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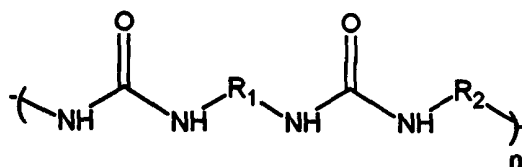
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(54) Title: NEW LINEAR BLOCK POLYMER



(1)

(57) Abstract: The present invention relates to a linear polymer with a molecular weight of at least 10⁴ Dalton, which linear polymer consists of internally and linearly linked sequences, which sequences can be described according to Formula (1) wherein 80 to 100% of R₂, which 80 to 100% of R₂ can be the same or different, comprise segments that are derived from diamines, which

diamines comprise ester groups, and each R₁, the same or different, can be derived from diisocyanate, and a method for preparing and a method for processing said linear polymer, use of said linear polymer, implants for humans and animals, material for promoting wound healing in humans and animals, and also pharmaceutical preparations, microencapsules, suspensions, emulsions, porous three-dimensional structures, material or cell material, which all comprise said linear polymer.

NEW LINEAR BLOCK POLYMER

FIELD OF THE INVENTION

5 The present invention relates to a new degradable linear polymer, a method for preparing and a method for processing said linear polymer, use of said linear polymer, implants for humans and animals, which implants comprise said linear polymer, and material for promoting wound healing in humans and animals, pharmaceutical preparations, microencapsules, suspensions,
10 emulsions, porous three-dimensional structures, material or cell material, which all comprise said linear polymer.

PRIOR ART

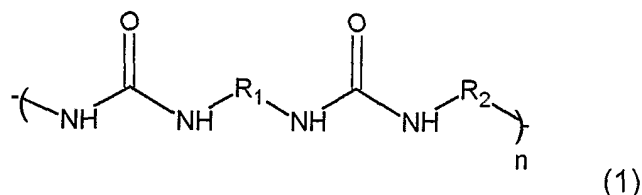
In the event of human or animal injury or disease, damaged organs or
15 damaged tissue must on occasions be temporarily or permanently replaced by some form of implant. In order for the function of such an implant to be acceptable, not only must the implant have properties, for example strength, that enable it to replace the functions of the damaged organ or tissue, and it must also be biocompatible. Various materials such as pure titanium and
20 certain plastics have been shown to have acceptable function, and are extensively used. It is often desirable that an implant promotes growth of damaged tissue, while at the same time the implant should, in many cases, be biologically degradable.

25 SE, C2, 505703 or US, A, 6210441, describes a linear block polymer with a molecular weight of 10^4 Dalton, preferably 10^5 Dalton, comprising urea and urethane groups together and with ester groups at such a distance from each other that after hydrolysis of the same, fragments are created that are so small that they can be excreted from a human body. Said linear block
30 polymer comprising urea and urethane groups is suitable material for implants for humans and animals.

DESCRIPTION OF THE INVENTION

The present invention relates to a linear polymer with a molecular weight of at least 10^4 Dalton, which linear polymer consists of internally and linearly linked sequences, which sequences can be described according to Formula

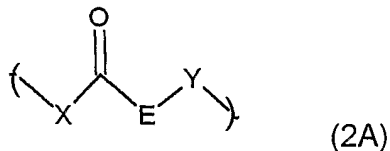
5 (1)



wherein

80 to 100% of R_2 , which 80 to 100% of R_2 can be the same or different, comprise a segment according to Formula (2A)

10



wherein

E is oxygen or nitrogen,

15

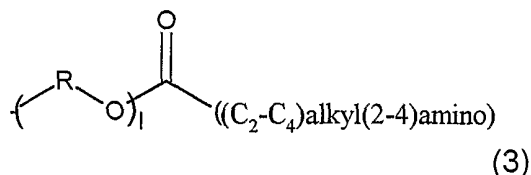
X and Y, which X and Y can be the same or different, are $(\text{C}_1\text{-C}_5)\text{alkyl}$, or are derived from $((\text{C}_1\text{-C}_4)\text{alkyl})[(2\text{-}4)\text{-amino}((\text{C}_2\text{-C}_4)\text{ alkanoate})]$, $[(1\text{-}4)\text{-amino}((\text{C}_1\text{-C}_4)\text{alkyl})]((\text{C}_2\text{-C}_4)\text{ alkanoate})$, $[(2\text{-}4)\text{-amino}((\text{C}_2\text{-C}_4)\text{ alkanoate})]((\text{C}_1\text{-C}_5)\text{alkyl})$, $((\text{C}_2\text{-C}_4)\text{ alkanoate})[(1\text{-}5)\text{-amino}((\text{C}_1\text{-C}_5)\text{alkyl})]$, $((\text{C}_1\text{-C}_4)\text{alkyl})[(2\text{-}4)\text{-amino}((\text{C}_2\text{-C}_4)\text{ carboxamide})]$, $[(1\text{-}4)\text{-amino}((\text{C}_1\text{-C}_4)\text{alkyl})]((\text{C}_2\text{-C}_4)\text{ carboxamide})$, $[(2\text{-}4)\text{-amino}((\text{C}_2\text{-C}_4)\text{ carboxamide})]((\text{C}_1\text{-C}_5)\text{alkyl})$ or from $((\text{C}_2\text{-C}_4)\text{ carboxamide})[(1\text{-}5)\text{-amino}((\text{C}_1\text{-C}_5)\text{alkyl})]$,

20

and provided that Y is not C₁-alkyl, or

Y is derived from a substituent according to Formula (3)

5

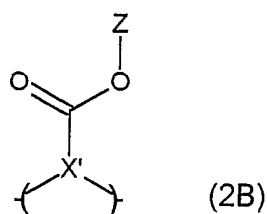


wherein R is (C₁-C₇)alkyl, and

I is from 1 to 20, and

10 X is as has been defined above;

said 80 to 100% of R₂, the same or different, comprise a segment according to Formula (2B)



15

wherein X' is ((C₁-C₅)alkyl) and

20 Z is hydrogen, (C₁-C₄)alkyl, benzyl, tert.-butyl, phenacyl, isopropyl, neopentyl, sec-butyl or tosyl; and/or

said 80 to 100% of R₂, the same or different, can be derived from a first group of diamine that are based on amino acids esterified with diols, and/or

from a second group of diamines that are based on amino acids esterified with amino alcohols; and

when not 100% of R_2 comprise a segment according to Formula (2A) or (2B),
5 or can be derived from said first or second groups of diamines, each other R_2 can be derived from a third group of diamines that are aliphatic or aromatic diamines; and

each R_1 , the same or different, can be derived from a diisocyanate, wherein
10 said diisocyanate can be diphenylmethyl diisocyanate (MDI), hexamethylene diisocyanate (HDI), 1,4'-diisocyanatobutane or 4,4',-dicyclohexylmethane diisocyanate (H_{12} MDI), or said diisocyanate can be ethyl-2,6-diisocyanatohexanoate (LDI), isophorone diisocyanate (IPDI), toluene-2,4-diisocyanate (TDI) or 1,3-bis(isocyanatomethyl)cyclohexane.

15

When X and/or Y in Formula (2A) is or are "derived from", the amino group that is part of the moiety that X or Y is derived from forms the respective amine bond with R_2 in Formula (1). In the same way, when R_2 can be "derived from" diamines, the amines that are part of the diamines form the
20 amine bonds to R_2 in Formula (1). Furthermore, R_1 can be "derived from" a diisocyanate, wherein each isocyanate gives rise to urea bonding with R_2 in Formula (1). In other words, links of urea are formed that join together R_1 and R_2 in Formula (1).

25 Each alkyl and each alkanoate in Formula (1) can, independently of each other, be straight or branched, saturated or unsaturated, and/or substituted with, for example, methyl, phenyl, 4-hydroxyphenyl, 4-aminobutyl, 2-butyl, 2-hydroxymethyl, 3-aminopropyl, 2-aminoethyl, 2-mercaptomethyl, or similar. When R_2 comprises a segment, the term "comprises" is to be taken to denote
30 that each alkyl and each alkanoate in the segment can be as described above.

Said linear polymer is degradable and is of the polyurea type when the polymer chain according to Formula (1) contains urea groups. The urea groups in the polymer form intermolecular hydrogen bonds, which provides the cohesive forces that are required to hold the molecules together to a material. Furthermore, particularly strong intermolecular forces are obtained by the urea groups especially when several urea groups have the opportunity to interact. By giving several urea groups the opportunity to interact, a polymer is obtained that gives material that is stronger than material from polymers in which urea groups do not have the possibility to interact to the same extent. Said linear polymer can be a block polymer or an alternating co-polymer. The urea groups in said linear polymer are responsible for the cohesion of the material and the blocks in a block polymer that contain urea groups are often known as "hard". In a block polymer, the cohesion is a function of the number and lengths of the blocks that contain urea groups. When said linear polymer according to Formula (1) is a block polymer, the "hard" block is the block that is comprised in R_2 and the neighbouring urea groups. In a corresponding manner, the blocks in a block polymer that give the material its extensibility and elasticity are known as "soft". When said linear polymer according to Formula (1) is a block polymer, a "soft" block can be comprised in R_1 .

