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Description

The present invention relates to novel adhesion barriers based on hydrophilic polyisocyanate prepolymers for use in surgery.

Adhesions are among the most frequent complications after interventions in the abdominal and pelvic region. Adhesions are fibrous bands which generally form within the first seven days after an operation, in the course of the healing process. They cause tissues and organs which are normally separated from one another to grow together, which can give rise to a multiplicity of complications such as, for example, chronic pain, infertility or a life-threatening intestinal occlusion. Products able to reduce the formation of adhesions have been developed in recent years to avoid such complications. Success has so far been limited, however.

Methods of preventing adhesions are peritoneal cavity lavage; the use of pharmacologically active agents such as anti-inflammatories or fibrinolytics; and also the application of mechanical barriers to separate the tissue. Adhesion barriers consist of an inert or absorbable material which is applied to the organs in question. Research has been done on a multiplicity of materials such as polysaccharides (US 4886787, US 5356883), hyaluronic acid (US 4141973, US 5246698), alginates (US 5266326), chitin (US 5093319), chitosan (US 4532134, US 5679658), xanthan (US 4994277), dextran (US 5605938), cellulose and derivatives thereof (Journal of spinal disorders & techniques (2006), 19(4), 270-5), human serum albumin (US 5583114), collagen (US 2005175659), glucosamine (US 5462976), polyoxyalkylene copolymers (US 4911926, US 5366735, US 5135751, US 5681576), polyester (US 5612052, US 6136333), etc. A large proportion of these materials have not been commercialized for lack of efficacy, lack of biodegradability or because of interactions with the wound-healing process.

Commercially available are products in membrane form such as INTERCEED™ (Johnson & Johnson), SEPRAFILM™ (Genzyme Corp.) and REPEL-CV™ (Life Medical Corp.), which are absorbed within 28 days. However, since the barriers are laid onto the organ in question, there is a risk of slippage.

Barriers which like the hyaluronic acid derivative SEPRACOAT™ (GenzymeCorp.) and LUBRICOAT™ (Lifecore Biomedical Inc.) are applied as a liquid are often too quickly degraded by the body, limiting their barrier effect. In addition, there is a risk of migration and hence of no protective effect at all.

5 Hydrogels are water-containing polymers whose chains are linked covalently to form a three-dimensional network. In water, they swell rapidly and with a substantial increase in volume. Owing to their high water content, they are being investigated for use as adhesion barriers. Besides hydrogels based on natural polysaccharides (alginates, hyaluronic acid) it is in particular
10 hydrophilic polyethylene glycol-based systems (US 2005266086, DE-A 69929278, US 7025990, US 6514534, US 2003/0077242), such as the commercially available SPRAYGEL™ (Confluent Surgical), which have been the subject of intensive research. The excessive rate of degradation and the acidity of the degradation products while using lactic acid-based polyesters
15 occasionally proved disadvantageously. Besides the polyethylene glycol-based hydrogel formation, there are frequent mentions (WO 0009087, US 20030077242, US 20050271727) of the redox-initiated free-radical polymerization. Redox initiators used include ascorbic acid and peroxides. Besides possible tissue irritation, one of the problems which arises is the
20 aqueous consistency of the two reactants resulting in no adhesion on the organ in question.

Isocyanate-capped polymers such as polyester- and polyether-urethanes are described in US 2004/0068078 and WO 2004/021983 as inter alia postoperative adhesion barriers. TDI (toluylene diisocyanate) and IPDI
25 (isophorone diisocyanate) are preferably used as isocyanates, whereby the prepolymers contain a monomeric polyisocyanate content such as of TDI of 0.05 to 1 mEq to cause good adherence to the tissue. In the presence of significant biological fluids or of certain types of tissue, greater amounts thereof should preferably be present. Adherence occurs inter alia through reaction of
30 the isocyanate with the tissue. However, monomeric isocyanates, as well as tissue irritation, are known to lead to a sensitization and hence to allergic reactions. The reaction rate of the prepolymer on the tissue is substantially

slowed when aliphatic isocyanates such as HDI are used, and therefore such a system is not practicable for clinical use.

US 7129300 describes the production of absorbable 2-component systems consisting of a polyethylene oxide having two or more amine substituents and
5 a biodegradable diisocyanate or an isocyanate-capped polyethylene oxide with an absorbable diamine.

WO 2006/010278 describes the production and use of polyurethane prepolymers and polyurethane acrylates based on aliphatic isocyanates such as HDI. Low-molecular weight diols, diamines, triols, triamines or oligomers as
10 well as physiologically active compounds are used as chain extenders (curatives). Organic zinc, tin, magnesium and iron compounds are used as a catalyst. The invention is useable inter alia as an adhesion barrier but also for various implants. However, the use of a catalyst generally leads in general to a substantial acceleration in the rate of curing of the polymer and hence to an
15 increased heat generation. Therefore the application is limited for internal organs.

