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(54) Benævnelse: **Medicinske klæbemidler til stilning af svære blødninger og tætning af lækager**

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The present invention relates to new, rapidly curing adhesives based on hydrophilic polyisocyanate prepolymers for use in emergency medicine to stem heavy bleeding and seal leakages.

Various materials that are used as tissue adhesives are available commercially. They include the cyanoacrylates Dermabond® (octyl 2-cyanoacrylate) and Histoacryl Blue® (butyl cyanoacrylate). However, a prerequisite for efficient bonding of the cyanoacrylates is a dry substrate. Such adhesives fail when there is pronounced bleeding.

As an alternative to the cyanoacrylates, biological adhesives are available such as, for example, BioGlue®, a mixture of glutaraldehyde and bovine serum albumin, various collagen- and gelatin-based systems (FloSeal(®), and the fibrin adhesives (Tissucol). Such systems are used primarily to stem bleeding (hemostasis). In addition to the high costs, fibrin adhesives are distinguished by a relatively weak adhesive strength and rapid degradation, so that they can only be used for relatively small injuries on unstretched tissue. Collagen- and gelatin-based systems such as FloSeal® are solely used for hemostasis. In addition, because fibrin and thrombin are obtained from human material and collagen and gelatin is obtained from animal material, there is always the risk of infection in biological systems. Biological materials must furthermore be stored in cool conditions so that their use in emergency care such as for example in disaster areas, or in military deployment etc. is not possible. Traumatic wounds are treated in such cases with QuikClot® or QuikClot ACS+^{TM} which is a granular mineral that is introduced into the wound in emergency situations where it leads to coagulation by removing water. In the case of QuikClot, this is a strongly exothermic reaction which leads to burns. QuikClot ACS+^{TM} is gauze into which the salt is embedded. The system must be pressed firmly onto the wound in order to stem bleeding.

Reference to possible uses of polyurethane prepolymers as hemostatic agents is made in the articles "Isocyanate-terminated urethane prepolymer as bioadhesive material: evaluation of bioadhesion and biocompatibility, in vitro and in

vivo assays" (Journal of Biomaterials Science, Polymer Edition (2001), 12(7), 707-719) and "Development of a biodegradable bioadhesive containing urethane groups" (Journal of Materials Science: Materials in Medicine (2008), 19(1), 111-120).

It has now been found that formulations comprising specific hydrophilic polyurethane prepolymers and amino-functional curing agents show excellent performance as hemostatics for stemming blood. In addition, the formulations have advantageous adhesive qualities that enable, in addition to stemming blood, the film, which was formed by the formulation to become fixed on the injury site. Furthermore, this allows, particularly in cases with extensive injury, sections of tissue to be joined together again and fixed which is beneficial for the wound healing process.

The object of the present invention are formulations comprising

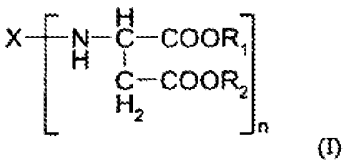
A) isocyanate-functional prepolymers obtainable from

Al) aliphatic isocyanates and

A2) polyols having number-average molecular weights of ≥ 400 g/mol and average OH functionalities of 2 to 6,

B) a curing component comprising

B1) amino-functional aspartic acid esters of the general formula (I)



(I)

wherein

X represents an n-valent organic group obtained by removal of the primary amino groupfrom an n-functional amine,

R_1, R_2 represent identical or different organic groups that do not contain a Zerewitinoff-active hydrogen and

n represents an integer of at least 2 and

B2) optionally organic fillers which have a viscosity as measured according to DIN 53019 at 23°C in the range from 10 to 6000 mPas

and

C) optionally reaction products of isocyanate-functional prepolymers as defined for component A) with aspartic acid esters as per component B1) and/or organic fillers as per component B2)

that are used to stem the loss of blood (hemostatic) or tissue fluids or that are used to seal leakages in cell tissues.

Another object of the present invention is the use of the aforementioned formulations for producing a composition for stemming the loss of blood (hemostatic) or tissue fluids or for sealing leaks in cell tissues.

The stemming of the loss of fluid or blood or the sealing of leaks in cell tissues that is essential to the invention can be carried out both in vivo and in vitro.