Furthermore, said degradable linear polymer according to the present invention is intended to be used in living tissue, in order to be subsequently eliminated when it has fulfilled its function, for example, a mechanical function. This is to take place through the polymer being degradable and being hydrolysed to fragments so small that these fragments can be transported away from the location at which the polymer has been applied and excreted or metabolised. The fragments are, for example, not to be larger than 2,000 Dalton, and should preferably be smaller than 1,000 Dalton. In humans, for example, hydrolysis occurs by the attack of water on ester groups in the chain of the linear polymer at pHs between 7.1 and 7.4, at a temperature of 37°C. The end products and intermediates that are formed by

hydrolysis of a linear polymer must not be toxic, and they must not irritate cells at the site of application or at other sites. It is very important to be able to vary the rate at which said linear polymer is degraded. Degradation of said linear polymer must not take place too rapidly, since the cells of the body must have sufficient time to carry out their repair work. Degradation that is too rapid has in several cases been shown to give such a high concentration of degradation products that these have caused damage to neighbouring tissue. On the other hand, it is not desirable that the mechanical properties should be maintained for an excessive period, since "stress shielding", and other effects, may arise, leading to degradation of tissue. An appropriate degradation time can be from approximately three months to approximately two years, depending on the application. Furthermore, the chemical structure of the linear polymer determines its rate of degradation. The structure of the ester groups primarily determines the rate of degradation, but the surroundings of the ester groups in the linear polymer also has a significant influence. The chemical surroundings exert an influence through the balance between hydrophobic groups and hydrophilic groups, among other factors.

Said 80 to 100% of R_2 , the same or different, comprises one or several ester groups; wherein said linear polymer according to Formula (1) is degradable and comprises ester groups at such a distance from each other that after hydrolysis of said ester groups, fragments are created that are less than 2,000 Dalton, wherein the fragments can be excreted from a human or animal body. The created fragments are preferably less than 1,000 Dalton. For example, the fragments can, according to the present invention, be in the order of 400-500 Dalton. Furthermore, said ester groups may also make said linear polymer more soluble in water.

The fact that at least 80% of R_2 comprises a segment according to Formulas (2A), (2B) and/or can be derived from diamines that are based on amino acids esterified with diols, and/or from diamines that are based on amino acids esterified with amino alcohols, means that at least 80% of R_2 contains

ester groups between the amino groups. In this way, the fragments obtained after complete degradation (hydrolysis) of said linear polymer are sufficiently small, for example not larger than 2,000 Dalton and preferably less than 1,000 Dalton, which facilitates elimination of the degradation products when said linear polymer according to the invention is used in a human or animal body. The size of the fragments, that is, the size of the degradation products, makes a rapid and complete degradation of said linear polymer possible. Said linear polymer is degraded into such small fragments that further interaction between urea groups in the degradation products can be avoided.

Interaction between urea groups in the degradation products would oppose a complete degradation.

It is preferred that E in Formula (2A) is oxygen.

Furthermore, it is preferable that X and Y in Formula (2A), the same or different, are (C₁-C₅)alkyl, or are derived from ((C₁-C₄)alkyl)[(2-4)-amino((C₂-C₄) alkanoate)], [(1-4)-amino((C₁-C₄)alkyl)]((C₂-C₄) alkanoate), [(2-4)-amino((C₂-C₄) alkanoate)]((C₁-C₅)alkyl) or ((C₂-C₄) alkanoate)[(1-4)-amino((C₁-C₄)alkyl)].

Furthermore, another preferred embodiment is that X and Y, the same or different, in Formula (2A) are (C₁-C₅)alkyl, or are derived from ((C₁-C₄)alkyl)[(2-4)-amino((C₂-C₄) alkanoate)] or from [(2-4)-amino((C₂-C₄) alkanoate)]((C₁-C₅)alkyl).

When X and/or Y in Formula (2A) is or are derived from ((C₁-C₄)alkyl)[(2-4)-amino((C₂-C₄) alkanoate)], then ((C₁-C₄)alkyl)[(3-4)-amino((C₃-C₄) alkanoate)] is preferred.

Furthermore, when X and/or Y in Formula (2A) is or are derived from [(1-4)-amino((C₁-C₄)alkyl)]((C₂-C₄) alkanoate), then [(1-4)-amino((C₁-C₄)alkyl)]((C₃-C₄) alkanoate) is preferred.

Furthermore, when X and/or Y in Formula (2A) is or are derived from [(2-4)-amino((C₂-C₄) alkanooate)]((C₁-C₅)alkyl), then [(2-4)-amino((C₂-C₄) alkanooate)]((C₂-C₅)alkyl) is preferred.

5

When X and/or Y in Formula (2A) is or are derived from ((C₂-C₄) alkanooate)[(1-5)-amino((C₁-C₅)alkyl)], then ((C₂-C₄) alkanooate)[(2-5)-amino((C₂-C₅)alkyl)] is preferred.

- 10 When X and/or Y in Formula (2A) is or are derived from ((C₁-C₄)alkyl)[(2-4)-amino((C₂-C₄) carboxamide)], then ((C₁-C₄)alkyl)[(3-4)-amino((C₃-C₄) carboxamide)] is preferred.

Furthermore, when X and/or Y in Formula (2A) is or are derived from

- 15 [(1-4)-amino((C₁-C₄)alkyl)]((C₂-C₄) carboxamide), then [(1-4)-amino((C₁-C₄)alkyl)]((C₃-C₄) carboxamide) is preferred.

Furthermore, when X and/or Y in Formula (2A) is or are derived from [(2-4)-amino((C₂-C₄) carboxamide)]((C₁-C₅)alkyl), then

- 20 [(2-4)-amino((C₂-C₄) carboxamide)]((C₂-C₅)alkyl) is preferred.

When X and/or Y in Formula (2A) is or are derived from ((C₂-C₄) carboxamide)[(1-5)-amino((C₁-C₅)alkyl)], then ((C₂-C₄) carboxamide)[(2-5)-amino((C₂-C₅)alkyl)] is preferred.

25

It is preferred that R in Formula (3) is (C₂-C₆)alkyl.

Furthermore, it is preferred that I in Formula (3) is from 1 to 10, or from 1 to 5.

30

It is preferred that X in Formula (2B) is ((C₂-C₅)alkyl).

In said first group and second group of diamines, it is preferred that the amino acids comprise from 2 to 20 carbon atoms, from 2 to 15 carbon atoms, from 2 to 10 carbon atoms, or from 2 to 7 carbon atoms.

- 5 In said first group of diamines, it is preferred that the diamines are based on amino acids esterified with diols, wherein the diols comprise from 2 to 20 carbon atoms, from 2 to 15 carbon atoms, from 2 to 10 carbon atoms, or from 2 to 7 carbon atoms.
- 10 In said second group of diamines, it is preferred that the diamines are based on amino acids esterified with amino alcohols, wherein the amino alcohols comprise from 2 to 20 carbon atoms, or from 2 to 15 carbon atoms, or more preferably, from 2 to 10 carbon atoms, or from 2 to 7 carbon atoms.
- 15 In said third group of diamines, it is preferred that the diamines comprise from 2 to 30 carbon atoms, from 2 to 20 carbon atoms, from 2 to 15 carbon atoms, from 2 to 10 carbon atoms, or from 2 to 7 carbon atoms.

- Further, it is preferred that R_1 can be derived from a diisocyanate that
20 comprises from 2 to 30 carbon atoms, from 2 to 20 carbon atoms, from 2 to 15 carbon atoms, from 2 to 10 carbon atoms, or from 2 to 7 carbon atoms.

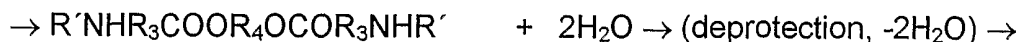
An important group is that formed when 80 to 100% of R_2 comprises segments according to Formula (2A) and/or Formula (2B).

25

Another important group, from which said 80 to 100% of R_2 can be derived, is that of diamines according to Formula (4C) that are based on protected amino acids according to Formula (4A) esterified with compounds (diols) according to Formula (4B) according to the following:

30





- 5 R' is a protective group and amino acids according to Formula (4A) are α - and/or ω -amino acids, examples of such amino acids are glycine (wherein R_3 is CH_2), alanine, lysine, ornithine, methionine, leucine, isoleucine, phenylalanine, tyrosine, glutamic acid or aspartic acid, or the esters of these with methyl, ethyl, benzyl, phenacyl, tert.-butyl, isopropyl, neopentyl, sec-
10 butyl or tosyl in the α - or ω -position, or from serine with a protected OH-group.

In the case of amino acids whose esters with methyl, ethyl, benzyl, phenacyl, tert.-butyl, isopropyl, neopentyl, sec-butyl or tosyl can be selected either in
15 the α - or ω -position, both variants are included.

Diols according to Formula (4B) can, for example, be selected from ethylene glycol, propylene glycol, butanediol, pentanediol, hexanediol, neopentyl glycol, diethylene glycol, triethylene glycol, tetraethylene glycol, pentaethylene glycol, polyethylene glycol (PEG), polytetramethylene oxide diol (PTMOG), 1,4-dihydroxymethyl benzene, polypropylene glycol and hydroxitelechelic polybutadiene, together with hybrids of these. Furthermore, compounds according to Formula (4B) can be, for example, hydroxitelechelic oligomers (that is, oligomers with hydroxyl groups at both ends). Examples of
20 such are hydroxitelechelic oligoesters, oligoamides and oligocarbonates. Compounds according to Formula (4B) can also contain other heteroatoms, such as S or N and/or ester groups, one example of which is 3-({[(tert-butoxycarbonyl)amino]actetyl}oxy)-2,2-bis(hydroxymethyl)propyl[(tert-butoxycarbonyl)amino] acetate.

Another important group from which said 80 to 100% of R_2 can be derived is the group of diamines that are derived from esters of protected amino acids according to Formula (4A), wherein the protected amino acids are esterified with amino alcohols. One example is the glycine ester of ethanolamine.