EP-A 1719530 describes the use of isocyanate-capped polyester macromers based on aliphatic dicarboxylic acids and dihydroxy components such as polyalkylene oxides or polyethylene glycols. Aromatic, aliphatic and alicyclic
20 isocyanates are described as possible isocyanates. Prepolymers formed from aromatics-based isocyanates such as TDI (as recited in the examples) have a reported crosslinking time on tissue of 1-10 min. The use of aromatic-based isocyanates, in which similar to the adhesions barriers the product is fully degraded, must be considered problematic for the application in the body due
25 to the resulting cleavage products. Systems based on aliphatic isocyanates are known from experience to have insufficient reactivity and hence too slow a cure time for practicable use *in vivo*. In addition, the viscosities of the compounds recited in EP-A 1719530 with an average of 60 000 mPas are too high for application, and therefore a solvent has to be used.

30 WO 2007/067624 describes a bioabsorbable 2-component system consisting of an isocyanate prepolymer based on glycolide, lactide, ϵ -caprolactone, p-dioxanone, trimethyl carbonate and polyalkylene oxide (for example

polyethylene glycols). The second component used is a polyamine. A gel forms when both components are applied to the tissue, which is useful as an adhesive or as an adhesion barrier. However, the prepolymers have an extremely high viscosity and therefore application will be difficult without solvent additives. Possible solvents mentioned include inter alia water, alcohols and ketones. Hydroxyl group-containing solvents, however, present the problem of rapid reaction with the prepolymer, so that there is a risk of gelling. Processing time, moreover, can become extremely rapid and thereby make processing problematical. The use of solvents *in vivo* must generally in most cases be considered problematical on account of possible cytotoxicity and also interaction with the tissue.

That aspartic esters are suitable in principle for crosslinking prepolymers is known in the prior art in the context of surface coatings and described in DE-A 10246708 or EP-A 1081171.

The non-prepublished European Patent Application Nr. 07021764.1 already describes wound adhesives based on a combination of hydrophilic polyisocyanate prepolymers and aspartates as hardeners. The prepolymers are based on polyether polyols and therefore are not biodegradable within 6 to 12 months. In addition, the systems described are strong adhesives and therefore unsuitable for use as an adhesion barrier.

The underlying object of the present invention is to produce an adhesion barrier which:

- forms a flexible film on the organs/tissue to be protected
- adheres to the organs/tissue to be protected
- is biodegradable in a time window of up to 6 months
- is biocompatible
- forms degradation products without cell and tissue toxicity
- solidifies rapidly in adapted to the kind of use

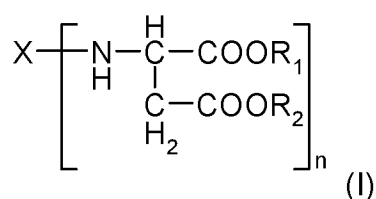
- displays no significant, tissue-damaging exothermicity while curing
- is by virtue of a fine-tuned viscosity easy to apply and unable to penetrate into deeper layers of tissue.

5 Tissue in the context of the present invention is to be understood as meaning cell assemblages consisting of cells of the same shape and function such as epithelial tissue, myocardial tissue, connective or stroma tissue, muscles, nerves and cartilage. Also included are all organs constructed of cell assemblages such as the liver, kidneys, lungs, heart, uterus, etc.

10 It has now been found that this object is achieved by a combination of isocyanate-functional polyester prepolymers based on aliphatic isocyanates having residual monomer contents of less than 1% by weight in combination with amino-functional aspartic esters. Crosslinking catalysts are not needed for crosslinking on the tissue.

The present invention accordingly provides polyurea systems comprising

15 A) amino-functional aspartic esters of the general formula (I)



where

X is an n-valent organic residue obtained by removal of the primary amino groups of an n-valent amine,

20 R₁, R₂ are the same or different organic residues devoid of any Zerevitinov-active hydrogen and

n is an integer of at least 2

and

B) isocyanate-functional prepolymers having residual monomer contents of less than 1% by weight, preferably less than 0.1% by weight and more preferably less than 0.03% by weight, obtainable by reaction of

B1) aliphatic isocyanates with

5 B2) a polyol component having number average molecular weights of ≥ 400 g/mol and average OH functionalities of 2 to 6 which contains polyester-polyether polyols and optionally polyester polyols and/or polyether polyols

and

10 C) optionally organic fillers having a DIN 53019 viscosity at 23°C in the range from 10 to 6000 mPas, and

D) optionally reaction products of isocyanate-functional prepolymers as per the definition of component B) with aspartic esters as per component A) and/or organic fillers as per C).

15 For the definition of Zerevitinov-active hydrogen, reference is made to Römpp Chemie Lexikon, Georg Thieme Verlag Stuttgart. Groups having Zerevitinov-active hydrogen are preferably understood as meaning OH, NH or SH.

Preferred meanings in the formula (I) are:

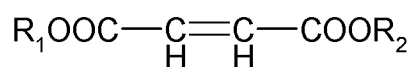
20 R_1, R_2 are the same or different optionally branched or cyclic organic residues devoid of any Zerevitinov-active hydrogen and having 1 to 20 and preferably 1 to 10 carbon atoms, more preferably methyl or ethyl groups,

n is an integer from 2 to 4, and

25 X is an n -valent organic optionally branched or cyclic organic residue having 2 to 20, preferably 5 to 10 carbon atoms, obtained by removing the primary amino groups of an n -functional primary amine.

