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Resorbable, physiologically safe copolymers and their use

The invention relates to resorbable, physiologically safe copolymers and their use.

It is known that high-polymer hydroxycarboxylic acids such as polylactide and polyglycolide are physiologically safe and have high body tolerance, with the result that they have already been used for some time in surgery as slowly resorbable stitches or as osteosynthesis implants. These high-polymer polycarboxylic acids are decomposed in the course of weeks to months and decomposed by the human or animal body in the usual manner via the citric acid cycle or fat metabolism. For this reason, polymers of this type can also be safely used as osteosynthesis implants, for example, providing the advantage that the secondary operation of removing the implants is no longer necessary or necessary only for the part of the implant not comprising a polymer.

Furthermore, DE-OS 36 20 685 discloses agents on the basis of flowable to solid oligomeric esters of lactic acid and/or glycolic acid for covering unwounded and/or wounded human or animal skin. These preparations essentially

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comprise the oligomeric esters as a resorbable carrier or film former and can additionally contain skin-care substances, regenerating or disinfecting substances or substances which stimulate the epithelium. Furthermore, film-forming polymers of lactic acid and glycolic acid in solvents such as ethyl acetate are known from FR-OS 21 26 270 and additionally contain pharmacological active substances and can be used as a spray dressing, for example.

Furthermore, US-PS 4,045,418 and 4,148,871 disclose copolymers of lactide and ϵ -caprolactone which are physiologically safe and can be used as subdermally implantable receptacles for medicines, for example. The tolerance and the biological degradability of such receptacles is reported on in, for example, Journal of Biomedical Materials Research, volume 13, pages 497 to 507, 1979 and in Naltrexone: Research Monograph 28, National Institute on Drug Abuse, 1983 by the working group Colin G. Pitt et al.

The hitherto known mono- and copolymers of lactic acid and glycolic acid have the disadvantage that they are compounds which are usually applied in solutions and which are themselves relatively hard and have little flexibility, with the result that sprayed-on films of this type quickly become brittle and cracked after the solvent

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has evaporated, with the additional problem that adhesion to the surface of the skin or wound is not particularly good. The hitherto used polymers of lactide and ϵ -caprolactone on the one hand are as a rule rigid thermoplastics which are suitable for manufacturing receptacles, for example, but not suited to topical application.

There is therefore still a need for physiologically safe polymers which can be used on the skin and which do not have the disadvantages described.

According to the invention, the use of copolymers of racemic lactide and ϵ -caprolactone, δ -valerolactone, racemic γ -decalactone or β -hydroxybutyric acid is now proposed, wherein the copolymers are prepared through conversion of the monomers in the molar ratio lactide to co-reactant of approximately 95-70 to 5-30 with the addition of metallic carboxylates, known per se, as initiator at temperatures of approximately 150°C for a duration of approximately 16 to 48 hours.

The copolymers according to the invention are to be regarded as poly- and oligomers in accordance with the chain length and are present as a mixture of mono-, oligo- and polymers. This concerns colourless, transparent compounds which, according to the molar ratio of the

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monomer parts, are viscous to rigid. The claimed compounds are prepared through conversion of the monomers in the molar ratio of lactide to co-reactant of approximately 95-70 to 5-30, wherein the increase in the lactide proportion leads to an increase in softening temperature. Conversion takes place with the addition of metallic carboxylates, known per se, as initiator at temperatures of approximately 150°C for a duration of approximately 16 to 48 hours. The ratio of reaction mixture to initiator is approximately 100 to 1 up to 3000 to 1, e.g. 100 to 1 to 500 to 1, wherein increasing this ratio in the reaction produces an increase in the proportion of relatively long molecular chains and consequently also raises the softening point. Tin-II-diethyl hexanoate is preferably used as initiator since it has emerged that other initiators known per se generally give a lower yield or lead to turbidity/coloration. It has furthermore been found that a temperature of 150°C and a conversion time of 16 to 48 hours is not to be exceeded since heating for too long can cause decomposition of the polymer to begin. The reaction is interrupted after the desired conversion period, either by cooling the conversion mixture or by the addition of chelation agents, for example. In order to remove remaining monomers, short-chained oligomers or, if applicable, also excess plasticisers, the reaction mass is generally precipitated with a 600 to 800-fold quantity of alcohol. If appropriate, the reaction mass can also be



washed with water or an aqueous solution since a large proportion of monomers, short-chained oligomers or plasticisers can also be removed by these means.

If so desired, plasticisers can be added to the reaction mass in order to modify the softening temperature and the diffusibility. Excess caprolactone, tributyl citrate or phthalic acid esters are preferably used as plasticisers. The proportion of plasticisers should as a rule not exceed 10% to 20% in terms of weight.