5

Important criteria for the choice of diamines from which said 80 to 100% of R_2 can be derived are the length of the chain of the diamine, the stiffness of the chain, the chemical structure of the ester group and its chemical surroundings. The first two properties, the length of the chain and its stiffness, primarily influence the mechanical properties of said linear polymer, while the latter two, the chemical structure of the ester group and its chemical surroundings, have a major influence on the degradation time of the same.

Other R_2 , in which said 80 to 100% of R_2 is not equal to 100%, can, the same or different, be derived from aliphatic or aromatic diamines, wherein examples of such diamines are primary diamines, for example, ethylene diamine, 1,3-diaminopropane, 1,3-diamino-2-hydroxypropane, 1,3-propandiol-bis-p-amino benzoate or ethylene glycolbisglycine ester diamine.

20

Said diisocyanates from which R_1 can be derived can be commercially available, such as diphenylmethyl diisocyanate (MDI), hexamethylene diisocyanate (HDI), 1,4'-diisocyanatobutane or 4,4'-dicyclohexylmethane diisocyanate (H_{12} MDI), or said diisocyanate can be ethyl-2,6-diisocyanatohexanoate (LDI), isophorone diisocyanate (IPDI), toluene-2,4-diisocyanate (TDI) or 1,3-bis(isocyanatomethyl)cyclohexane.

25

A yet further embodiment according to the present invention relates to a linear polymer wherein said linear polymer is a block polymer.

30

An embodiment according to the present invention relates to a linear polymer wherein said 80 to 100% of R_2 , the same or different, can be derived from diamines according to Formula (4C)



wherein the diamines according to Formula (4C) are based on protected amino acids according to Formula (4A)



that have been esterified with diols according to Formula (4B)



wherein R' is a protective group and amino acids according to Formula (4A) are α - and/or ω -amino acids, preferably glycine (wherein R_3 is CH_2), alanine, lysine, ornithine, methionine, leucine, isoleucine, phenylalanine, tyrosine, glutamic acid or aspartic acid, or the esters of these with methyl, ethyl, benzyl, phenacyl, tert.-butyl, isopropyl, neopentyl, sec-butyl or tosyl in the α - or ω -position, or from serine with a protected OH-group, and

diols according to Formula (4B) are selected from ethylene glycol, propylene glycol, butanediol, pentanediol, hexanediol, neopentyl glycol, diethylene glycol, triethylene glycol, tetraethylene glycol, pentaethylene glycol, polyethylene glycol (PEG), polytetramethylene oxide diol (PTMOG), 1,4-dihydroxymethylbenzene, polypropylene glycol and hydroxitelechelic polybutadiene, and also hybrids of these, and from hydroxitelechelic oligomers, preferably hydroxitelechelic oligoesters, oligoamides or oligocarbonates, wherein the compounds according to Formula (4B) can also contain heteroatoms, such as S or N and/or ester groups.

A further embodiment according to the present invention relates to a linear polymer, wherein said 80 to 100% of R₂, the same or different, can be derived from diamines that are derived from esters of amino acids with amino
 5 alcohols, for example the glycine ester of ethanolamine or
 3-({[(*tert*-butoxycarbonyl)amino]actetyl}oxy)-2,2-
 bis(hydroxymethyl)propyl[(*tert*-butoxycarbonyl)amino] acetate.

A yet further embodiment according to the present invention relates to a
 10 linear polymer wherein each R₁, the same or different, can be derived from
 a diisocyanate, which diisocyanate may be commercially available, such as
 diphenylmethyl diisocyanate (MDI), hexamethylene diisocyanate (HDI), 1,4'-
 diisocyanatobutane or 4,4',-dicyclohexylmethane diisocyanate (H₁₂MDI), or
 said diisocyanate can be ethyl-2,6-diisocyanatohexanoate (LDI), isophorone
 15 diisocyanate (IPDI), toluene-2,4-diisocyanate (TDI) or 1,3-
 bis(isocyanatomethyl)cyclohexane.

A yet further embodiment relates to a linear polymer according to Formula
 (1), wherein said 80 to 100% of R₂, which 80 to 100% of R₂ can be the same
 20 or different, can be derived from one or several of

2-aminoethyl 4-aminobutanoate,
 4-[(4-aminobutanoyl)oxy]butyl 4-aminobutanoate,
 5-[(2*S*)-2-amino-3-methoxy-3-oxopropyl] 1-methyl (2*S*)-2-
 25 aminopentanedioate,
 5-(2-aminoethyl) 1-methyl (2*S*)-2-aminopentanedioate,
 5-(3-aminopropyl) 1-methyl (2*S*)-2-aminopentanedioate,
 5-(4-aminobutyl) 1-methyl (2*S*)-2-aminopentanedioate,
 methyl (2*S*)-2-amino-3-[(3-aminopropanoyl)oxy] propanoate,
 30 2-[(2-aminoacetyl)oxy]ethyl 3-aminopropanoate,
 2-[(2-aminoacetyl)oxy]ethyl 4-aminobutanoate,
 2-[(2-aminoacetyl)oxy]ethyl aminoacetate,

- 4-(2-aminoethyl) 1-methyl (2R)-2-aminobutanedioate,
2-aminoethyl aminoacetate,
4-[(2-aminoacetyl)oxy]butyl aminoacetate,
2-[(3-aminopropanoyl)oxy]ethyl 3-aminopropanoate,
5 2-[(2-aminoacetyl)oxy]ethyl aminoacetate,
methyl (2S)-2-amino-3-[(aminoacetyl)oxy] propanoate,
tert-butyl 2,6-diaminohexanoate,
benzyl 2,6-diaminohexanoate,
2-aminoethyl [(aminoacetyl)amino] acetate,
10 2-aminoethyl 3-[(aminoacetyl)amino] propanoate and
2-aminoethyl 3-[(3-aminopropanoyl)amino] propanoate; and

salts, together with all possible stereoisomers either pure or as racemic compounds or as mixtures of stereoisomers, thereof.

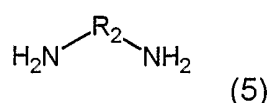
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Said linear polymer according to the present invention is of the polyurea type and can be prepared from the reaction between one or several different diisocyanates and one or several different diamines, wherein closely equivalent amounts of isocyanate and amino groups are required. The
20 reaction is carried out either in solution or through phase interface polymerisation. In the former case, the reactants are soluble in the solvent while the linear polymer formed can be either soluble or it can precipitate. In the latter case, two immiscible solvents are used, each of which dissolves one of the reactants. Polymerisation occurs at the interface between the
25 phases, from which the name of this procedure is derived.

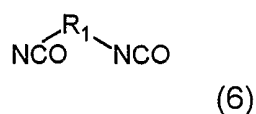
The molecular weight of the linear polymer that is formed can be regulated by modifying the stoichiometric balance or by the addition of what are known as chain-stoppers, such as primary or secondary monoamines. The molecular
30 weight distribution is influenced by the method of polymerisation and can be modified by extraction with solvent for, for example, low molecular weight

fractions, or by precipitation of high molecular weight fractions from the solution of the linear polymer.

The present invention also relates to a method for preparing said linear polymer, wherein said method comprises polymerisation, in which
 5 approximately n moles of one or several different diamines, that is, compounds according to Formula (5)



10 are linked with approximately n moles of one or several different diisocyanates, that is, compounds according to Formula (6)



, wherein

15

R₁ and R₂ are defined as they have been previously.

In order to achieve the desired value of molecular weight of said linear polymer according to Formula (1), molar ratios for -NH₂/-NCO are used from
 20 0.95 to 1.05 in the above-described polymerisation.

Polyureas are known to be difficult to process in that the melting point is higher than the temperature at which degradation starts to occur. Due to the tendency of the urea groups to interact via hydrogen bonds, polyureas have
 25 a strong tendency to form gels in solution and are difficult to dissolve at all. This can be counteracted to a certain extent by the addition of agents that interact with the urea groups, for example LiCl, LiBr, urea or guanidine

hydrochloride. The dissolving can thus take place in dimethylformamide in which LiCl has been dissolved to give a concentration of 1-5%.

The interaction between urea groups in said linear polymer can be influenced
5 by the chemical structure of the urea groups or in their vicinity. Thus, when said linear polymer according to the present invention, through said R_1 and/or said 80 to 100% of R_2 , comprises parts that can be derived from amino acids, substituents of α -carbon atoms in these amino acids lead to steric hindrance, giving weaker hydrogen bonds as a consequence. On the other hand,
10 interaction between stereoisomers can give increased close-packing, and consequently a stronger interaction between polymer chains.

A further embodiment according to the present invention relates to a linear polymer, wherein said R_1 and/or said 80 to 100% of R_2 comprise parts that
15 can be derived from amino acids, wherein said parts comprise amino acids with substituents on their α -carbon atoms.

Furthermore, the present invention relates to an embodiment of said linear polymer, wherein said 80 to 100% of R_2 is 100%, which means that said
20 other R_2 is not present, that is, the amount of said other R_2 is zero.

A yet further embodiment according to the present invention relates to a linear polymer, wherein the each of said alkyls and each of said alkanoates in Formula (1) can, independently of each other, be straight or branched,
25 saturated or unsaturated, and/or substituted with, for example, methyl, phenyl, 4-hydroxyphenyl, 4-aminobutyl, 2-butyl, 2-hydroxymethyl, 3-aminopropyl, 2-aminoethyl, 2-mercaptomethyl, or similar.