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

Tissue or cell tissue in the context of the present invention are understood as being cellular structures consisting of cells of the same form and function, such as surface tissue (skin), epithelial tissue, myocardial, connective or stromal tissue, muscles, nerves and cartilage. Also included, among other systems, are all organs comprised of cell groups, such as the liver, kidneys, lungs, heart, etc.

The isocyanate-functional prepolymers used in A) are obtainable by reaction of isocyanates with hydroxyl-functional polyols, optionally with the addition of catalysts as well as auxiliaries substances and additives.

Examples of isocyanates which can be used in AI) include 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 isomers of bis(4,4'-isocyanatocyclohexyl)-methanes or their mixtures of any desired isomer content,

1,4-cyclohexylene diisocyanate, 4-isocyanatomethyl-1,8-octane diisocyanate (nonane triisocyanate), and alkyl 2,6-diisocyanatohexanoates (lysine diisocyanate) with C1-C8 alkyl groups.

In addition to the monomeric isocyanates mentioned there can also be used higher molecular mass derivatives thereof with uretdione, isocyanurate, urethane, allophanate, biuret, iminooxadiazinedione or oxadiazinetrione structures or mixtures thereof.

Preference is given to isocyanates A) of the afore-mentioned type having only aliphatically or cycloaliphatically bonded isocyanate groups, or mixtures thereof. It is likewise preferred for the isocyanates or isocyanate mixtures AI) having a mean NCO functionality of from 2 to 4, more preferably of from 2 to 2.6 and most preferably of from 2 to 2.4.

In a particularly preferred embodiment AI) is hexamethylene diisocyanate.

For the synthesis of the prepolymer in A2) it is in principle possible to use all of the polyhydroxy compounds having 2 or more OH functions per molecule that are known per se to the skilled person. These may be, for example, polyester polyols, polyacrylate polyols, polyurethane polyols, polycarbonate polyols, polyether polyols, polyester polyacrylate polyols, polyurethane polyacrylate polyols, polyurethane polyester polyols, polyurethane polyether polyols, polyurethane polycarbonate polyols, polyester polycarbonate polyols or any desired mixtures thereof with one another.

The polyols used in A2) preferably have an average OH functionality of from 3 to 4.

The polyols used in A2) further preferably have a number-average molecular weight of from 400 to 20000 g/mol, more preferably of from 2000 to 10000 g/mol and most preferably of from 4000 to 8500.

Polyether polyols are preferably polyalkylene oxide polyethers based on ethylene oxide and optionally propylene oxide.

These polyether polyols are based preferably on difunctional or higher functional starter molecules, such as difunctional or higher polyfunctional alcohols or amines.

Examples of such starters are water (considered to be a diol), ethylene glycol, propylene glycol, butylene glycol, glycerol, TMP, sorbitol, pentaerythritol, triethanolamine, ammonia or ethylenediamine.

Preferred polyalkylene oxide polyethers correspond to those of the aforementioned type and contain 50% to 100%, preferably 60% to 90% ethylene oxide-based units, based on the amounts of alkylene oxide units present in total.

Preferred polyester polyols are the polycondensates known per se of diols and optionally triols and tetraols as well as dicarbonic and optionally tricarbonic and tetracarbonic acids or hydroxycarbonic acids or lactones. Polyesters can also be prepared by using the corresponding polycarbonic acid anhydrides or corresponding polycarbonic acid esters of lower alcohols instead of the free polycarbonic acids.

Examples of suitable diols are ethylene glycol, butylene glycol, diethylene glycol, triethylene glycol, polyalkylene glycols such as polyethylene glycol, and also 1,2-propanediol, 1,3-propanediol, butane-1,3-diol, butane-1,4-diol, hexane-1,6-diol and isomers, neopentyl glycol or neopentyl glycol hydroxypivalic acids, wherein preference is given to hexane-1,6-diol and isomers, butane-1,4-diol, neopentyl glycol and neopentyl glycol hydroxypivalic acid. In addition it is also possible to use polyols such as trimethylolpropane, glycerol, erythritol, pentaerythritol, trimethylolbenzene or trishydroxyethyl isocyanurate.