It will be appreciated that mixtures of two or more aspartic esters can also be used, and therefore n in the formula (I) may also be a non-integral mean value.

The amino-functional polyaspartic esters A) are prepared in a known manner by reaction of the corresponding primary at least difunctional amines $X(NH_2)_n$ with maleic or fumaric esters of the general formula



- 5 Preferred maleic or fumaric esters are dimethyl maleinate, diethyl maleinate, dibutyl maleinate and the corresponding fumaric esters.

Preferred primary at least difunctional amines $X(NH_2)_n$ are ethylenediamine, 1,2-diaminopropane, 1,4-diaminobutane, 1,3-diaminopentane, 1,5-diaminopentane, 2-methyl-1,5-diaminopentane, 1,6-diaminohexane, 2,5-diamino-2,5-dimethylhexane, 2,2,4- and/or 2,4,4-trimethyl-1,6-diaminohexane, 1,11-diaminoundecane, 1,12-diaminododecane, 1-amino-3,3,5-trimethyl-5-aminomethylcyclohexane, 2,4- and/or 2,6-hexahydrotoluylenediamine, 2,4'- and/or 4,4'-diaminodicyclohexylmethane, 3,3'-dimethyl-4,4'-diamino-dicyclohexylmethane, 2,4,4'-triamino-5-methyldicyclohexylmethane and polyetheramines having aliphatically attached primary amino groups having a number average molecular weight M_n in the range from 148 to 6000 g/mol.

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Particularly preferred primary at least difunctional amines are 1,3-diaminopentane, 1,5-diaminopentane, 2-methyl-1,5-diaminopentane, 1,6-diaminohexane, 1,13-diamino-4,7,10-trioxatridecane. 2-Methyl-1,5-diaminopentane is very particularly preferred.

20

In one preferred embodiment of the invention is $R_1 = R_2 = \text{ethyl}$, whereby X is based on 2-methyl-1,5-diaminopentane as a n-valent amine.

The preparation of the amino-functional aspartic esters A) from the starting materials is carried out according to DE-A 69 311 633 preferably within the temperature range from 0 to 100°C, whereby the starting materials are being used in such ratios that for each primary amino group there is at least one, preferably exactly one, olefinic double bond, whereby any starting materials used in excess being removed by distillation after the reaction. The reaction

25

can be carried out without a solvent or in the presence of suitable solvents such as methanol, ethanol, propanol or dioxane or mixtures thereof.

The systems according to the invention are obtained by mixing the prepolymers B) with the amino-functional aspartic esters A) as well as where
5 appropriate the components C) and/or D). The ratio of free or blocked amino groups to free NCO groups is preferably 1:1.5 and more preferably 1:1.

Immediately after the individual components have been mixed together, the systems according to the invention have a shear viscosity at 23°C of preferably
10 500 to 20 000 mPas and more preferably 500 to 8000 mPas measured according to DIN 53019.

The time needed for complete crosslinking and curing of the adhesion barrier at 23°C is typically in the range from 30 s to 10 min, preferably in the range from 30 s to 8 min and more preferably in the range from 1 min to 5 min.

The isocyanate-functional prepolymers used in B) are obtainable by reaction
15 of isocyanates B1) with polyols B2) optionally in the presence of catalysts as well as auxiliary materials and additives.

The isocyanates or isocyanate mixtures used in B1) preferably have an average NCO functionality in the range from 2 to 2.6 and more preferably in the range from 2 to 2.4.

20 In B1), isocyanates are for example monomeric aliphatic or cycloaliphatic di- or triisocyanates such as 1,4-butylene diisocyanate (BDI), 1,6-hexamethylene diisocyanate (HDI), isophorone diisocyanate (IPDI), 2,2,4- and/or 2,4,4-trimethylhexamethylene diisocyanate, the isomeric bis (4,4'-isocyanatocyclohexyl)methanes or their mixtures of any desired isomeric
25 content, 1,4-cyclohexylene diisocyanate, 4-isocyanatomethyloctane 1,8-diisocyanate (nonane triisocyanate) and also alkyl 2,6-diisocyanatohexanoate (lysine diisocyanate) having C1-C8-alkyl groups.

Besides the aforementioned monomeric isocyanates, it is also possible to use their higher molecular weight descendent products of uretdione, isocyanurate,

urethane, allophanate, biuret, iminooxadiazinedione or oxadiazinetriene structure and also mixtures thereof.

5 B1) preferably utilizes isocyanates of the aforementioned kind with exclusively aliphatically or cycloaliphatically attached isocyanate groups or mixtures thereof.

Hexamethylene diisocyanate is very particularly preferred for use in B1).

Polyol component B2) utilizes polyols having an average OH functionality in the range from 2.3 to 4.

10 B2) preferably utilizes polyether-ester-polyols and preferably their mixtures with polyether polyols.

Such preferred polyether-ester polyols further have a hydroxyl number of 30 to 140 mg KOH/g, preferably 35 to 130 mg KOH/g, and also an acid number of 0.05 to 10 mg KOH/g, preferably 0.1 to 3 mg KOH/g and more preferably 0.15 to 2.5 mg KOH/g.

