacting the prepolymer with a diol, and optionally with a cross-linking catalyst, to form a cross-linked prepolymer,

iii) foaming the crosslinked prepolymer with an aqueous foaming agent to form a polyurethane foam,

wherein a pharmacologically active agent is added to the cross-linked prepolymer before or after step iii).

13. Process for preparing a polyurethane foam sheet according any claim 12 wherein the molar ratio of aliphatic diisocyanate and/or cycloaliphatic diisocyanate to polyol is from 1:1 to 5:1, more preferably from 2:1 to 4:1., preferably wherein the polyol is a polyol and/or polyglycolide has a number average molecular weight (Mn) ranging from 2,000 to 18,000, even more preferably from 4,000 to 16,000.

14. Process for preparing a polyurethane foam sheet according claim 12 or 13, wherein the foaming agent is water or sodium hydrogen carbonate, preferably water.

15. Process for preparing a polyurethane foam sheet according any of claims 12-14, comprising step iv) wherein the polyurethane foam is dried in a vacuum, oven or desiccator.

16. Process for preparing a polyurethane foam sheet according to claims 12-15, wherein the pharmacologically active agent is added during step ii), preferably wherein the pharmacologically is lidocaine.

17. Process for preparing a polyurethane foam sheet according to any claims 12-16, wherein the pharmacologically active agent is added after step iii), preferably wherein the pharmacologically active agent is chlorhexidine.

18. Process for preparing a polyurethane foam sheet according to claims 12-17, wherein a pharmacologically active agent is added during step ii), and wherein a second pharmacologically active agent is added after step iii).

19. Process for preparing a polyurethane foam sheet according to claims 12-18, wherein the pharmacologically active agent added during step ii) does not react with the pre-polymer or cross-link catalyst.

20. Polyurethane foam sheet according to any one of claims 1-11 or obtainable by a process according to claims 12-19 for use in a method of treatment or prophylaxis of the human or animal body.

21. Polyurethane foam sheet for use in a method of treatment or prophylaxis according to claim 20, wherein the treatment involves at least partially covering a percutaneous element of a prosthesis with the polyurethane foam sheet, preferably an osseointegrated prosthesis.

22. Polyurethane foam sheet for use in a method of treatment or prophylaxis according to claim 21 or 20, wherein a side of the polyurethane foam sheet abuts the skin and does not extend into the tissue / wherein the method of treatment does not involve an invasive surgical procedure.

23. Polyurethane foam sheet for use in a method of treatment or prophylaxis according to claims 20-22, wherein the treatment is selected from the treatment of infection(s), pain or inflammation associated with an osseointegration prosthetic.

24. Polyurethane foam sheet for use in a method of treatment or prophylaxis according to claims 20-23, wherein the foam sheet provides 0.1-50 wt.%, based on the weight of the polyurethane, of a pharmacologically active agent.

AMENDED CLAIMS

received by the International Bureau on 16 January 2020 (16.01.2020)

Claims

1. A flexible, polyurethane foam sheet comprising a pharmacologically active agent dispersed within said foam,
wherein the polyurethane is a copolymer having the structure according to formula (I):
$[HS\text{-}SS]_n$,
wherein HS denotes a hard block segment being prepared from an aliphatic diisocyanate and/or cycloaliphatic diisocyanate and a diol chain extender,
wherein SS denotes a soft block segment being a polyol having a number average molecular weight in the range of 1,000 to 20,000 g/mol,
wherein the polyurethane has a number average molecular weight (Mn) ranging from 4000 to 50,000 g/mol, preferably between 15,000 and 50,000.

2. Polyurethane foam sheet according to claim 1, wherein the aliphatic and cycloaliphatic diisocyanates are selected from the group consisting of 4,4'-Methylene dicyclohexyl diisocyanate, , 1,4-trans cyclohexane-diisocyanate isophorone diisocyanate, 1,6-diisocyanatohexane or hexamethylene diisocyanate trimer, 1,4-butane diisocyanate, lysine diisocyanate and combinations thereof.

3. Polyurethane foam sheet according to claim 1 or 2, wherein the polyol is a polyether polyol or polyglycolide polyol.

4. Polyurethane foam sheet according any of the preceding claims, wherein the polyether polyol and/or polyglycolide has a number average molecular weight (M_n) ranging from 2,000 to 18,000, even more preferably from 4,000 to 16,000.