Dicarbonic acids that can be used are phthalic acid, isophthalic acid, terephthalic acid, tetrahydrophthalic acid, hexahydrophthalic acid, cyclohexanedicarbonic

acid, adipic acid, azelaic acid, sebacic acid, glutaric acid, tetrachlorophthalic acid, maleic acid, fumaric acid, itaconic acid, malonic acid, suberic acid, 2-methylsuccinic acid, 3,3-diethylglutaric acid and/or 2,2-dimethylsuccinic acid. The corresponding anhydrides can also be used as an acid source.

Where the average functionality of the polyol to be esterified is > than 2, it is additionally possible to use monocarbonic acids, such as benzoic acid and hexanecarbonic acid.

Preferred acids are aliphatic or aromatic acids of the aforementioned type. Particularly preferred are adipic acid, isophthalic acid and phthalic acid.

Hydroxycarbonic acids that can be used as additional reactants for preparation of a polyester polyol with terminal hydroxyl groups, are, for example, hydroxycaproic acid, hydroxybutyric acid, hydroxydecanoic acid, hydroxystearic acid and the like. Suitable lactones are caprolactone, butyrolactone and homologues. Caprolactone is preferred.

It is likewise possible to use polycarbonates containing hydroxyl groups, preferably polycarbonate diols, having number-average molecular weights M_n of from 400 to 8000 g/mol, preferably of from 600 to 3000 g/mol. They are obtainable by reaction of carbonic acid derivatives, such as diphenyl carbonate, dimethyl carbonate or phosgene, with polyols, preferably diols.

Examples of such diols are ethylene glycol, 1,2- and 1,3-propanediol, 1,3- and 1,4-butanediol, 1,6-hexanediol, 1,8-octanediol, neopentyl glycol, 1,4-bishydroxymethylcyclohexane, 2-methyl-1,3-propanediol, 2,2,4-trimethylpentane-1,3-diol, dipropylene glycol, polypropylene glycols, dibutylene glycol, polybutylene glycols, bisphenol A and lactone-modified diols of the aforementioned type.

For the prepolymer synthesis, polyether polyols of the aforementioned type are preferable used.

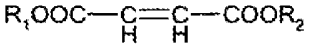
For the preparation of the prepolymer the compounds of component Al) are reacted with those of component A2) at an NCO/OH ratio of preferably from 4:1 to 20:1, more preferably 8:1, and then the content of unreacted compounds of component Al) can be separated off by means of suitable methods. Thin-film distillation is conveniently used for this purpose, there being obtained low-residual-monomer products having residual monomer contents of less than 1%, preferably less than 0.5% and most preferably less than 0.1% by weight.

Optionally, stabilizers such as benzoyl chloride, isophthaloyl chloride, dibutyl phosphate, 3-chloropropionic acid or methyl tosylate may be added during or after the preparation.

The reaction temperature is from 20 to 120°C, preferably from 60 to 100°C.

Preferably in formula (I):
R_1, R_2 represent identical or different, optionally branched or cyclic, organic groups having from 1 to 20, preferably of from 1 to 10 carbon atoms that do not contain a Zerewitinoff-active hydrogen,
n represents an integer from 2 to 4 and
X represents an n-valent organic, optionally branched or cyclic, organic group having from 2 to 20, preferably from 5 to 10, carbon atoms, which is obtainable by removing the primary amino groups of an n-functional primary amine.

The amino-functional polyaspartic acid esters B1) are prepared using conventional methods by reacting the corresponding primary, at least difunctional amines $X(NH_2)_n$ with maleic or fumaric acid esters of the general formula



Preferred maleic or fumaric acid esters are dimethyl maleate, diethyl maleate, dibutyl maleate and the corresponding fumaric acid 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-aminomethyl-cyclohexane, 2,4- and/or 2,6-hexahydrotolylenediamine, 2,4'- and/or 4,4'-diamino-dicyclohexylmethane, 3,3'-dimethyl-4,4'-diaminodicyclohexylmethane, 2,4,4'-triamino-5-methyl-dicyclohexylmethane and polyetheramines having aliphatically bonded primary amino groups with a number-average molecular weight M_n of from 148 to 6000 g/mol.

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-l,5-diaminopentane is especially preferred.

Preferably R_1, and R_2 independently of one another are C_1 to C_{10} alkyl groups, more preferably methyl or ethyl groups.

In a preferred embodiment of the invention $R_1 = R_2$ = ethyl, wherein X is based on 2-methyl-1,5-diaminopentane as the n-functional amine.