15 Polyether esters essential to the present invention are liquid at room temperature and have a DIN 53019 shear viscosity at 23°C of 200 to 8000 mPas, preferably 400 to 4000 mPas.

20 Such polyether-ester-polyols are preferably prepared in the prior art by polycondensation of polycarboxylic acids, anhydrides of polycarboxylic acids and also esters of polycarboxylic acids with volatile alcohols, preferably C1 to C6 monools such as methanol, ethanol, propanol or butanol, with molar excess, low molecular weight and/or higher molecular polyol; whereby polyols containing ether groups optionally mixed with other polyols free of ether groups are being used as a polyol.

25 The polyether ester synthesis obviously may also utilize mixtures of the higher molecular and of the low molecular polyols.

Such molar excess low molecular polyols are polyols having molar masses of 62 to 299 daltons, having 2 to 12 carbon atoms and hydroxyl functionalities of at least 2, which may further be branched or unbranched and whose hydroxyl

groups are primary or secondary. These low molecular polyols can also have ether groups. Typical representatives are ethylene glycol, 1,2-propanediol, 1,3-propanediol, 1,4-butanediol, 2,3-butanediol, 2-methyl-1,3-propanediol, 1,5-pentanediol, 1,6-hexanediol, 3-methyl-1,5-pentanediol, 1,8-octanediol, 1,10-decanediol, 1,12-dodecanediol, cyclohexanediol, diethylene glycol, triethylene glycol and higher homologues, dipropylene glycol, tripropylene glycol and higher homologues, glycerol, 1,1,1-trimethylolpropane and also oligotetrahydrofurans having hydroxyl end groups. Obviously mixtures can also be used within this group.

Higher molecular polyols in molar excess are polyols having molecular weights of 300 to 3000 daltons, which are obtained by ring-opening polymerization of epoxides, preferably ethylene oxide and/or propylene oxide, and also by acid-catalysed, ring-opening polymerization of tetrahydrofuran. Ring-opening polymerization of epoxides may utilize either alkali metal hydroxides or double metal cyanide catalysts.

Useful starters for ring-opening epoxide polymerization include all at least bifunctional molecules from the group of the amines and the abovementioned low molecular polyols. Typical representatives are 1,1,1-trimethylolpropane, glycerol, o-TDA, ethylenediamine, 1,2-propylene glycol, etc. and also water, including mixtures thereof. It will be appreciated that mixtures can also be used within the group of excess higher molecular polyols.

The construction of the higher molecular polyols insofar as it deals with hydroxyl group-terminated polyalkylene oxides formed from ethylene oxide and/or propylene oxide, may be effected randomly or blockwise, in which mixed blocks can be present as well.

Polycarboxylic acids are both aliphatic and aromatic carboxylic acids, which can be cyclic, linear, branched or unbranched and which have between 4 and 24 carbon atoms.

Examples are succinic acid, glutaric acid, adipic acid, sebacic acid, 1,10-decanedicarboxylic acid, 1,12-dodecanedicarboxylic acid, phthalic acid, terephthalic acid, isophthalic acid, trimellitic acid, pyromellitic acid. Preference

is given to succinic acid, glutaric acid, adipic acid, sebacic acid, lactic acid, phthalic acid, terephthalic acid, isophthalic acid, trimellitic acid, pyromellitic acid. Particular preference is given to succinic acid, glutaric acid and adipic acid.

5 The group of the polycarboxylic acids further comprises hydroxy carboxylic acids or inner anhydrides thereof, for example caprolactone, lactic acid, hydroxybutyric acid, ricinolic acid, etc. Also included are monocarboxylic acids, in particular those having more than 10 carbon atoms, such as soybean oil fatty acid, palm oil fatty acid and groundnut oil fatty acid, subject to the proviso
10 that their proportion of the total reaction mixture constructing the polyether-ester-polyol does not exceed 10% by weight and additionally the resulting lesser functionality is compensated by co-use of at least trifunctional polyols, whether as part of the low molecular polyols or as part of the high molecular polyols.

15 The preparation of the polyether-ester-polyol is effected in accordance with the prior art at elevated temperature in the range from 120 to 250°C, initially under atmospheric pressure, later by applying a vacuum of 1 to 100 mbar, preferably but not necessarily with use of an esterification or transesterification catalyst, whereby the reaction is completed to such an extent that the acid number
20 decreases to values in the range from 0.05 to 10 mg KOH/g, preferably 0.1 to 3 mg KOH/g and more preferably 0.15 to 2.5 mg KOH/g.

Furthermore, an inert gas can be used as part of the atmospheric pressure phase before a vacuum is applied. It will be appreciated that liquid or gaseous entrainers can also be used alternatively or for individual phases of the
25 esterification. For example, the water of the reaction can be removed using nitrogen as a carrier gas, but also with the use of an azeotropic entrainer, for example benzene, toluene, xylene, dioxane, etc.

The polyether polyols optionally used as a blending component in B2 have a molecular weight in the range from 100 to 2000 g/mol, preferably in the range
30 from 100 to 1000 g/mol and more preferably in the range from 100 to 400 g/mol and consist wholly or partly of polyethylene oxide polyols.