The copolymers according to the invention can be dissolved in suitable organic solvents such as acetic ester, acetone, methylene chloride or THF. They can be rolled out, without anything further being added, into films which can, however, also be produced by evaporation, for example. Other processing methods suitable for synthetic materials can also be applied.

Both the monomers and the polymers are decomposed by hydrolysis in vivo and in vitro. The copolymers and their decomposition products are medically safe and non-allergenic. The monomers are metabolised further in vivo via the citric acid cycle or via fatty acid metabolism. It has emerged that the higher the lactide proportion, the shorter the times for hydrolytic decomposition.

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The polymers claimed according to the invention can be used for various medical and cosmetic purposes. One of the main areas of application is use as a surgical incision film. The compounds which are present in solution in a suitable solvent such as methylene chloride, acetone or acetic ester can be easily mixed with known disinfectants. Combination with locally acting anaesthetics is also possible. When using acetic ester, a disinfecting effect is already produced on the basis of this solvent.

Copolymers with a molar ratio of between 70 to 30 up to 85 to 15 and a ratio of co-reactant to initiator of approximately 300 to 1 up to 500 to 1 and a polymerisation time of 24 hours are the most suitable for topical uses. This relates to washed copolymers, but unwashed copolymers with molar ratios of between 80 to 20 up to 90 to 10 and a ratio of co-reactant to initiator of 100 to 1 up to 400 to 1 with the same polymerisation time can also be used. The same compounds can be used in the same way for incision films, the great advantage lying above all else in their environmentally friendly nature, ease of application, the unlimitedness of the surfaces to be covered and the low production and preparation costs, with the additional advantage that in relation to lactide/ glycolide polymers, substantially improved adhesion to skin and wound surfaces and a high level of flexibility and mouldability can be

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observed. Furthermore, the preparations according to the invention are marked by their low resolvability by aqueous fluids such as blood, lymph, etc. The natural hydrolytic decomposition of the spray film takes approximately 3-30 weeks in vitro.

Furthermore, the agents according to the invention can be used particularly favourably as a fluid glove when handling allergens. Thus they are also a real alternative for those who suffer from allergies to detergents or washing agents. On account of their long-lasting quality and good adhesion, such solutions can also be used as camouflage aids and, particularly when combined with sun protection factors, as a long-lasting sun screen which makes renewed application after swimming, for example, unnecessary for days.

In a further embodiment, copolymers of the invention can be formed in which the ratio of racemic lactide and ϵ -caprolactone is selected in the ratio of 85-80 to 20-15 and the ratio of monomer to initiator lies in the region of over 500 up to approximately 3000 to 1, copolymers being produced which are distinguished by particularly good flexibility and adhesion when metallic carboxylates are used as initiator at a polymerisation temperature of 150°C for a polymerisation time of 16 to 48

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hours. When processed into films, these polymers are distinguished by good gas permeability and particularly good adhesion to the skin and are so flexible that even in unfavourable conditions, cracking cannot be detected, even under great stress.

In place of lactide and caprolactone, a mixture of racemic lactide, containing some glycolide, and ϵ -caprolactone in the ratio of 80 to 15 to 5 up to 85 to 10 to 5 can also be used. Similarly, valerolactone can also be used in place of ϵ -caprolactone without any modification of the excellent properties.

In order to produce sprays, the copolymers are simply dissolved in a suitable solvent in the required amount and can then be sprayed as an aerosol. Suitable solvents are, for example, acetic ester, acetone or other esters or ketones.

In spray form the copolymers can preferably be used as a fluid glove or, after the addition of appropriate active substances, as a sun screen agent or insect repellent.

In order to produce films, the polymers can be heated until they soften and then rolled out into films or be processed into films of a defined thickness in the usual manner by extrusion. 5 to 15 g of the copolymer are



generally dissolved in 100 ml acetic ester and then processed further, for example by evaporation of the solvent after the solution is poured out onto silanised glass. Through the addition of plasticisers, which are physiologically safe, the softening temperature and also the diffusibility of the films can be modified.

Through spraying onto a rolling mill and subsequent pressing, the copolymers can also be processed into a bonded material.

The copolymers prepared according to this embodiment of the invention are, as already mentioned, particularly well suited as sprays or as films for covering the skin. In both cases, locally acting antibiotics, sun screen agents, skin care preparations or insect repellants can be mixed with the copolymers before being processed into a spray or film.

In a further advantageous embodiment, the copolymers are mixed with hydrophilic substances, such as lactide or glycerin, in a suitable organic solvent, such as acetic ester. After evaporation of the solvent, the hydrophilic substances can be washed out with water or other solvents for the low-molecular constituents, as a result of which a spongy structure is produced. The water resorption capacity increases considerably as a result of the spongy

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structure. If so desired, a film of the same copolymers can additionally be deposited on the spongy matrix by heating for a short time or in another known manner.