Preferably, n in formula (I) for the description of the functionality of the n-functional amine is an integer of from 2 to 6, more preferably of from 2 to 4.

The preparation of the amino-functional aspartic acid esters B1) from said starting materials is accomplished in accordance with DE-A 69 311 633 preferably within the temperature range of from 0 to 100°C, whereby the starting materials are employed in ratios such that for each primary amino group at least one, preferably precisely one olefinic double bond is lost, and after the reaction any starting materials used in excess can be separated off by distillation. The reaction may take place dry or in the presence of suitable solvents such as methanol, ethanol, propanol or dioxane or mixtures of such solvents.

The organic liquid fillers used in B2) are preferably non-cytotoxic when their cytotoxicity is measured in accordance with ISO 10993.

As organic fillers liquid polyethylene glycols may for example be used such as PEG 200 to PEG 600, their monoalkyl and/or dialkyl ethers such as PEG 500 dimethyl ether, liquid polyether polyols and polyester polyols, liquid polyesters such as Ultramoll (Lanxess AG, Leverkusen, DE) and also glycerol and its liquid derivatives such as Triacetin (Lanxess AG, Leverkusen, DE), for example.

The organic fillers of component B2) are preferably hydroxyl- or amino-functional compounds, preferably purely hydroxyl-functional compounds. Preferred purely hydroxyl-functional compounds are polyether polyols and/or polyester polyols, more preferably polyether polyols.

The preferred organic fillers of component B2) preferably possess average OH functionalities of from 1.5 to 3, more preferably of from 1.8 to 2.2, most preferably of from 2.0.

The preferred organic fillers of component B2) preferably possess repeating units derived from ethylene oxide.

The viscosity of the organic fillers of component B2) is preferably from 50 to 4000 mPas at 23°C as measured according to DIN 53019.

In a preferred embodiment of the invention polyethylene glycols are used as organic fillers of component B2). They preferably have a number-average molecular weight of from 100 to 1000 g/mol, more preferably of from 200 to 400 g/mol. The weight ratio of B1) to B2) is 1:0 to 1:20, preferably 1:0 to 1:12.

The weight ratio of component B2, based on the total amount of the mixture of B1, B2 and A, is in the range from 0 to 100%, preferably 0 to 60%.

In order to further reduce the average equivalent weight of the compounds used in total for crosslinking the prepolymer, based on the NCO-reactive groups, it is also possible, in addition to the compounds used in B1) and B2), to prepare the amino- or hydroxyl-functional reaction products of isocyanate-functional prepolymers with aspartic acid esters and/or organic fillers B2), provided the latter are amino- or hydroxyl-functional, in a separate pre-reaction and then to use them as a higher molecular weight curing component C).

Preferably, ratios of isocyanate-reactive groups to isocyanate groups of from 50:1 to 1.5:1, more preferably of from 15:1 to 4:1 are used in the pre-extension.

The isocyanate-functional prepolymer to be used for this purpose may correspond to the one of component A) or alternatively, may be comprised of constructed of the components listed as possible constituents of the isocyanate-functional prepolymers in the context of this specification.

The advantage of this modification by pre-extension is that the equivalent weight and equivalent volume of the curing component can be modified within clear limits. Commercially available 2-chamber metering systems can accordingly be used for the application in order to obtain an adhesive system with existing chamber volume ratios that can be adjusted to the desired ratio of NCO-reactive groups to NCO groups.

If required, one of the two components may be colored.

The formulations essential to the invention are obtained by mixing the prepolymer with the curing component B) and/or C). Component B) and/or C) may also include a biologically active component D). The ratio of NCO-reactive NH groups to free NCO groups is preferably 1:1.5 to 1:1, more preferably 1:1.

Immediately after the mixing of the individual components with one another, the formulations essential to the invention have a shear viscosity of preferably from

1000 to 10000 mPas at 23°C, more preferably from 2000 to 8000 mPas and most preferably from 2500 to 5000 mPas.

The rate at which complete crosslinking and curing of the adhesive is achieved at 23°C is typically from 30 s to 10 min, preferably 1 min to 8 min.

The formulations essential to the invention may be applied for stemming the loss of blood and tissue fluids as well as for sealing leaks in the human or animal body, and also as a tissue adhesive, preferably for *in vivo* applications, for example, for emergency treatment of polytrauma after accidents or surgeries.