When B2 utilizes polyether polyols alongside the polyesters or polyether esters, their proportion will comprise not more than 70% by weight and preferably not more than 50% by weight based on the entire component B2.

5 Preferably the mass fraction of the entire component B2 that is attributable to ethylene oxide is preferably in the range from 40% to 95% by weight and more preferably in the range from 60% to 90% by weight.

Component B2 preferably has an ester group concentration (in moles per kg) of 0.5 to 5.5 and more preferably 1 to 3.5.

10 The prepolymers prepared from B1 and B2 have a DIN EN ISO 11909 average NCO content of 2% to 10% by weight and preferably 2.5% to 8% by weight.

The organic liquid fillers used in C) are preferably non-cytotoxic according to ISO 10993 cytotoxicity measurement.

15 Useful organic fillers include for example 23°C liquid polyethylene glycols such as PEG 200 to PEG 600, their monoalkyl and dialkyl ethers such as PEG 500 dimethyl ether, liquid polyether and polyester polyols, liquid polyesters such as, for example, Ultramoll (Lanxess AG, Leverkusen, Germany), and also glycerol and its liquid derivatives such as, for example, Triacetin (Lanxess AG, Leverkusen, Germany).

20 The organic fillers of component C) preferably comprise hydroxy- or amino-functional, preferably purely hydroxy-functional compounds. Particular preference is given to polyols. Preferred polyols are polyethers and/or polyester polyols and more preferably polyether polyols.

25 The preferred organic fillers preferably have average OH functionalities in the range from 1.5 to 3, more preferably in the range from 1.8 to 2.2 and more preferably 2.0.

The preferred organic fillers of the component preferably have repeat units derived from ethylene oxide.

The viscosity of the organic fillers is preferably in the range from 50 to 4000 mPas, more preferably in the range from 50 to 2000 mPas at 23°C measured according to DIN 53019.

5 One preferred embodiment of the invention utilizes polyethylene glycols as organic fillers. These polyethylene glycols preferably have a number average molecular weight in the range from 100 to 1000 g/mol and more preferably in the range from 200 to 400 g/mol.

The weight ratio of the filler component C) to the aspartate component A) is in the range from 0:1 to 20:1 and preferably in the range from 0:1 to 12:1.

10 The weight ratio of the filler relative to the total amount of the mixture of A and B is in the range from 0 to 100% and preferably in the range from 0 to 60%.

To further reduce the average equivalent weight of all the compounds used for prepolymer crosslinking, based on the NCO-reactive groups, it is also possible, in addition to the compounds used in A), to prepare the amino- or hydroxy-
15 functional reaction products of isocyanate-functional copolymers with aspartic esters and/or organic fillers, provided the latter are amino- or hydroxy-functional, in a separate prereaction and then to use these reaction products as higher molecular curative component.

20 The pre-extending step preferably utilizes ratios of isocyanate-reactive groups to isocyanate groups in the range from 50:1 to 1.5:1 and more preferably in the range from 15:1 to 4:1.

The isocyanate-functional prepolymer to be used for this can correspond to that of component B) or else be constructed differently from the components listed as possible constituents of the isocyanate-functional prepolymers in the
25 context of this application.

Modification through pre-extension has the advantage that the equivalent weight and equivalent volume of the curative component is modifiable within distinct limits. As a result, commercially available 2-chamber dispensing systems can be used for application in order to obtain an adhesive system

which, given existing ratios for the chamber volumes, be fine tuned to the desired ratio of NCO-reactive groups to NCO groups.

A further embodiment of this invention is a process for preparing the urea systems according to the present invention as well as their use in a process for sealing, uniting or for covering cell tissues.

Covering cell tissues is preferably understood as meaning preparing postoperative adhesion barriers.

In the case of coatings for preparing postoperative adhesion barriers, it can be sensible to colour one or more of the components A) to D) used to make the barrier easier to see.

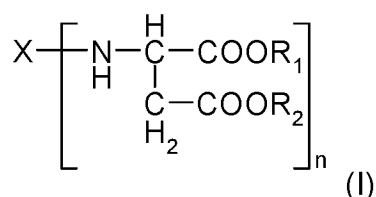
In the *in vivo* application of a coating to produce a postoperative adhesion barrier, the necessary components are applied, with the aid of a two-chamber dispensing system and a suitable applicator, to the organ to be protected and there form a protective polymeric film within 10 minutes. This polymeric film adheres to the organ surface without penetrating into the tissue. The film can be mechanically removed without damaging the tissue.

Further embodiments of the invention are the inventive polyurea-systems for producing means for sealing, uniting or covering cell tissues.

Films and composite parts obtainable using polyurea systems according to this invention are also part of this invention.