Polyureas normally need to be processed from solutions of the polymers.
30 Fibres can thus be prepared by dry or wet spinning, that is, the extrusion of the polymer solution through a mouthpiece with removal of the solvent either

by evaporation or by precipitation by non-solvent. Films can be prepared in a similar manner by spreading out the polymer solution in a thin layer on a plate, followed by evaporation and/or precipitation. Naturally, this can take place continuously on a cylinder or an infinite loop in combination with an oven.

One method for preparing hollow articles is by dipping, that is, a mould is repeatedly dipped into the polymer solution and dried and/or coagulated between each dipping. The mould is subsequently removed, which can take place by dissolving it, melting it, or by a mechanical method.

Furthermore, the polymer can be applied to, for example, woven fabric, film or surfaces by, for example, coating, impregnation, lamination or casting, followed by evaporation of the solvent and/or coagulation with a non-solvent.

The present invention also relates to a method for processing said linear polymer, wherein said method comprises preparing fibres through dry or wet spinning of said linear polymer.

A yet further embodiment according to the present invention relates to a method for processing said linear polymer, wherein said method comprises preparing film of said linear polymer or application of said linear polymer onto, for example, woven fabric, film or surfaces by, for example, coating, impregnation, lamination or casting.

A further embodiment according to the present invention relates to a method for processing said linear polymer, wherein said method comprises dipping of a mould that is dipped into a solution of said linear polymer.

The present invention also relates to the use of said linear polymer described above, in the form of, for example, fibres or film, as, for example, material in implants for humans and animals, for example, as implants for tendons,

ligaments, blood vessels, sutures, discs or menisci, for pharmaceutical preparations, in microencapsulation, in suspensions, in emulsions, in porous three-dimensional materials, such as porous polymers materials, or similar.

- 5 Porous polymer material is described in, for example, Swedish patent application SE, A, 0004856-1, which is here referred to in its entirety. SE, A, 0004856-1 describes among other things a method for preparing an open porous polymer material. Swedish patent application SE, C2, 514064, which describes porous films, is also referred to here in its entirety.

10

Furthermore, the invention relates to the use of said linear polymer according to the present invention in, for example, pharmaceutical preparations, during microencapsulation, in suspensions, in emulsions or similar.

- 15 The present invention also relates to the use of said linear polymer as material for artificial blood vessels, in order to prevent adhesions, as an obstacle to adhesion or in order to promote wound healing in humans and animals.

- 20 A further embodiment according to the present invention relates to the use of said linear polymer as cell material for culturing of cells, menisci, discs and other applications that are covered by the concept of "tissue engineering".

- Furthermore, the invention relates to implants, for example, for tendons,
25 ligaments, blood vessels, sutures, discs or menisci, for humans and animals, wherein said implants comprise said linear polymer.

- The present invention also relates to pharmaceutical preparations, microencapsules, suspensions, emulsions or porous three-dimensional
30 structures that comprise said linear polymer.

The present invention also relates to material for artificial blood vessels, in order to prevent adhesions, as an obstacle to adhesion or in order to promote wound healing in humans and animals, wherein said material comprises said linear polymer.

5

Furthermore, the present invention relates to a cell material for culturing of cells, menisci, discs and other applications that are covered by the concept of "tissue engineering", wherein said cell material comprises said linear polymer.

10

Polyureas in the form of fibres can be used in ligaments, tendons, sutures or porous three-dimensional structures. In combination with impregnation or lamination, they can be used as, for example, artificial blood vessels or to prevent adhesions.

15

They can be used in the form of film for, for example, culturing of cells, as an adhesion obstacle or for wound treatment.

As cell material they can be used as the matrix for culturing of cells, menisci, discs and other applications that are covered by the concept of "tissue engineering".

20

The material can be adapted to different applications by varying its degradation time with the aid of the chemical structure.

EXAMPLES

The following examples describe the invention, without in any way limiting it.

5 **Example 1****2-{4-[(ammonioacetyl)oxy] butoxy}-2-oxethanaminium
bis(trifluoroacetate)**

- 10 a) 4-{2-[(*tert*-butoxycarbonyl)amino]acetyl}oxy)butyl
[*tert*-butoxycarbonyl)amino] acetate

17.52 g (100 mmol) *tert*-butoxycarbonyl glycine was dissolved in 50 ml dichloromethane (DCM) and the solution was added into a jacketed glass
15 reactor cooled to 0°C. 4.5g (50 mmol) butanediol was mixed with 50 ml dichloromethane and added into the reactor under stirring. When the mixture in the reactor had reached 0°C, a solution of 20.6 g (100 mmol) dicyclohexyl carbodiimide (DCC) in 100 ml dichloromethane was added. A catalytic amount of dimethylaminopyridine (DMAP) was added in order to catalyse
20 the reaction. The temperature in the reactor rose rapidly to 10°C, after which it sank to its original value. The reaction was allowed to proceed for 3 hours at 0°C, after which it was warmed to approximately 30°C for one hour, and then left under stirring at room temperature until the next day. Processing of the reaction mixture commenced with filtration through a 40-100 µm glass
25 filter, wherein the filtration separates out precipitated dicyclohexylurea (DCU). The dichloromethane that passed the filter was extracted with a 1M potassium hydrogen sulphate solution, followed by extraction with distilled water and with a saturated sodium hydrogen carbonate solution. The dichloromethane phase was then washed three times with distilled water.
30 The washed dichloromethane phase was dried over water-free magnesium sulphate and evaporated to give an oil that crystallised slowly. Yield 80-90%.

If the oil contains contaminant in the form of dicyclohexylurea, the oil can be dissolved in ethyl acetate and the contaminant filtered out, in order to then evaporate off the ethyl acetate and regain the final product in a more pure condition. Yield: 16.4 g (approximately 80%).

5

^1H NMR (300 MHz, CDCl_3 , ppm): 1.42 (s, 9H, OtBu), 1.70-1.75 (m, 2H, CH_2), 3.89 (d, 2H, $\text{CN}_2\text{-N}$), 4.15-4.20 (m, 2H, $\text{CH}_2\text{-O}$) and 5.0-5.1 (m, 1H, NH). C_2 -symmetry halves the spectrum.

IR: ν_{max} (Solid sample/ATR-FTIR), 3363s (N-H), 1730s (C=O, ester), 1676s (C=O, urethane).

10

MS: ESMS; m/z (calculated) $\text{C}_{18}\text{H}_{32}\text{N}_2\text{O}_8$ 404.455; (obtained) 405.2 [MH^+] and 427.2 [MNa^+].

b) 2-{4-[(ammonioacetyl)oxy] butoxy}-2-oxethanaminium bis(trifluoroacetate)

15

Deprotection of tert-butyloxycarbonyl protective groups by acidolysis.

50 ml dichloromethane (DCM) was added to 12.1g of the product from Step a) (molecular weight (Mw)=404.6, 30 mmol). 20 ml trifluoroacetic acid (TFA) was added under stirring to the partially dissolved substrate. Everything now became dissolved, while the solution took on a faint yellow colour and a powerful production of carbon dioxide could be seen. The procedure was interrupted after 45 minutes by evaporating the reaction to dryness (a yellow oil). 50 ml dry diethylether was added to the oil, and the heterogeneous mixture stirred vigorously. The TFA salt was now precipitated under the stirring and the crystalline substance was washed twice with 50 ml diethyl ether. The crystals were then filtered out from the diethyl ether and vacuum-dried.

25

30 Yield: 12.45 g (theoretical 12.96 g) 96%.

IR: ν_{\max} (solid sample/ATR-FTIR) 70°C, melted, 3050s (N-H), 1764s (C=O) and 1679s (C=O, TFA).

MS: ESMS; m/z (calculated) $C_8H_{16}N_2O_4$ 204.22; (obtained) 204.8 $[MH^+]$ and 409.1 $[2MH^+]$.

5

Example 2

4-[(2-aminoacetyl)oxy]butyl aminoacetate

- 10 a) 4-[(2-[(benzyloxy)carbonyl]amino)acetyl]oxy]butyl
[(benzyloxy)carbonyl]amino} acetate

Benzyloxycarbonylglycine, Z-Gly-OH (20.9 g, 100 mmol), was added into a 0.5 l jacketed reactor. 1,4-butane diol (4.56 g, 50 mmol) dispersed in 100 ml
15 dichloromethane (DCM) was then added. A catalytic amount of dimethylaminopyridine (DMAP) was added and the mixture then cooled to 0°C. Dicyclohexyl carbodiimide (DCC) dissolved in 100 ml DCM was added under stirring, wherein dicyclohexylurea (DCU) was precipitated. The mixture was then allowed slowly to reach room temperature, at which it was
20 allowed to proceed under stirring for three days. The reaction mixture was processed by filtering out the DCU that had formed, after which the remaining solution was washed by extraction with a 1M potassium hydrogen sulphate solution, distilled water, saturated sodium hydrogen carbonate and, finally, three times with distilled water. The thus purified organic phase was then
25 dried over water-free magnesium sulphate, filtered and then evaporated to give a colourless oil that crystallised on reaching room temperature.

Yield: 20 g (theoretical 23 g) 87%.

¹HNMR (300 MHz, CDCl₃, ppm): 1.71 (m, 2H, CH₂), 3.96 (d, 2H, CH₂-N), 4.17 (m, 2H, CH₂-O), 5.12 (s, 2H, CH₂, benzyl), 5.3 (m, 1H, N-H) and 7.32 (s, 5H, phenyl).

IR: ν_{\max} (solid sample/ATR-FTIR), 3300s (N-H), 1736s (C=O), 1201s (C-O).