Examples:

Unless indicated otherwise, all percentages are by weight.
PEG = polyethylene glycol

Example 1 (prepolymer A)

465 g of HDI and 2.35 g of benzoyl chloride were placed in a 1 l four-necked flask. Within a period of 2 h 931.8 g of a polyether having an ethylene oxide content of 71% and a propylene oxide content of 29% (in each case based on the total alkylene oxide content) started on TMP (3-functional) were added at 80°C and then stirred for one additional hour. Excess HDI was then distilled off by thin-film distillation at 130°C and 0.1 Torr, yielding 980 g (71%) of the prepolymer with a NCO content of 2.53%. The residual monomer content was < 0.03% HDI.

Example 2 (aspartate B)

1 mol 2-methyl-1,5-diaminopentane was slowly added drop-wise to 2 mol of diethyl maleate under nitrogen atmosphere at a rate that prevented the reaction temperature from exceeding 60°C. The mixture was then heated to 60°C until

diethyl maleate was no longer detectable in the reaction mixture. The product was purified by distillation.

Example 3 (Application of the formulations essential to the invention for stemming severe bleeding and sealing leaks)

The formulations essential to the invention were applied by means of a commercial two-chamber applicator with static mixer. One chamber contained a mixture of 0.45 g of PEG 200 and 0.55 g of aspartate B. The second chamber contained 4 g of prepolymer A. The two components were mixed by pushing the piston.

In vivo experiments on hemostasis—animal model: rat

The experiment was carried out with a Wista rat weighing 350 grams. Anesthesia was induced with diethyl ether and subsequently, intraperitoneally, using ketamine/xylazine. The trachea was then intubated with a 14-gauge venous catheter. Ventilation was carried out with an air/oxygen mixture (FiO_2=0.5). The rat was fixed to a heated support. Preparation for surgery was carried out aseptically and with local lidocaine infiltration.

The abdomen was opened up by anterior longitudinal and transverse abdominal incisions to provide wide access to the liver and spleen.

Example 3a - Diffuse bleeding

The surface of the liver was injured using sandpaper to produce diffuse bleeding. The formulation essential to the invention was applied to the surface of the liver. After approximately 2 minutes the film had cured and had stemmed the bleeding at the liver surface.

Example 3b - Liver resection

The tip of the left lobe of the liver was removed. This produced an incision area of approximately 1 cm^2 that transversed the hepatic tissue, with severe bleeding. The formulation essential to the invention was applied, and had stemmed the bleeding within 2 minutes.

Example 3c – Lung punctures

The rib cage was opened by medial sternotomy and widened via right-lateral thoracotomy. The tip of the median lobe of the right-hand lung was excised, producing a wound area of approximately 1 cm^2, resulting in strong venous and arterial bleeding. In addition, a medium-sized bronchus was severed that caused air to leak. The tissue adhesive was applied to the wound area of the lung, and immediately both the venous and arterial bleeding was stemmed. The air leak caused a large air bubble in the adhesive to form, which then burst; an air-filled fistula remained. After approximately 1 minute, a drop of the adhesive was applied to the air leak once more and pressed down firmly using a plastic spatula. This sealed the air leak.

After a total of 3 minutes the film had cured and had successfully stemmed bleeding and sealed the air leak.

Example 3d - Puncture of the ascending aorta

The ascending aorta was surgically prepared and exposed. A large puncture was made into the ascending aorta with a 0.5 mm thick needle to produce a squirting bleed. The formulation essential to the invention was applied to the bleeding site and pressed gently onto the hole using a plastic spatula. The bleeding came to a halt within 2 minutes.

In vivo experiments on hemostasis—animal model: pig

The experiment was carried out on a female, 30 kg domesticated pig under inhalative mask anesthesia. The skin incision was performed ventral to the left

sternocleidomastoid muscle. The carotid aorta was exposed in the region of the bulb. The carotid aorta presented with a diameter of approximately 5-6 mm.

Example 3e - Minor arterial bleeding

Using a scalpel, the carotid artery was opened in the region of the bulb by careful preparation to produce a minor squirting bleed from the artery. After brief initial rinsing of the mixing cannula, approximately 4 ml of the formulation essential to the invention were applied to the source of the bleed, and compressed by compression by the surrounding tissue, in particular by the sternocleidomastoid muscle. The bleeding came to a halt after approximately 1 ½ min. The surrounding tissue had bonded to the carotid artery. A pulse could be felt on the carotid artery, distal to the site of incision.