According to a first embodiment, the invention relates to polyurea systems comprising

A) amino-functional aspartic esters of the general formula (I)



where

X is an n-valent organic residue obtained by removal of the primary amino groups of an n-valent amine,

5 R₁, R₂ are the same or different organic residues devoid of any Zerevitinov-active hydrogen and

n is an integer of at least 2

and

B) isocyanate-functional prepolymers having residual monomer contents of less than 1% by weight obtainable by reaction of

10 B1) aliphatic isocyanates with

B2) a polyol component having number average molecular weights of ≥ 400 g/mol and average OH functionalities of 2 to 6 which contains polyester-polyether polyols and optionally polyester polyols and/or polyether polyols,

15 and

C) optionally organic fillers having a DIN 53019 viscosity at 23°C in the range from 10 to 6000 mPas, and

20 D) where appropriate, reaction products of isocyanate-functional prepolymers as per the definition of component B) with aspartic esters as per component A) and/or organic fillers as per C).

25 According to a second embodiment, the invention relates to polyurea systems according to embodiment 1, characterized in that the polyether ester polyols used in B2) have a hydroxyl number of 30 to 140 mg KOH/g, an acid number of 0.05 to 10 mg KOH/g and a DIN 53019 shear viscosity at 23°C of 200 to 8000 mPas.

According to a third embodiment, the invention relates to polyurea systems according to embodiment 1 or 2, characterized in that B2 utilizes polyether

polyols having a number average molecular weight of 100 to 2000 g/mol and having all or some of the ether groups derived from ethylene oxide.

According to a fourth embodiment, the invention relates to polyurea systems according to embodiment 3, characterized in that the proportion of polyether polyols comprises not more than 50% by weight based on the entire component B2.

According to a fifth embodiment, the invention relates to polyurea systems according to any of embodiments 1 to 4, characterized in that the component B2 has an ester group concentration (in moles per kg) of 0.5 to 5.5.

According to a sixth embodiment, the invention relates to polyurea systems according to any of embodiments 1 to 5, characterized in that the organic fillers of component C) comprise hydroxy-functional compounds, preferably polyethylene glycols.

According to a seventh embodiment, the invention relates to a process for preparing urea systems according to any one of embodiments 1 to 6 by mixing the components A), B), where appropriate C) and where appropriate D), wherein the ratio of free or blocked amino groups to free NCO groups amounts to 1:1 the weight ratio of filler component C) to aspartate component A) ranges from 0:1 to 20:1.

According to a eighth embodiment, the invention relates to polyurea systems obtainable by a process according to embodiment 7.

According to a ninth embodiment, the invention relates to a polyurea-system for the usage in a process for sealing, uniting or covering cell tissues.

According to a tenth embodiment, the invention relates to the use of polyurea systems for producing means for sealing, uniting or covering cell tissues.

According to an eleventh embodiment, the invention relates to films and composite parts obtainable using polyurea systems according to any one of embodiments 1 to 6 or 8.

According to a twelvth embodiment, the invention relates to a postoperative adhesion barrier obtainable using polyurea systems according to any one of embodiments 1 to 6 or 8.

- 5 According to a thirteenth embodiment, the invention relates to a 2-chamber dispensing system comprising a polyurea system according to any one of embodiments 1 to 6 or 8 wherein one chamber comprises the prepolymer of component A) and the other chamber comprises the curative component B) and where appropriate C) and D).

Examples:

Unless stated otherwise, all percentages are by weight.

Example A: (aspartate synthesis)

5 To 2 mol of diethyl maleate was gradually added dropwise 1 mol of 2-methyl-1,5-diaminopentane under nitrogen atmosphere such that the reaction temperature does not exceed 60°C. The reaction mixture was then heated at 60°C until diethyl maleate was no longer detectable in the reaction mixture.

Example B: (polyester synthesis)

10 **Raw materials**

Polyether 1 is a 1,2-propylene glycol-started, KOH-catalysed polyether glycol from BMS AG having a hydroxyl number of 56 mg KOH/g and having about 50% by weight each of ethylene oxide and propylene oxide units, the chain ends being tipped with ethylene oxide.

15 Polyether 2 is a 1,2-propylene glycol-started, KOH-catalysed, hydroxyl-terminated polyethylene oxide from BMS AG having a hydroxyl number of 190 mg KOH/g.

20 Polyether 3 is a 1,1,1-trimethylolpropane-started, KOH-catalysed, hydroxyl-terminated polyethylene oxide from BMS AG having an hydroxyl number of 550 mg KOH/g.

The ester group concentration portrayed in Table 1 corresponds to the number of moles of carboxyl groups used for 1 kg of product.

25 The reported "fraction of ethylene oxide groups" computes from the ethylene oxide group content of the starting polyether 1 (50% by weight), polyether 2 (100%), polyether 3 (100%) and diethylene glycol (100%), or their proportion of the starting materials of the polyester recipe.

In a 6 l flask equipped with thermometer, column, reflux divider with head thermometer, descending condenser and 1 l receiver, 98 g (1.07 mol) of glycerol, 935 g (0.47 mol) of polyether 1, 1615 g (2.73 mol) of polyether 2 and 467 g (3.2 mol) of adipic acid were gradually heated to 200°C at atmospheric pressure and under nitrogen with stirring, while water of reaction distilled off. After 5 hours, 68 mg of tin dichloride dihydrate were added and at the same time vacuum was applied to ultimately produce a pressure of 15 mbar. After a further 20 hours, the reaction had ended. Analysis gave the values recited in Table 1.