5. Polyurethane foam sheet according any of the preceding claims, wherein the chain extender is selected from the group consisting of ethylene glycol, 1,2-propylene glycol, 1,3-propanediol, 1,4-butanediol, 1,6-hexanediol, diethylene glycol, 2-methyl-1,3-propanediol, 3-methyl-1,5-pentanediol, 2,2-dimethyl-1,3-propanediol, 2,2,4-trimethyl-1,5-pentanediol, 2-methyl-2-ethyl-1,3-propanediol and combinations thereof.

6. Polyurethane foam sheet according to any of the preceding claims, wherein the polyurethane foam sheet has a porosity in the range of 50-80 %, preferably in the range of 60-70%.

7. Polyurethane foam sheet according to any of the preceding claims, wherein the HS segment is present in an amount ranging from 51 to 70 wt.% and the SS segment is present in an amount ranging from 30 to 49 wt.% of the total weight of the polyurethane.

8. Polyurethane foam sheet according any of the preceding claims, wherein the pharmacologically active agent is selected from the group consisting of an analgesics, anti-inflammatory agents, antimicrobial agents and combinations thereof.

9. Polyurethane foam sheet according any of the preceding claims according to any of the preceding claims, wherein the pharmacologically active agent is an analgesic selected from the group consisting of lidocaine, procaine, bupivacaine, tetracaine, aptocaine and salts thereof, preferably the analgesic is lidocaine or lidocaine hydrochloride monohydrate

10. Polyurethane foam sheet according any of the preceding claims according to any of the preceding claims, wherein the pharmacologically active agent is an antimicrobial agent selected from the group consisting of triclosan, povidone iodine, polyhexamethyelene biguanide and chlorhexidine, preferably the antimicrobial agent is chlorhexidine or chlorhexidine digluconate.

11. Polyurethane foam sheet according to any of the preceding claims, wherein the polyurethane foam is a flexible, self-adhesive sheet, wherein the sheet preferably has a square or rectangular shape, preferably a rectangular shape, wherein the rectangular shape preferably has a width of 5-20mm, length of 10-100mm and a thickness of 0.5-3mm.

12. Process for preparing a flexible, polyurethane foam sheet comprising a pharmacologically active according to claims 1-11, wherein the process comprises the steps of:

i) reacting an aliphatic and/or cylcoaliphatic diisocyanate with a polyol, to form a prepolymer,

ii) reacting the prepolymer with a diol, and optionally with a cross-linking catalyst, to form a cross-linked prepolymer,

iii) foaming the crosslinked prepolymer with an aqueous foaming agent to form a polyurethane foam,

wherein a pharmacologically active agent is added to the cross-linked prepolymer before or after step iii).

13. Process for preparing a polyurethane foam sheet according any claim 12 wherein the molar ratio of aliphatic diisocyanate and/or cycloaliphatic diisocyanate to polyol is from 1:1 to 5:1, more preferably from 2:1 to 4:1., preferably wherein the polyol is a polyol and/or polyglycolide has a number average molecular weight (Mn) ranging from 2,000 to 18,000, even more preferably from 4,000 to 16,000.

14. Process for preparing a polyurethane foam sheet according claim 12 or 13, wherein the foaming agent is water or sodium hydrogen carbonate, preferably water.

15. Process for preparing a polyurethane foam sheet according any of claims 12-14, comprising step iv) wherein the polyurethane foam is dried in a vacuum, oven or desiccator.

16. Process for preparing a polyurethane foam sheet according to claims 12-15, wherein the pharmacologically active agent is added during step ii), preferably wherein the pharmacologically is lidocaine.

17. Process for preparing a polyurethane foam sheet according to any claims 12-16, wherein the pharmacologically active agent is added after step iii), preferably wherein the pharmacologically active agent is chlorhexidine.

18. Process for preparing a polyurethane foam sheet according to claims 12-17, wherein a pharmacologically active agent is added during step ii), and wherein a second pharmacologically active agent is added after step iii).

19. Process for preparing a polyurethane foam sheet according to claims 12-18, wherein the pharmacologically active agent added during step ii) does not react with the pre-polymer or cross-link catalyst.

20. Polyurethane foam sheet according to any one of claims 1-11 or obtainable by a process according to claims 12-19 for use in a method of treatment or prophylaxis of the human or animal body.

21. Polyurethane foam sheet for use in a method of treatment or prophylaxis according to claim 20, wherein the treatment involves at least partially covering a percutaneous element of a prosthesis with the polyurethane foam sheet, preferably an osseointegrated prosthesis.

22. Polyurethane foam sheet for use in a method of treatment or prophylaxis according to claim 21 or 20, wherein a side of the polyurethane foam sheet abuts the skin and does not extend into the tissue / wherein the method of treatment does not involve an invasive surgical procedure.