- 5 MS: ESMS; m/z (calculated) C₂₄H₂₈N₂O₈ 472.488; (obtained) 473.1 [MH⁺] and 495.1 [MNa⁺].

b) 4-[(2-aminoacetyl)oxy]butyl aminoacetate

- 10 9.44 g (20 mmol) of benzyloxycarbonyl-protected diamine from Step a) were dissolved in a mixture of 100 ml ethyl acetate and 50 ml methanol and transferred to a hydrogenation reactor. A catalytic amount of palladium on active carbon (Pd/C, 10%, Merck) was added under a nitrogen atmosphere, after which the suspension solution was evacuated three times with a water
15 vacuum pump, with respect to dissolved gases. Hydrogen gas was loaded into the reactor between evacuations. A hydrogen gas pressure of 4 bar was then applied under vigorous stirring. Hydrogen gas was rapidly consumed, and hydrogen gas was consequently added at regular intervals. The product started to precipitate out in the reaction after a few hours, and it was
20 consequently necessary to warm it to 40°C. Stirring was continued until the next day when the reaction mixture was warm-filtered through a 1 µm glassfibre filter and evaporated to give an oil that crystallised.

Yield: 4.1 g (100%).

25

¹HNMR (300 MHz/D₂O, ppm): 1.56 (m, 2H, CH₂), 3.59 (m, 2H, CH₂-N), 3.99 (m, 2H, CH₂-O) and 4.18 (t, 1H, partially exchanged, N-H).

IR: ν_{\max} (solid sample/ATR-FTIR), 3300s (N-H), 1736s (C=O), 1201s (C-O).

MS: ESMS; m/z (calculated) C₈H₁₆N₂O₄ 204.22; (obtained) 204.8 [MH⁺].

30

Example 3**4-(2-ammonioethoxy)-4-oxo-1-butanaminium bis(trifluoroacetate)**

- 5 a) 2-[(*tert*-butoxycarbonyl)amino]ethyl 4-[(*tert*-butoxycarbonyl)amino]
butanoate

8.13 g (Mw=203, 40 mmol) of Boc-GABA-OH and 6.45 g (40 mmol, Mw=161)
of Boc-aminoethanol were added to a reaction vessel together with a small
10 amount of DCM (40 ml). DCC, 8.24 g, 40 mmol dissolved in 40 ml DCM was
added at room temperature. A catalytic amount of DMAP was also added.
DCU was precipitated within a few seconds. The mixture was stirred
overnight. The reaction mixture was filtered and evaporated to give an oil that
was dissolved in ethyl acetate and refiltered. The reaction mixture was
15 extracted by washing with sodium hydrogen carbonate solution, dried and
evaporated to dryness. The residue crystallised. Yield 11 g, approximately
80%.

¹HNMR (300 MHz/CDCl₃, ppm): 1.42 (s, 18H, tBu), 1.8 (m, 2H, -CH₂-), 2.36
20 (t, 2H, -CH₂-CO-), 3.15 (d, 2H, -CH₂-N, GABA), 3.39 (d, 2H, CH₂-N,
aminoethanol), 4.16 (d, CH₂-O), 4.7 (s, 1H, NH) and 5.15 (s, 1H, NH).

IR: ν_{\max} (Solid sample/ATR-FTIR), 3339s (N-H), 1727s (C=O) and 1685s
(C=O, tBu).

MS: ESMS; m/z (calculated) C₁₆H₃₀N₂O₆ 346.42; (obtained) 369.2 [MNa⁺]

25

- b) 4-(2-ammonioethoxy)-4-oxo-1-butanaminium bis(trifluoroacetate)

3.79 g (10.9 mmol) of Boc-protected diamine from Step a) was dissolved in a
mixture of 15 ml DCM and 15 ml TFA at room temperature. Carbon dioxide
30 was produced when the reaction mixture was stirred. The reaction mixture
was evaporated to dryness after two hours. The residue, which contained an
excess of TFA, was precipitated at alkali pH by a sodium carbonate solution

and extracted three times with chloroform. The chloroform phases were combined, dried, and evaporated to dryness. The residue, an oil that crystallised. Yield: 3.3 g (theoretical 4.08 g) 81%.

- 5 IR: ν_{max} (Solid sample/ATR-FTIR), 3340s, 2927s, 2855s, 1686s (C=O), 1641s (C=O, TFA).

MS: ESMS; m/z (Calculated) $\text{C}_6\text{H}_{14}\text{N}_2\text{O}_2$ 146.19 ; obtained 146.8 $[\text{MH}^+]$.

Example 4

10

4-[(4-aminobutanoyl)oxy]butyl 4-aminobutanoate

a) 4-[(4-[(benzyloxy)carbonyl]amino}butanoyl) oxy]butyl
4-[(benzyloxy)carbonyl]amino} butanoate

15

7.99 g (33.6 mmol, $M_w=237$) Z-GABA-OH and 1.51 g (16.8 mmol, $M_w=90.13$) butanediol were mixed in a reactor together with 100 ml DCM and a catalytic amount of DMAP. The mixture was cooled to 0°C, after which 7.2 g (approximately 35 mmol, $M_w=206$) of DCC dissolved in 50 ml DCM
20 was added under stirring. DCU started to precipitate immediately. The mixture was allowed to reach room temperature slowly and stirred overnight.

The reaction mixture was warmed for a short period to 30°C before processing. After cooling, the DCU was filtered out and the residue washed
25 by extraction with potassium hydrogen sulphate (1M), distilled water, sodium hydrogen carbonate (saturated) and three times with distilled water. The organic phase was then dried over water-free magnesium sulphate and evaporated to give an oil. The oil was dissolved in absolute ethanol and placed in the cold to crystallise. The crystals were filtered out and dried.
30 Yield: approximately 8 g (theoretical 8.8 g) 90%.

^1H NMR (300 MHz/ CDCl_3 , ppm): 1.69 (d, undissolved, 2H, O-C- CH_2), 1.82 (m, 2H, C- CH_2 -C), 2.35 (t, 2H, CH_2 -CO), 3.22 (m, 2H, N- CH_2), 4.07 (d, undissolved, 2H, O- CH_2), 4.94 (m, 1H, N-H), 5.08 (s, 2H, benzyl) and 7.3 (s, 5H, phenyl).

- 5 MS: ESMS; m/z (calculated) $\text{C}_{28}\text{H}_{36}\text{N}_2\text{O}_6$ 528.59; (obtained) 529.2 [MH^+] and 551.2 [MNa^+].

IR: ν_{max} (Solid sample/ATR-FTIR), 3332s (N-H), 1722s (C=O) and 1686s (C=O).

10 b) 4-[(4-aminobutanoyl)oxy]butyl 4-aminobutanoate

- Approximately 8 g (approximately 16 mmol, $\text{Mw}=528$) of the product from Step a) was dissolved in absolute ethanol. A catalytic amount of palladium on active carbon (Pd/C 10%) was added and dissolved gases evacuated from the mixture. A hydrogen gas pressure of 4 bar was then applied and the mixture stirred vigorously. When no more hydrogen gas was consumed in the reaction mixture, the procedure was interrupted and the catalyst filtered out. The residual solution was evaporated to an oil, 6 g, which dried slowly. Yield: approximately 3.5 g (80%).

20

IR: ν_{max} (Solid sample/ATR-FTIR), 3300s (N-H) and 1682s (C=O).

MS: ESMS; m/z (calculated) $\text{C}_{12}\text{H}_{24}\text{N}_2\text{O}_4$ 260.33; (obtained) 261 [MH^+].

Example 5**5-[(2S)-2-amino-3-methoxy-3-oxopropyl] 1-methyl (2S)-2-aminopentandioate**

5

a) 5-((2S)-2-([(benzyloxy)carbonyl]amino)-3-methoxy-3-oxopropyl) 1-methyl (2S)-2-([(benzyloxy)carbonyl]amino)pentandioate

8.86 g (30 mmol, Mw=295.3) Z-Glu-OMe and 7.6 g (30 mmol, Mw=253.3) Z-Ser-OMe were dissolved in 100 ml DCM, after which a catalytic amount of DMAP was added. The mixture was cooled to 0°C, and 6.39 g (31 mmol, Mw=206) of DCC dissolved in 20 ml DCM was added under stirring. The mixture was allowed to reach room temperature and was stirred overnight. DCU precipitated out from the reaction mixture slowly.

15

The mixture was processed after being warmed to 30°C for approximately one hour. The residue was dissolved in ethyl acetate after filtering and evaporation, on which further DCU precipitated out. The product mixture was allowed to stand for three days before being refiltered. The reaction mixture was washed by extraction with potassium hydrogen sulphate (1M), distilled water, sodium hydrogen carbonate (saturated) and finally three times with distilled water. The organic phase was then dried over water-free magnesium sulphate, filtered and evaporated to dryness.

25 Yield: 17 g (theoretical 16 g).

¹HNMR (300 MHz/CDCl₃, ppm): 1.92 (m, 2H, C-CH₂-C), 2.18 (m, 1H, -CH-CO), 2.38 (m, 2H, CH₂-CO), 3.72 (s, 3H, OCH₃), 3.76 (s, 3H, OCH₃), 4.38 (m, 2H, CH₂-O), 4.64 (m, 1H, α-H), 5.06 (s, 2H, benzy), 5.11 (s, 2H, benzy), 5.43 (d, 1H, N-H), 5.91 (d, 1H, N-H), 7.32 (s, 5H, phenyl) and 7.324 (s, 5H, phenyl).

30

IR: ν_{\max} (Solid sample/ATR-FTIR), 3330s (N-H) and 1720s (C=O, broad).

MS: ESMS; m/z (calculated) $C_{26}H_{30}N_2O_{10}$ 530.52; (obtained) 531.3 $[MH^+]$ and 553.3 $[MNa^+]$.