Table 1: Synthesis and characterization of inventive polyester polyols, batch size per 3 kg of product

Example		B-1	B-2	B-3	B-4	B-5	B-6	B-7	B-8	B-9	B-10
adipic acid	[g]	467	426	218	289	562		733	493	201	292
succinic acid	[g]						473				
glycerol	[g]	98		118	98					99	82
TMP	[g]								256		
polyether 1	[g]	935	931	1527	2150			954	937	2748	2148
polyether 2	[g]	1615	906	1191	534	1735	1829	326	1179		546

Polyether 3	[g]		842				842	842	842	256		
diethylene glycol	[g]								326			
tin dichloride dihydrate	[mg]	68	68	68	68	68	68	68	68	68	68	68
functionality		3	3.5	2.5	3	3.5	3.5	3.5	3.5	3.5	3	3
OH number exp.	[mg KOH/g]	52.1	121.4	98.3	43.5	122	121	120	115	44.4	38.4	
acid number	[mg KOH/g]	0.9	0.3	0.3	1.2	0.2	0.3	0.2	0.3	0.6	0.7	
viscosity	[mPas, 75°C]	620	180	100	440	2110	2490	3230	1850	2340	4450	
fraction of ethylene oxide units	[% by weight]	67	71	64	52	82	85	69	61	45	53	

ester concentration	group concentration	[mol/kg]	2.13	1.95	1.00	1.32	2.56	2.67	3.35	2.25	0.92	1.33
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Example C: Prepolymer synthesis**Example C-2a,**

236.95 g of HDI and 0.4 g of benzoyl chloride were placed as initial charge in a 500 ml four-neck flask. 162.6 g of polyester 2 from Example B-2, dewatered at 100°C, were added at 80°C during 2 h and subsequently stirred in for 1 h. Then, thin film distillation at 140°C and 0.1 Torr was used to distil off excess HDI (hexamethylene diisocyanate) to leave 280 g of the prepolymer having an NCO content of 5.67%. The residual monomer content was < 0.03% of free HDI.

Example C-2b, (Prepolymer-Synthesis)

281.88 g of HDI and 0.4 g of benzoyl chloride were placed as initial charge in a 500 ml four-neck flask. A mixture of 96.75 g of polyester 2 from Example B-2 and 20.97 g of polyethylene glycol of molar mass 200 Da (PEG 200), dewatered at 100°C, were added at 80°C during 2 h and subsequently stirred in for 1 h. Then, thin film distillation at 140°C and 0.1 Torr was used to distil off excess HDI to leave 311 g of the prepolymer having an NCO content of 7.88%. The residual monomer content was < 0.03% of free HDI.

Example C-2c, (Prepolymer-Synthesis)

267.82 g of HDI and 0.4 g of benzoyl chloride were placed as initial charge in a 500 ml four-neck flask. A mixture of 91.92 g of polyester 2 from Example B-2 and 39.85 g of PEG 400, dewatered at 100°C, were added at 80°C during 2 h and subsequently stirred in for 1 h. Then, thin film distillation at 140°C and 0.1 Torr was used to distil off excess HDI to leave 302 g of the prepolymer having an NCO content of 7.57%. The residual monomer content was < 0.03% of free HDI.

Example D: Production of adhesion barrier**Example D**

10 g of prepolymer B were thoroughly mixed in a beaker with equivalent amounts of the amino-functional aspartic ester (aspartate A). The reaction mixture was immediately thereafter applied thinly to kidneys, liver and muscle tissue. Cure time and temperature and also adherence to the tissue were determined.

Example	D-1	D-2a	D-2b	D-2c	D-3	D-4
prepolymer of polyester	C-1	C-2a	C-2b	C-2c	C-3	C-4
NCO content of prepolymer [%] measured to DIN EN ISO 11909	3.06	5.67	7.88	7.57	4.38	2.57
cure time [min]	2	1	2	1.5	3	3
cure temperature [°C]	35	40	41	40	42	35

Example	D-5	D-6	D-7	D-8	D-9	D-10
prepolymer of polyester	C-5	C-6	C-7	C-8	C-9	C-10
NCO content of prepolymer [%] measured to DIN EN ISO 11909	5.95	5.92	6.0	5.72	2.01	2.07
cure time [min]	1.5	1	1	1.5	2	3
cure temperature [°C]	41	43	42	47	28	37

A shiny, transparent film had formed at the reported times in all recited examples. Good adherence without penetration of the polymer into the tissue was observed in all cases. The barriers could be mechanically removed without damaging the tissue.

Comparative Examples:**Example 1**

When prepolymer A-1 was applied to tissue without aspartate admixture, no cure took place within 30 min.

Example 2

Prepolymer A-1 was prepared as described in Example B using TDI instead of HDI. The prepolymer obtained was admixed with different amounts of water and applied to tissue. No cure took place within 15 min.