Example 3f - Severe arterial bleeding

Using vessel scissors the carotid artery was opened to over half of its diameter, resulting in a strongly squirting arterial bleed. 5 ml of the formulation essential to the invention were applied to the site of the bleed and compressed with the surrounding tissue over approximately 2 min. The bleeding came to a halt after 2 minutes.

Example 3g - Venous bleeding

The right aural vein was opened using a scalpel over a length of approximately 10 mm, resulting in a severe bleed. The formulation essential to the invention was applied without compression. The bleed came to a halt after approximately 1 minute.

Patentkrav

1. Formuleringer indeholdende

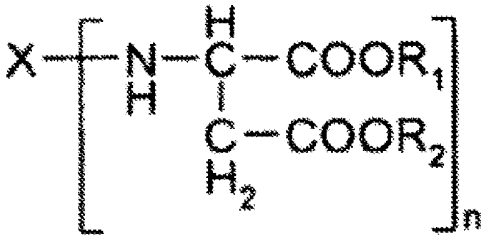
A) isocyanat-funktionelle præpolymerer, der kan fås ud fra

A1) aliphatiske isocyanater og

A2) polyoler med talgennemsnitlige molekylvægte ≥ 400 g/mol og gennemsnitlige OH-funktionaliteter fra 2 til 6,

B) en hærderkomponent indeholdende

B1) amino-funktionelle asparaginsyreestere med den almene formel (I)



(I)

hvor

X er en n-valent organisk rest, der kan fås ved fjernelse af de primære aminogrupper i en n-valent amin,

R_1, R_2 er ens eller forskellige organiske rester, der ikke har noget Zerewitinoff-aktivt hydrogen, og

n er et heltal på mindst 2

og eventuelt

B2) organiske fyldstoffer med en ifølge DIN 53019 målt viskositet ved 23°C i området fra 10 til 6000 mPas, og

C) eventuelt omsætningsprodukter af isocyanat-funktionelle præpolymerer ifølge definitionen for komponent A) med asparaginsyreestere ifølge komponent B1) og/eller organiske fyldstoffer ifølge komponent B2) til anvendelse til stilning

af blodudtræden eller vævsvæsker eller til anvendelse til tætning af lækager i cellevæv.

2. Anvendelse af formuleringer indeholdende

A) isocyanat-funktionelle præpolymerer, der kan fås ud fra

A1) aliphatiske isocyanater og

A2) polyoler, der har talgennemsnitlige molekylvægte ≥ 400 g/mol og gennemsnitlige OH-funktionaliteter fra 2 til 6

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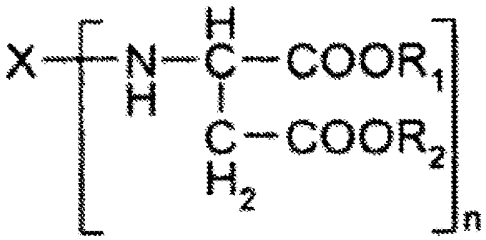

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3. Anvendelse ifølge krav 2, **kendetegnet ved,** at de i A2) anvendte polyoler har talgennemsnitlige molekylvægte på fra 4000 til 8500 g/mol.

4. Anvendelse ifølge krav 2 eller 3, **kendetegnet ved,** at der i A2) anvendes polyalkylenoxid-polyethere.

5. Anvendelse ifølge krav 4, **kendetegnet ved,** at polyalkylenoxid-polyetherne indeholder fra 60% til 90% ethylenoxidbaserede enheder baseret på de samlet optrædende mængder af alkylenoxidenheder.

6. Anvendelse ifølge et af kravene 2 til 5, **kendetegnet ved,** at polyetherpolyoler anvendes som organiske fyldstoffer i komponent B2).

7. Anvendelse ifølge et af kravene 2 til 6, **kendetegnet ved,** at den vedrører et vævsklæbemiddel til humant eller animalsk væv.

8. Anvendelse ifølge et af kravene 2 til 7, **kendetegnet ved,** at den vedrører en *in vivo*-anvendelse.