5

b) 5-[(2S)-2-amino-3-methoxy-3-oxopropyl] 1-methyl (2S)-2-aminopentandioate

Benzyloxycarbonyl-protected diamine, 16 g, 30 mmol, $M_w=530.5$, was dissolved in 50 ml absolute ethanol and a catalytic amount of palladium on active carbon (Pd/C 10%) was added, after which dissolved gases were evacuated from the mixture by applying a water vacuum. A hydrogen gas pressure of 2.5 bar was then applied and the mixture stirred vigorously. When no further hydrogen gas was consumed in the reactor on the following day, the procedure was interrupted and the contents filtered through celite and evaporated to an oil.

Yield: 7.65 g (theoretical 7.86 g) 97%

IR: ν_{\max} (Solid sample/ATR-FTIR), 3360s (N-H), 3280s (N-H), 1733s (C=O), 1676s (C=O) and 1204s (C-O).

MS: ESMS; m/z (calculated) $C_{10}H_{18}N_2O_6$ 262.26; (obtained), 262.9 $[MH^+]$ and 284.9 $[MNa^+]$.

Example 6

25

2-{2-[(aminoacetyl)oxy]ethoxy}-2-oxoetanaminium dichloride

a) 2-{2-[(*tert*-butoxycarbonyl)amino]acetyl}oxy)ethyl [*tert*-butoxycarbonyl)amino]acetate

30

35.04 g (200 mmol) *tert*-butyloxycarbonylglycine and 6.21 g (100 mmol) ethylene glycol were dissolved in 300 ml dichloromethane (DCM). The

mixture was cooled to 0°C, and a catalytic amount of dimethylaminopyridine (DMAP) was then added. A solution of 41.4 g (200 mmol) dicyclohexyl carbodiimide (DCC) in 150 ml DCM was then added under vigorous stirring. The reaction was then allowed to reach room temperature and was allowed
5 to proceed until the next day.

Processing of the reaction commenced with filtration, followed by evaporation of the filtrate and its dissolution in approximately 20 ml ethyl acetate. This solution was washed with 1M KHSO₄, distilled water, saturated NaHCO₃, and
10 then three times with distilled water. The solution was then dried over magnesium sulphate and evaporated to give an oil that crystallised. Yield 35 g. The crystals were recrystallised from warm ethyl acetate (100 ml) and then finally mixed to a slurry in n-hexane and filtered.

15 Yield: 33 g (theoretical 37.6 g) 88%.

¹H NMR (300 MHz, CDCl₃, ppm): 1.42 (s, 9H, OtBu), 3.92 (d, 2H, N-CH₂-CO), 4.36 (s, 2H, O-CH₂-C) and 5.1 (m, 1H, N-H). C₂-symmetry halves the NMR spectrum.

20

IR: ν_{max} (solid sample/ATR-FTIR), 3340s (N-H), 1762s (C=O, ester) and 1673s (C=O, urethane).

MS: ESMS; m/z (calculated) C₁₆H₂₈N₂O₈ 376.18457; (obtained) 377 [M+H]⁺ and 399.1 [M+Na]⁺.

25

b) 2-{2-[(aminoacetyl)oxy]ethoxy}-2-oxoetanaminium dichloride

13.2 g (35 mmol) of the Boc-protected diamine from Step a) were treated with 50 ml 5M HCl in IPA under nitrogen gas in a round-bottomed flask under
30 stirring. The mixture thickened rapidly, and 50 ml isopropylalcohol (IPA) were consequently added. The mixture was evaporated to dryness after 1 hour.

The evaporated reaction mixture was triturated with diethyl ether and re-evaporated. The residue after evaporation was a colourless crystalline powder. The yield was quantitative.

- 5 ^1H NMR (300 MHz, DMSO, ppm): 3.85 (s, 2H, N-CH₂-CO), 4.4 (s, 2H, O-CH₂) and 8.45 (s, 3H, NH₃⁺). C2-symmetry halves the NMR spectrum.

IR: ν_{max} (Solid sample/ATR-FTIR), 2950s (N-H) and 1744s (C=O).

- 10 MS: ESMS; m/z (calculated) C₆H₁₂N₂O₄ (free base) 176.07971; (obtained) 176.9 [M+H]⁺ and 198.9 [M+Na]⁺.

Example 7

- 15 **Preparation of a linear polymer according to the present invention through the polymerisation of L-lysine diisocyanate (LDI) with 2-[(2-aminoacetyl)oxy]ethyl aminoacetate (the product from Example 6)**

Molar ratio	n (mmol)	Mw (g/mol)	m (g)	Substance
1	2.383	226.23	0.539	L-lysine diisocyanate (LDI)
1	2.383	432.28	1.030	2-{2-[(aminoacetyl)oxy]ethoxy}-2-oxoetanaminium dichloride
2	4.765	101.19	0.482	Triethylamine
~100	238.3	119	28.4	Chloroform
~100	238.3	18	4.3	Deionised water

20

Procedure

Glass equipment was dried at 77°C ~2 hours.

- LDI was weighed out into a 250 ml flanged flask, nitrogen gas was applied. 2-{2-[(aminoacetyl)oxy]ethoxy}-2-oxoetanaminium dichloride (the product from Example 6) was weighed out into a 25 ml beaker and dissolved in deionised water. Chloroform (21 g, 74% of the total quantity) was added to the weighed LDI and stirring commenced. Triethylamine was weighed out and dissolved in the remaining amount of chloroform (7.4 g). When it appeared that all LDI has dissolved in the chloroform (2-{2-[(aminoacetyl)oxy]ethoxy}-2-oxoetanaminium) dichloride and water were added.
- Triethylamine and chloroform were added dropwise using a pipette during approximately 3 minutes. Lumps of gel could be observed in the solution. Acetone (10 ml) was added after stirring for 20 minutes, and then deionised water (200 ml). The water was separated out and new water (200 ml) added. This water also was separated out and the sticky mass of polymer dried in a vacuum oven.
- m_{polymer} : 0.80 g
Yield: ~ 78%
- The dried polymer was dissolved in DMSO to a concentration of 18% and it was possible to cast a film. A sample of the dried polymer was subjected to analysis by SEC ("Size Exclusion Chromatography"). According to SEC (using an RI detector) the polymer has a peak after approximately 15.0 minutes, which corresponds to a molecular weight of 180,000 relative to a polystyrene standard.

Example 8

Preparation of a linear polymer according to the present invention through the polymerisation of 4,4'-diphenylmethane diisocyanate (MDI) with 2-[(2-aminoacetyl)oxy]ethyl aminoacetate (the product from Example 6)

Molar ratio.	n (mmol)	Mw (g/mol)	m (g)	Substance
1	2.576	250	0.644	4,4'-diphenylmethane diisocyanate (MDI)
1	2.576	432.28	1.114	2-{2-[(aminoacetyl)oxy]ethoxy}-2-oxoetanaminium dichloride
2	5.152	101.19	0.521	Triethylamine
~100	257.6	119	30.7	Chloroform
~100	257.6	18	4.6	Deionised Water

Procedure

- 10 Glass equipment was dried at 77°C for approximately 2 hours.
- MDI was weighed out into a 250 ml flanged flask, nitrogen gas was applied.
- 2-{2-[(aminoacetyl)oxy]ethoxy}-2-oxoetanaminium dichloride (the product from Example 6) was weighed out into a 25 ml beaker and dissolved in deionised water. Chloroform (21 g, 74% of the total quantity) was added to
- 15 the weighed MDI and stirring commenced. Triethylamine was weighed out and dissolved in the remaining amount of chloroform (7.4 g). When it appeared that all MDI had dissolved in the chloroform, 2-2-[(aminoacetyl)oxy]ethoxy}-2-oxoetanaminium dichloride and water were added.
- 20 Triethylamine and chloroform were added dropwise using a pipette during approximately 3 minutes, under stirring.

Acetone (8 ml) was added after stirring for 20 minutes, and then deionised water (200 ml). The water was separated out and new water (200 ml) added. This water also was separated out and the organic phase was then evaporated in a Rotavapor. A yellow-white powder was obtained.

5

m_{polymer} : 0.814 g

Yield: ~70%

The dried polymer was dissolved in DMSO to a concentration of 18% and it was possible to cast a film. A sample of the dried polymer was subjected to analysis by SEC. According to SEC (using UV and RI detectors) the polymer has a peak after approximately 14.13 minutes, which corresponds to a molecular weight of 400,000 relative to a polystyrene standard.

15 **Example 9**

Degradation experiments of a linear polymer according to the present invention wherein the polymer was prepared in analogy with Example 7 by the polymerisation of L-lysine diisocyanate (LDI) with 4-[(2-aminoacetyl)oxy]butyl aminoacetate

4-[(2-aminoacetyl)oxy]butyl aminoacetate was prepared in analogy with the preparation according to Examples 1-6. Thereafter, a linear polymer is prepared in analogy with Example 7 by the polymerisation of L-lysine diisocyanate (LDI) with 4-[(2-aminoacetyl)oxy]butyl aminoacetate. The linear polymer prepared was in the form of a film and had a molecular weight of 450,000 relative to a polystyrene standard. The polymer was held in a bath with phosphate buffer (at pH 7.0) at 67°C. The polymer film had disintegrated after seven days, that is, it was broken down to such a degree that it was not possible to obtain a sample for analysis by SEC.