23. Polyurethane foam sheet for use in a method of treatment or prophylaxis according to claims 20-22, wherein the treatment is selected from the treatment of infection(s), pain or inflammation associated with an osseointegration prosthetic.

24. Polyurethane foam sheet for use in a method of treatment or prophylaxis according to claims 20-23, wherein the foam sheet provides 0.1-50 wt.%, based on the weight of the polyurethane, of a pharmacologically active agent.

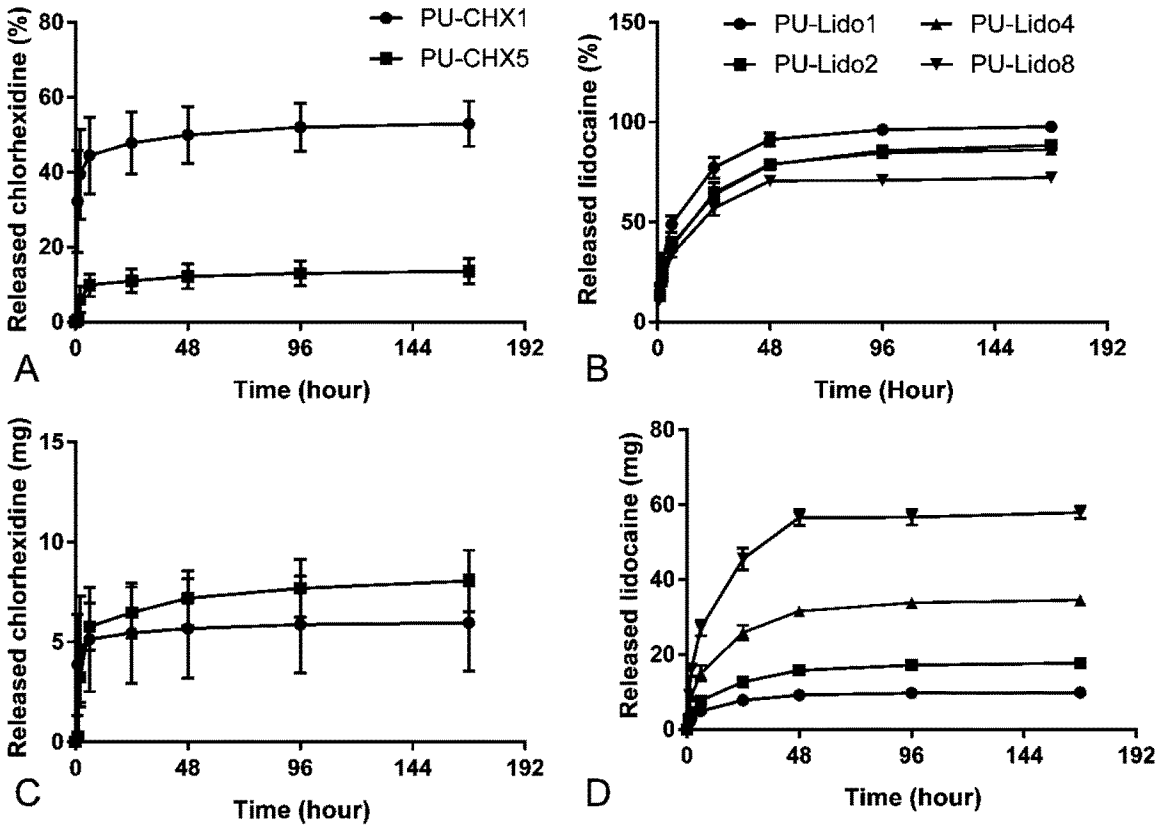
PU-CHX1
PU-CHX5
Released chlorhexidine (%)
Time (hour)
A
PU-Lido1
PU-Lido2
PU-Lido4
PU-Lido8
Released lidocaine (%)
Time (Hour)
B
Released chlorhexidine (mg)
Time (hour)
C
Released lidocaine (mg)
Time (hour)
D

Fig. 1

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2019/073109

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61L27/18 A61L27/54 A61L27/56 A61L31/06 A61L31/14
A61L31/16 A61L15/26 A61L15/42 A61L15/44
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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2012/007929 A1 (HEMCON MEDICAL TECHNOLOGIES IP LTD [IE]; REAL KEITH [IE] ET AL.) 19 January 2012 (2012-01-19) page 2, lines 9-15 page 3, lines 13, 14 page 4, lines 1-14 page 7, lines 5-8, 17-26 page 11, lines 7-9 ----- -/--	1-24

[X] 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

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

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

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

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"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
7 November 2019	19/11/2019

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Lamers, Wolfram

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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