Example 3, Synthesis of polyether polyol prepolymer from EP 2 011 808

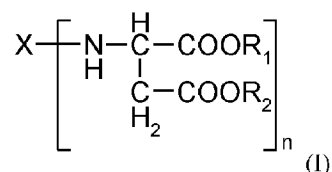
465 g of HDI and 2.35 g of benzoyl chloride were placed as initial charge in a 1 l four-neck flask. 931.8 g of a polyether having an ethylene oxide content of 63% and a propylene oxide content of 37% (each based on total alkylene oxide content) started on TMP (3-functional) were added at 80°C during 2 h and subsequently stirred in for 1 h. Then, thin film distillation at 130°C and 0.1 Torr was used to distil off excess HDI to leave 980 g (71%) of the prepolymer having an NCO content of 2.53%. The residual monomer content was < 0.03 % HDI.

Example 4, Adhesion barrier

10 g of the prepolymer of Example 3 were thoroughly stirred in a beaker with equivalent amounts of the amino-functional aspartic ester (aspartate A). The reaction mixture was immediately thereafter applied thinly to kidneys, liver and muscle tissue. A cure took place within 2 min to form a transparent film. In the process, the polymer penetrated into the tissue and could not be removed without damage.

Patentkrav**1. Polyurinstofsystemer der omfatter**

A) aminofunktionelle asparaginsyreestere med den almene formel (I)



5 hvor

X er en n-valent organisk gruppe der er opnået ved fjernelse af de primære aminogru-
pper af en n-valent amin,

R₁, R₂ er de samme eller forskellige organiske radikaler uden noget Ze-
revitinov-aktivt hydrogen og

10 n er et heltal på mindst 2

og

B) isocyanatfunktionelle præpolymerer med restmonomerindhold på
mindre end 1 vægt-% der er opnået ved omsætning af

B1) alifatiske isocyanater med

15 B2) en polyolkomponent der har antalsgennemsnitsmolekylvægte på ≥
400 g/mol og gennemsnitlig OH-funktionalitet på 2 til 6, der indeholder
polyester-polyetherpolyoler og eventuelt polyesterpolyoler og/eller poly-
etherpolyoler

og

20 C) eventuelt organiske fyldstoffer der har en DIN 53019-viskositet ved 23
°C i området fra 10 til 6000 mPas, og

D) eventuelt reaktionsprodukter af isocyanatfunktionelle præpolymerer
ifølge definitionen af komponent (B) med asparaginsyreestere ifølge
komponent (A) og/eller organiske fyldstoffer ifølge (C).

25

**2. Polyurinstofsystemerne ifølge krav 1, kendetegnet ved, at polyetherester-
polyoler der er anvendt i (B2) har et hydroxyltal på 30 til 140 mg KOH/g, et syre-
tal på 0,05 til 10 mg KOH/g og en DIN 53019 forskydningsviskositet ved 23 °C
på 200 til 8000 mPas.**

30

3. Polyurinstofsystemer ifølge krav 1 eller 2, **kendetegnet ved, at** polyetherpolyolen i (B2) anvendes med en antalsgennemsnitsmolekylvægt på 100 til 2000 g/mol, hvor ethergrupperne helt eller delvist er afledt af ethylenoxid.
- 5 4. Polyurinstofsystemerne ifølge krav 3, **kendetegnet ved, at** andelen af polyetherpolyoler udgør højst 50 vægt-%, der er baseret på den samlede B2-komponent.
- 10 5. Polyurinstofsystemer ifølge et hvilket som helst af kravene 1 til 4, **kendetegnet ved, at** komponenten B2 har en estergruppekoncentration (i mol pr. kg) på 0,5 til 5,5.
- 15 6. Polyurinstofsystemer ifølge et hvilket som helst af kravene 1 til 5, **kendetegnet ved, at** de organiske fyldstoffer i komponent (C) omfatter hydroxyfunktionelle forbindelser, fortrinsvis polyethylenglycoler.
- 20 7. Fremgangsmåde til fremstilling af urinstofsystemer ifølge et hvilket som helst af kravene 1 til 6 ved at blande komponenterne (A), (B), hvor det er relevant (C) og hvor det er relevant (D), hvor forholdet mellem frie eller blokerede amino-grupper og frie NCO-grupper udgør 1 : 1, vægtforholdet mellem fyldstofkomponent (C) og aspartatkomponenten (A) ligger på fra 0 : 1 til 20 : 1.
- 25 8. Polyurinstofsystemer der er opnåelige ved en fremgangsmåde ifølge krav 7.
- 30 9. Polyurinstofsystem til anvendelse i en proces til forsegling, forbindelse eller afdækning af cellevæv.
10. Anvendelse af polyurinstofsystemer ifølge et hvilket som helst af kravene 1 til 6 eller 8 til fremstilling af midler til forsegling, forbindelse eller afdækning af cellevæv.
11. Film og sammensatte dele der kan opnås ved anvendelse af polyurinstofsystemer ifølge et hvilket som helst af kravene 1 til 6 eller 8.

12. Postoperativ adhæsionsbarriere der kan opnås ved anvendelse af polyurinstofsystemer ifølge et hvilket som helst af kravene 1 til 6 eller 8.

- 5 13. To-kammerdispenseringsystem der omfatter et polyurinstofsystem ifølge et hvilket som helst af kravene 1 til 6 eller 8, hvor det ene kammer omfatter præpolymeren af komponent (A) og det andet kammer omfatter hærderkomponenten (B) og hvor det er relevant (C) og (D).