Example 10

Degradation experiments of a linear polymer according to the present invention wherein the polymer was prepared in analogy with Example 8
5 by the polymerisation of 4,4'-diphenylmethane diisocyanate (MDI) with 4-[(2-aminoacetyl)oxy]butyl aminoacetate

4-[(2-aminoacetyl)oxy]butyl aminoacetate was prepared in analogy with the preparation according to Examples 1-6. Thereafter, a linear polymer is
10 prepared in analogy with Example 8 by the polymerisation of 4,4'-diphenylmethane diisocyanate (MDI) with the HCl salt of 4-[(2-aminoacetyl)oxy]butyl aminoacetate. The linear polymer prepared was in the form of a film and had a molecular weight of 400,000 relative to a polystyrene standard. The polymer was held in a bath with phosphate buffer (at pH 7.0)
15 at 67°C. A sample for SEC analysis was taken after five days in the phosphate buffer, wherein the molecular weight was reduced to 175,000 relative to a polystyrene standard.

Example 11

20

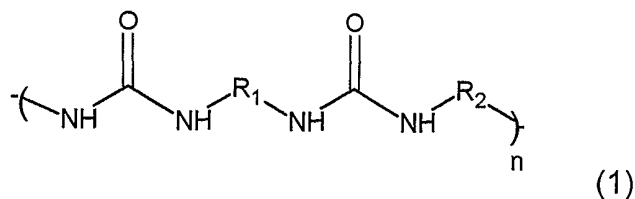
Degradation experiments of a linear polymer according to the present invention wherein the polymer was prepared in analogy with Example 8
by the polymerisation of 4,4'-diphenylmethane diisocyanate (MDI)
with 4-[(2-amino-4-methylpentanoyl)oxy]butyl 2-amino-4-
25 methylpentanoate

4-[(2-amino-4-methylpentanoyl)oxy]butyl 2-amino-4-methylpentanoate is prepared in analogy with the preparation according to Examples 1-6. Thereafter, a linear polymer is prepared in analogy with Example 8 by the
30 polymerisation of 4,4'-diphenylmethane diisocyanate (MDI) with the HCl salt of 4-[(2-amino-4-methylpentanoyl)oxy]butyl 2-amino-4-methylpentanoate. The linear polymer prepared was in the form of a film and had a molecular

weight of 435,000 relative to a polystyrene standard. The polymer was held in a bath with phosphate buffer (at pH 7.0) at 67°C. SEC analysis was carried out after 55 days, and the molecular weight had then been reduced to between 200,000 and 300,000 relative to a polystyrene standard.

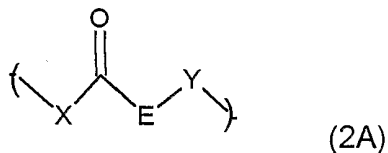
CLAIMS

1. A linear polymer with a molecular weight of at least 10^4 Dalton, which linear polymer consists of internally and linearly linked sequences, which
 5 sequences can be described according to Formula (1)



wherein

- 80 to 100% of R_2 , which 80 to 100% of R_2 can be the same or different, comprise a segment according to Formula (2A)
 10



wherein

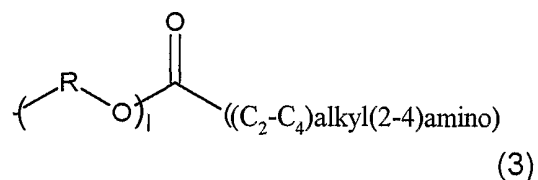
- E is oxygen or nitrogen,
 15

- X and Y, which X and Y can be the same or different, are $(\text{C}_1\text{-C}_5)\text{alkyl}$, or are derived from $((\text{C}_1\text{-C}_4)\text{alkyl})[(2\text{-}4)\text{-amino}((\text{C}_2\text{-C}_4)\text{ alkanoate})]$,
 $[(1\text{-}4)\text{-amino}((\text{C}_1\text{-C}_4)\text{alkyl})][(\text{C}_2\text{-C}_4)\text{ alkanoate}]$,
 $[(2\text{-}4)\text{-amino}((\text{C}_2\text{-C}_4)\text{ alkanoate})][(\text{C}_1\text{-C}_5)\text{alkyl}]$,
 20 $[(\text{C}_2\text{-C}_4)\text{ alkanoate}][(1\text{-}5)\text{-amino}((\text{C}_1\text{-C}_5)\text{alkyl})]$,
 $((\text{C}_1\text{-C}_4)\text{alkyl})[(2\text{-}4)\text{-amino}((\text{C}_2\text{-C}_4)\text{ carboxamide})]$,
 $[(1\text{-}4)\text{-amino}((\text{C}_1\text{-C}_4)\text{alkyl})][(\text{C}_2\text{-C}_4)\text{ carboxamide}]$,
 $[(2\text{-}4)\text{-amino}((\text{C}_2\text{-C}_4)\text{ carboxamide})][(\text{C}_1\text{-C}_5)\text{alkyl}]$ or from
 $[(\text{C}_2\text{-C}_4)\text{ carboxamide}][(1\text{-}5)\text{-amino}((\text{C}_1\text{-C}_5)\text{alkyl})]$,

and provided that Y is not C₁-alkyl, or

Y is derived from a substituent according to Formula (3)

5

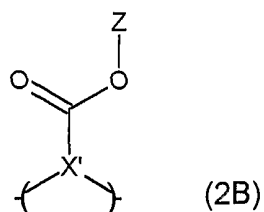


wherein R is (C₁-C₇)alkyl, and

I is from 1 to 20, and

10 X is as has been defined above;

said 80 to 100% of R₂, the same or different, comprise a segment according to Formula (2B)



15

wherein X' is ((C₁-C₅)alkyl) and

20 Z is hydrogen, (C₁-C₄)alkyl, benzyl, tert.-butyl, phenacyl, isopropyl, neopentyl, sec-butyl or tosyl; and/or

said 80 to 100% of R₂, the same or different, can be derived from a first group of diamine that are based on amino acids esterified with diols, and/or

from a second group of diamines that is based on amino acids esterified with amino alcohols; and,

when not 100% of R_2 comprise a segment according to Formula (2A) or (2B),
 5 or can be derived from said first or second groups of diamines, each other R_2 can be derived from a third group of diamines that are aliphatic or aromatic diamines; and

each R_1 , the same or different, can be derived from a diisocyanate, wherein
 10 said diisocyanate can be diphenylmethyl diisocyanate (MDI), hexamethylene diisocyanate (HDI), 1,4'-diisocyanatobutane or 4,4',-dicyclohexylmethane diisocyanate (H_{12} MDI), or said diisocyanate can be ethyl-2,6-diisocyanatohexanoate (LDI), isophorone diisocyanate (IPDI), toluene-2,4-diisocyanate (TDI) or 1,3-bis(isocyanatomethyl)cyclohexane.

15

2. The linear polymer according to claim 1, characterised in that E in the segment according to Formula (2A) is oxygen, and/or

X and Y, the same or different, are (C_1-C_5) alkyl, or are
 20 derived from $((C_1-C_4)alkyl)[(2-4)-amino((C_2-C_4)alkanoate)]$,
 $[(1-4)-amino((C_1-C_4)alkyl)][(C_2-C_4)alkanoate]$,
 $[(2-4)-amino((C_2-C_4)alkanoate)][(C_1-C_5)alkyl]$ or
 $((C_2-C_4)alkanoate)[(1-5)-amino((C_1-C_5)alkyl)]$.

25 3. The linear polymer according to claim 1 or 2, characterised in that said linear polymer is degradable.

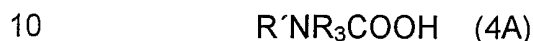
4. The linear polymer according to any one of claims 1 to 3, characterised in that said linear polymer is a block polymer.

30

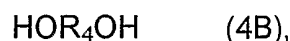
5. The linear polymer according to any one of claims 1, 3 or 4 characterised in that said 80 to 100% of R_2 , the same or different, can be derived from diamines according to Formula (4C)



wherein the diamines according to Formula (4C) are based on protected amino acids according to Formula (4A)



that have been esterified with diols according to Formula (4B)



15

wherein R' is a protective group and amino acids according to Formula (4A) are α - and/or ω -amino acids, preferably glycine (wherein R_3 is CH_2), alanine, lysine, ornithine, methionine, leucine, isoleucine, phenylalanine, tyrosine, glutamic acid or aspartic acid, or the esters of these with methyl, ethyl, benzyl, phenacyl, tert.-butyl, isopropyl, neopentyl, sec-butyl or tosyl in the α - or ω -position, or from serine with a protected OH-group, and

20

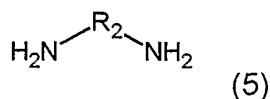
diols according to Formula (4B) are selected from ethylene glycol, propylene glycol, butane diol, pentane diol, hexane diol, neopentyl glycol, diethylene glycol, triethylene glycol, tetraethylene glycol, pentaethylene glycol, polyethylene glycol (PEG), polytetramethylene oxide diol (PTMOG), 1,4-dihydroxymethylbenzene, polypropylene glycol and hydroxitelechelic polybutadiene, and also hybrids of these, and from hydroxitelechelic oligomers, preferably hydroxitelechelic oligoesters, oligoamides or oligocarbonates, wherein the compounds according to Formula (4B) can also contain heteroatoms, such as S or N and/or ester groups.