The invention is explained in more detail below with the aid of the examples:

Example 1

Preparation of the copolymers

In order to prepare the copolymers, D,L-lactide and ϵ -caprolactone are slowly heated to 150°C in a molar ratio of 85 to 15, corresponding to 70.2 grams to 9.8 grams. 1.16 ml tin-II-diethyl hexanoate (1.5M in benzene) (ratio reaction mass to initiator = 100 to 1) is then added as polymerisation initiator. Polymerisation takes place in an oil bath over 24 hours at 150°C. The mixture is then cooled and at 70°C made up to 1 litre with ethyl acetate. This solution then remains on a shaking machine for 36 hours and can be used as such thereafter.

The copolymers of lactide and the other lactones such as valerolactone, heptalactone, decalactone or also of β -hydroxy acids such as β -hydroxybutyric acid can also be prepared in a corresponding manner under consideration of the molar ratios.



Example 2

Preparation of a surgical incision film

D, L-lactide and ϵ -caprolactone are slowly heated to 150°C in a molar ratio of 90 to 10, corresponding to 73.5 grams to 6.5 grams. Polymerisation is initiated by the addition of 0.6 ml tin-II-diethyl hexanoate (1.5M in benzene) (ratio of reaction mass to initiator = 200 to 1). The mass is then heated in a oil bath at 150°C for 24 hours. The mass is then cooled and at 70°C can be made up to 1 litre with acetic ester and treated on a shaking machine for 36 hours. The finished solution can then be used directly as a liquid spray.

The appropriately prepared solutions can be used in the same way as a sun screen spray or as a make-up base. When used as a sun screen, the usual UVA and UVB filters known per se are added to the finished solution.

Example 3

Preparation of a fluid glove

The solution prepared according to Example 1 is decanted

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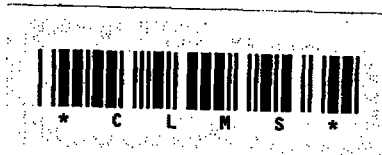
into pump sprays or aerosol sprays known per se.

Example 4

Racemic lactide and ϵ -caprolactone are slowly heated to 150°C in a molar ratio of 80 to 20 = 65.4g to 13.0g. Polymerisation is initiated by the addition of 0.06 ml tin-II-diethyl hexanoate (1.5M in benzene) (ratio of reaction mass to initiator = 1900 to 1). The mass is then heated in an oil bath at 150°C for 16 hours. After cooling, the mass at 70°C is made up to 1l with acetic ester and shaken for 36 hours. If so desired, the copolymers can also undergo a washing operation after polymerisation in order to liberate them of monomers, short-chained oligomers and/or plasticisers. To this end, as described in the main patent, the copolymers are either precipitated with a 600 to 800-fold quantity of alcohol or the reaction mass is washed with water or aqueous alcohol since a large proportion of the monomers and the short-chained oligomers can also be removed by these means.

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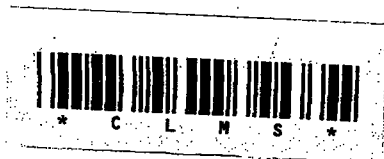
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Claims

1. Use of copolymers of racemic lactide and ϵ -caprolactone, δ -valerolactone, γ -decalactone or β -hydroxybutyric acid, prepared through conversion of the monomers in the molar ratio lactide to co-reactant of approximately 95-70 to 5-30 with the addition of metallic carboxylates, known per se, as initiator at temperatures of approximately 150°C for a duration of approximately 16 to 48 hours, for the topical treatment of human or animal skin.
2. Use of copolymers according to Claim 1, in which the molar ratio of monomer to initiator is from 100 to 1 to 3000 to 1.
3. Use of copolymers according to Claim 3 in which the molar ratio of monomer to initiator is from 100 to 1 to 500 to 1.
4. Use of copolymers according to Claim 1 in which the racemic lactide may optionally contain some racemic glycolide.
5. Use of copolymers according to Claim 4 in which the ratio of racemic lactide and, if applicable, racemic

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glycolide to ϵ -caprolactone or δ -valerolactone is approximately 85-80 to 15-20, the ratio of monomer to initiator being from 500 to 1 to 3000 to 1.

6. Use of the copolymers according to Claims 1 to 3 as a surgical incision film.
7. Use of the copolymers according to Claims 1 to 3 as a fluid glove.
8. Use of the copolymers according to Claims 1 to 3 as a sun screen agent.
9. Use of the copolymers according to Claims 1 to 3 as a camouflage aid.
10. Use of copolymers according to Claim 5 in which locally acting antibiotics are added to the monomers before formation of the copolymers.
11. Use of copolymers according to Claim 5 as carriers in insect repellent sprays.

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