25

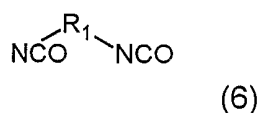
30

6. The linear polymer according to any one of claims 1, 3 or 4 characterised in that said 80 to 100% of R_2 , the same or different, can be derived from diamines that are derived from esters of amino acids with amino alcohols.
- 5
7. The linear polymer according to any one of claims 1 to 6, characterised in that each R_1 , the same or different, can be derived from a diisocyanate, which can be commercially available, such as diphenylmethyl diisocyanate (MDI), hexamethylene diisocyanate (HDI), 1,4'-diisocyanatobutane or
- 10 4,4',-dicyclohexylmethane diisocyanate (H_{12} MDI), or said diisocyanate can be ethyl-2,6-diisocyanatohexanoate (LDI), isophorone diisocyanate (IPDI), toluene-2,4-diisocyanate (TDI) or 1,3-bis(isocyanatomethyl)cyclohexane.
8. The linear polymer according to any one of claims 1, 3, 4 or 7,
- 15 characterised in that said 80 to 100% of R_2 , which 80 to 100% of R_2 can be the same or different, can be derived from one or several of
- 2-aminoethyl 4-aminobutanoate,
 4-[(4-aminobutanoyl)oxy]butyl 4-aminobutanoate,
 20 5-[(2S)-2-amino-3-methoxy-3-oxopropyl] 1-methyl
 (2S)-2-aminopentanedioate,
 5-(2-aminoethyl) 1-methyl (2S)-2-aminopentanedioate,
 5-(3-aminopropyl) 1-methyl (2S)-2-aminopentanedioate,
 5-(4-aminobutyl) 1-methyl (2S)-2-aminopentanedioate,
 25 methyl (2S)-2-amino-3-[(3-aminopropanoyl)oxy] propanoate,
 2-[(2-aminoacetyl)oxy]ethyl 3-aminopropanoate,
 2-[(2-aminoacetyl)oxy]ethyl 4-aminobutanoate,
 2-[(2-aminoacetyl)oxy]ethyl aminoacetate,
 4-(2-aminoethyl) 1-methyl (2R)-2-aminobutanedioate,
 30 2-aminoethyl aminoacetate,
 4-[(2-aminoacetyl)oxy]butyl aminoacetate,
 2-[(3-aminopropanoyl)oxy]ethyl 3-aminopropanoate,

- 2-[(2-aminoacetyl)oxy]ethyl aminoacetate,
methyl (2S)-2-amino-3-[(aminoacetyl)oxy] propanoate,
tert-butyl 2,6-diaminohexanoate,
benzyl 2,6-diaminohexanoate,
- 5 2-aminoethyl [(aminoacetyl)amino] acetate,
2-aminoethyl 3-[(aminoacetyl)amino] propanoate and
2-aminoethyl 3-[(3-aminopropanoyl)amino] propanoate; and
- salts, together with all possible stereoisomers either pure or as racemic
- 10 compounds or as mixtures of stereoisomers, thereof .
9. The linear polymer according to any one of the preceding claims,
characterised in that said R_1 and/or said 80 to 100% of R_2 comprise parts
that can be derived from amino acids, wherein said parts comprise amino
- 15 acids with substituents on their α -carbon atoms.
10. The linear polymer according to any one of the preceding claims,
characterised in that said 80 to 100% of R_2 is 100%.
- 20 11. The linear polymer according to any one of the preceding claims
characterised in that said each alkyl and said each alkanoate in Formula (1)
can, independently of each other, be straight or branched, saturated or
unsaturated, and/or substituted with, for example, methyl, phenyl, 4-
hydroxyphenyl, 4-aminobutyl, 2-butyl, 2-hydroxymethyl, 3-aminopropyl, 2-
- 25 aminoethyl, 2-mercaptomethyl, or similar.
12. A method for preparing a linear polymer according to any one of the
preceding claims, characterised in that said method comprises
polymerisation, in which approximately n moles of one or several different
- 30 compounds according to Formula (5)



are linked with approximately n moles of one or several different compounds according to Formula (6)



, wherein

5

R₁ and R₂ are defined according to any one of the preceding claims.

13. A method for processing a linear polymer according to any one of claims 1 to 11, characterised in that said method comprises the preparation of fibres
10 by dry or wet spinning of said linear polymer.

14. A method for processing a linear polymer according to any one of claims 1 to 11, characterised in that said method comprises preparation of film of said linear polymer or application of said linear polymer onto woven material,
15 film or surfaces by coating, impregnation, lamination or casting.

15. A method for processing a linear polymer according to any one of claims 1 to 11, characterised in that said method comprises dipping a mould that is dipped into a solution of said linear polymer.

20

16. Use a linear polymer according to any one of claims 1 to 11, in the form of, for example, fibres or film as, for example, material in implants for humans and animals, for example, as implants for tendons, ligaments, blood vessels, sutures, discs or menisci, for pharmaceutical preparations, in
25 microencapsulation, in suspensions, in emulsions, in porous three-dimensional structures, such as porous polymer materials, or similar.

17. The use of a linear polymer according to any one of claims 1 to 11 in pharmaceutical preparations, during microencapsulation, in suspensions, in emulsions or similar.
- 5 18. The use of a linear polymer according to any one of claims 1 to 11, in material for artificial blood vessels, material for preventing adhesions, material that prevents adhesion or material for promoting wound healing in humans and animals.
- 10 19. Use of a linear polymer according to any one of claims 1 to 11, in a cell material for culturing of cells, menisci, discs and other applications that are covered by the concept of "tissue engineering".
20. Implants, for example tendons, ligaments, blood vessels, discs or
15 menisci, for humans and animals, characterised in that said implants comprise a linear polymer according to any one of claims 1 to 11.
21. Pharmaceutical preparations, microencapsules, suspensions, emulsions or porous three-dimensional structures that comprise a linear polymer
20 according to any one of claims 1 to 11.
22. Material for artificial blood vessels, for preventing adhesions, as
obstacles to adhesion or for promoting wound healing in humans and
animals, characterised in that said material comprises a linear polymer
25 according to any one of claims 1 to 11.
23. Cell material for culturing of cells, menisci, discs and other applications that are covered by the concept of "tissue engineering", characterised in that said material comprises a linear polymer according to any one of claims 1 to
30 11.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 01/02901

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C08G 18/10, C08G 18/32, A61K 27/00

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)

IPC7: C08G, A61K

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

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 0045869 A1 (ARTIMPLANT AB), 10 August 2000 (10.08.00) --	1-23
A	WO 9722643 A1 (POLYRAND AB), 26 June 1997 (26.06.97) --	1-23
A	EP 0129396 A2 (HOWMEDICA INC.), 27 December 1984 (27.12.84) --	1-23
A	US 6221997 B1 (WOODHOUSE ET AL), 24 April 2001 (24.04.01) --	1-23

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

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

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

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Date of the actual completion of the international search

11 April 2002

Date of mailing of the international search report

17-04-2002

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 01/02901

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5236966 A (GRAHAM ET AL), 17 August 1993 (17.08.93) --	1-23
A	US 4689353 A (HARRIS), 25 August 1987 (25.08.87) --	1-15
A	US 4049632 A (MAGNUSSON ET AL), 20 Sept 1977 (20.09.77) -- -----	1-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

28/01/02

International application No.

PCT/SE 01/02901

Patent document cited in search report				Publication date		Patent family member(s)	Publication date
WO	0045869	A1	10/08/00	AU	2836400	A	25/08/00
				AU	3177799	A	27/09/99
				BR	0007926	A	06/11/01
				CN	1338950	T	06/03/02
				CZ	20012590	A	14/11/01
				EP	1076736	A	21/02/01
				EP	1148896	A	31/10/01
				HU	0101084	A	30/07/01
				NO	20004510	A	08/09/00
				NO	20013448	A	07/08/01
				SE	514064	C	18/12/00
				SE	9900345	A	03/08/00
WO	9722643	A1	26/06/97	AT	201704	T	15/06/01
				AU	709440	B	26/08/99
				AU	1154797	A	14/07/97
				BR	9612032	A	28/12/99
				CA	2240061	A	26/06/97
				CN	1214057	A	14/04/99
				CZ	9801793	A	11/11/98
				DE	69613144	D,T	29/11/01
				DK	866816	T	10/09/01
				EP	0866816	A,B	30/09/98
				SE	0866816	T3	
				ES	2159769	T	16/10/01
				HU	9901201	A	28/07/99
				IL	124884	D	00/00/00
				JP	2000502142	T	22/02/00
				NO	982703	A	14/07/98
				NZ	324479	A	28/05/99
				PL	327246	A	07/12/98
				PT	866816	T	31/10/01
				SE	505703	C	29/09/97
				SE	9504495	A	16/06/97
				SI	866816	T	00/00/00
				SK	79798	A	10/03/99
				US	6210441	B	03/04/01
EP	0129396	A2	27/12/84	SE	0129396	T3	
				AT	28652	T	15/08/87
				CA	1209158	A	05/08/86
				DE	3465093	D	00/00/00
				JP	1058209	B	11/12/89
				JP	1577765	C	13/09/90
				JP	60011524	A	21/01/85
				US	4485227	A	27/11/84
US	6221997	B1	24/04/01	NONE			

INTERNATIONAL SEARCH REPORT

Information on patent family members

28/01/02

International application No.

PCT/SE 01/02901

Patent document cited in search report			Publication date	Patent family member(s)		Publication date
US	5236966	A	17/08/93	CA	2064889 A	16/02/91
				DE	69013926 D,T	23/03/95
				EP	0489068 A,B	10/06/92
				SE	0489068 T3	
				ES	2065544 T	16/02/95
				GB	2235462 A,B	06/03/91
				GB	8918589 D	00/00/00
				GB	9017755 D	00/00/00
				WO	9102763 A	07/03/91
				ZA	9006467 A	29/04/92

US	4689353	A	25/08/87	NONE		

US	4049632	A	20/09/77	NONE		
